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<table>
<thead>
<tr>
<th>EJB BOARD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abd El Hakim Mahmoud (Cairo Univ.)</td>
</tr>
<tr>
<td>Abd El Monem Rabie (Alex. Univ.)</td>
</tr>
<tr>
<td>Abd El Rehim Yousef (Zakazik Univ.)</td>
</tr>
<tr>
<td>Adel Salah (Zakazik Univ.)</td>
</tr>
<tr>
<td>Ahmed Abdel Rahman (Monoufeya Univ.)</td>
</tr>
<tr>
<td>Ahmed Al Halfawy (Cairo Univ.)</td>
</tr>
<tr>
<td>Ahmed El Gazzar (Benha Univ.)</td>
</tr>
<tr>
<td>Ahmed El Noury (Ain Shams Univ.)</td>
</tr>
<tr>
<td>Amgad Abdel Raouf (Tanta Univ.)</td>
</tr>
<tr>
<td>Amr Badr El Din (Benha Univ.)</td>
</tr>
<tr>
<td>Ehab Atta (Alex. Univ.)</td>
</tr>
<tr>
<td>Emad Koraa (Ain Shams Univ.)</td>
</tr>
<tr>
<td>Gamal El Khoury (Tanta Univ.)</td>
</tr>
<tr>
<td>Gamal Rabie Agmy (Assiut Univ.)</td>
</tr>
<tr>
<td>Hafez Abdel Hafeez (Azhari Univ.)</td>
</tr>
<tr>
<td>Hatem El Mallawany (Alex. Univ.)</td>
</tr>
<tr>
<td>Hesham Tarraf (Cairo Univ.)</td>
</tr>
<tr>
<td>Hoda Abou Yousef (Cairo Univ.)</td>
</tr>
<tr>
<td>Ibrahim Radwan (Azhari Univ.)</td>
</tr>
<tr>
<td>Khaled Eid (Cairo Univ.)</td>
</tr>
<tr>
<td>Khaled Wagih (Ain Shams Univ.)</td>
</tr>
<tr>
<td>Magda Yehia Elseify (Ain Shams Univ.)</td>
</tr>
<tr>
<td>Magdy Abou Rayan (Alex. Univ.)</td>
</tr>
<tr>
<td>Magdy Zedan (Mansoura Univ.)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>ADVISORY BOARD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mokhtar Madkour (Ain Shams Univ.)</td>
</tr>
<tr>
<td>Mohamed Awad Tag El Din (Ain Shams Univ.)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>INTERNATIONAL FACULTY BOARD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmed Boseila (Germany)</td>
</tr>
<tr>
<td>Alaa El Gendy (USA)</td>
</tr>
<tr>
<td>Atul Mehta (USA)</td>
</tr>
<tr>
<td>Heinrich D. Becker (Germany)</td>
</tr>
<tr>
<td>Henri G. Colt (USA)</td>
</tr>
<tr>
<td>James R. Jett (USA)</td>
</tr>
<tr>
<td>Majdy M. Idrees (KSA)</td>
</tr>
<tr>
<td>Petr Pohnenek (Czech Republic)</td>
</tr>
<tr>
<td>Richard W. Light (USA)</td>
</tr>
<tr>
<td>Roland M. du Bois (UK)</td>
</tr>
</tbody>
</table>

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The Egyptian Journal of Bronchology (EJB) welcomes submission of papers on clinical, experimental, cultural and historical topics from authors of diverse clinical and scientific interests and expertise, provided the paper has relevance to bronchoology and related fields.

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Any information requests or correspondence including paper submission, subscription order, change of address of subscriber and, advertising in the Journal, should be addressed to:

ESSB Secretariat
Conference Organizing Bureau
Dr. Shahenda El Hawary
14, El Khalil St., Lebanon Sq., Mohandessin,
Giza 12411, Egypt
Tel.: (202) 33023642 33027672 Fax: (202) 33027672
E-mail: cobshahi@link.net
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<table>
<thead>
<tr>
<th>Page</th>
<th>Section</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Editorial</td>
<td>Cancer-related medical emergencies</td>
<td>Gamal M. Agmy</td>
</tr>
<tr>
<td>10</td>
<td>Airways in Health and Disease</td>
<td>Chronic obstructive pulmonary disease in treated pulmonary tuberculosis patients</td>
<td>Mohamed W. Zakaria, Heba A. Moussa</td>
</tr>
<tr>
<td>14</td>
<td>Airways in Health and Disease</td>
<td>Evaluation of serum troponin I in patients with acute exacerbations of chronic obstructive pulmonary disease</td>
<td>Neven Hazansan, Ayman Abd Elrahman, Mohamed El Mahdy, Osama El Shaer, Mohamed Hassan, Mahmoud El-Habasby</td>
</tr>
<tr>
<td>20</td>
<td>Airways in Health and Disease</td>
<td>Telomere length in chronic obstructive pulmonary disease</td>
<td>Galal-Eldin M. Magdy, Ahmad S. Entesar, Hafez R. Manal, Sobh M. Eman, Alrayes H. Mona</td>
</tr>
<tr>
<td>34</td>
<td>Airways in Health and Disease</td>
<td>Evaluation of nasal optiflow device in the management of chronic obstructive pulmonary disease patients with acute exacerbations</td>
<td>Adel M. Saeed, Khaled M. Wagih, Nasra A. Hussein</td>
</tr>
<tr>
<td>43</td>
<td>Airways in Health and Disease</td>
<td>Study of serum C-reactive protein level and sputum eosinophils in patients with bronchial asthma</td>
<td>Abdeldeek H. Al-Aarag, Aber M. Ravey, Mona M. EL-Rehissy, Marwa M. Abdelrahim</td>
</tr>
<tr>
<td>48</td>
<td>Airways in Health and Disease</td>
<td>Measurement of exhaled nitric oxide in healthy Egyptian population: normal ranges and factors affecting</td>
<td>Aber M. Rawy</td>
</tr>
<tr>
<td>55</td>
<td>Interstitial Lung Diseases and Lung in Systemic Diseases</td>
<td>Factors predicting pulmonary hypertension in idiopathic pulmonary fibrosis patients</td>
<td>Samiaa H. Saidek, Soheir M. Kasiem</td>
</tr>
<tr>
<td>59</td>
<td>Interstitial Lung Diseases and Lung in Systemic Diseases</td>
<td>Pulmonary involvement in juvenile-onset systemic lupus erythematosus patients asymptomatic for respiratory disease</td>
<td>Hala M. Lotfy, Eman F. Halawa, Mohamed El Baz</td>
</tr>
<tr>
<td>64</td>
<td>Interstitial Lung Diseases and Lung in Systemic Diseases</td>
<td>Serum surfactant protein D as a prognostic factor in idiopathic pulmonary fibrosis</td>
<td>El-Milgy Dawaalat, Zakaria Mohamed W., Rashed Laila, Abu-Hussein Haidi</td>
</tr>
<tr>
<td>73</td>
<td>Pleural Diseases</td>
<td>The diagnostic utility of pleural fluid viscosity in lymphocytic pleural effusion</td>
<td>Sayed Labiba, Ibraheem Dwidar, Eman Riad, Basma B. Hasan</td>
</tr>
<tr>
<td>79</td>
<td>Pleural Diseases</td>
<td>Role of ultrasound in the management of pleural diseases in respiratory intensive care patients</td>
<td>Leila A. Helala, Ashraf Madkour, Nehad M. Osman, Waleed M. Hetta, Inas M. Abdel Hakim</td>
</tr>
</tbody>
</table>
Respiratory Infections
92 Ultrasound-assisted medical thoracoscopy
   Amr Shoukri

Respiratory Infections
96 Extrapulmonary tuberculosis situation in El-Behira Governorate, Egypt
   Nabil A. Abdelghaffar Hibah

Case Report
101 Incidence of tuberculosis before and after DOTS (direct observed therapy short course strategy) implementation in El-Behira Governorate, Egypt
   Ali K. Alwani, Abdelsadek H. Al-Aarag, Magdy M. Omar, Nabil A. Abdelghaffar Hibah

Case Report
109 Behçet’s disease: case reports
   Gamal M. Agmy
Pulmonary tumor embolism

The lungs are a prominent target for the embolization of any material larger than \( \sim 10 \mu m \) that gains access to the venous circulation. This includes thrombi, air, amniotic fluid, fat, injected foreign material, and tumor. It is important that the correct type of pulmonary emboli be identified, as treatment and prognosis vary considerably.

Pathophysiology

Tumor cells gain access to the circulatory system through the invasion of small veins, or the release of tumor fragments into the tumor's neovasculature. Most of the circulating tumor cells are then destroyed by circulatory mechanical forces, shear forces, or the host's immune system. However, some tumor cells reach the lungs and become trapped within pulmonary capillaries.

Tumor cells trapped within pulmonary capillaries may trigger the coagulation cascade and obstruct the pulmonary vessels. The obstruction is primarily due to both the tumor cells and the associated clot, but reactive concentric medial hypertrophy and intimal fibrosis of the pulmonary vessels may also contribute. Such secondary changes may progress to complete and irreversible obstruction of pulmonary vessels, whereas occlusion by pure thrombi or thromboemboli is generally followed by recanalization. When the pulmonary vasculature becomes obstructed, ventilation-perfusion matching becomes impaired and pulmonary vascular resistance increases, which may impair gas exchange and cause Cor pulmonale.

Intraluminal tumor emboli do not proliferate or spread locally; thus, they should not be considered as metastases. Lung metastasis requires malignant cells to adhere to lung-specific adhesion molecules on the endothelium, produce enzymes that degrade the basement membrane and lung extracellular matrix, and grow in association with lung-specific growth factors. It has been proposed that tumor emboli may contribute to lymphangitic carcinomatosis; however, this is uncertain, as the two entities are not universally found together and their clinical manifestations are different.

Acute tumor lysis syndrome

What it is

Acute tumor lysis syndrome is a severe metabolic derangement caused by the release of intracellular contents from malignant cells rapidly dying after recent cancer treatment.

When to consider it

Acute tumor lysis syndrome should be considered in cases of high-grade non-Hodgkin lymphoma and acute lymphocytic leukemia after any form of cancer treatment. Spontaneous tumor lysis syndrome (in the absence of recent cancer treatment) can occur in aggressive lymphomas and leukemias (Burkitt lymphoma, acute lymphocytic leukemia, large T-cell lymphoma). TLS is uncommon in solid tumors but can occur in testicular cancer, small-cell lung cancer, neuroblastoma, and breast cancer. Renal failure is a predisposing factor. Any type of cancer treatment can precipitate tumor lysis syndrome, including glucocorticoids, radiation therapy, tamoxifen, and systemic chemotherapy.

What to watch out for

Hyperkalemia, hyperphosphatemia, hypocalcemia (caused by binding with excess phosphate), and hyperuricemia. Hyperkalemia may cause cardiac arrhythmias; excess phosphate and uric acid may cause or worsen renal failure. Acute kidney injury during acute tumor lysis syndrome is an independent and an important marker for mortality risk.

Acute tumor lysis syndrome: what to do

Give intravenous volume

Upon the first suspicion for acute tumor lysis syndrome, authors recommend aggressive intravenous fluids at twice the expected maintenance rate.
Do not alkalinize urine
Authors do not recommend alkalinization of the urine (to increase uric acid solubility), because it may precipitate calcium phosphate and xanthine crystals, which can worsen nephropathy.

Hyperkalemia
Hyperkalemia can be treated with kayexalate, insulin/dextrose, sodium bicarbonate (cautiously to avoid inadvertent hyperkalemia, metabolic alkalosis, or the creation of calcium crystals), or calcium gluconate.

Hyperphosphatemia
Hyperphosphatemia can be treated by flushing with intravenous fluids and giving phosphate binders as needed. Renal replacement therapy may be considered in severe cases or when medical management fails.

Hypocalcemia
Authors suggest that hypocalcemia should not be treated unless symptoms are present, so as to avoid the risk of nephropathy.

Hyperuricemia
Rasburicase (recombinant urate oxidase) catabolizes uric acid and rapidly normalizes uric acid levels; authors recommend rasburicase as a first-line therapy for patients with tumors prone to rapid lysis, or those who have acute tumor lysis syndrome with pre-existing renal failure and high uric acid levels. Rasburicase is contraindicated in patients with G6PD deficiency, and it can cause hemolytic anemia or methemoglobinemia. Rasburicase is currently recommended on faith and its plausible mechanism; no randomized trial has shown that it prevents renal failure or death. Allopurinol is used prophylactically before chemotherapy, but is not recommended for acute tumor lysis syndrome.

Acute kidney injury
Renal replacement therapy (dialysis) is recommended for patients with acute tumor lysis syndrome and significant acute kidney injury, who are not responding well to medical management, or who have potentially life-threatening electrolyte disturbances. No one knows whether hemodialysis or continuous renal replacement is a superior method.

Superior vena cava syndrome
What it is
Superior vena cava (SVC) syndrome is obstruction of flow through the SVC into the right atrium; hence its other name, SVC obstruction syndrome.

What causes superior vena cava syndrome (Who gets it?)
SVC syndrome is caused by compression or invasion by mediastinal masses (tumors and/or lymphadenopathy), stenosis of the SVC, or thrombosis.

In the preantibiotic era, infections (tuberculosis) were the most common cause of SVC syndrome. By the 1980s, malignancy accounted for 90% of the cases of SVC syndrome. With the increase in the placement of catheters in the large vessels over recent decades, line-related thrombosis, vessel stenosis, and other benign causes such as fibrosing mediastinitis now account for an estimated 20–40% of cases of SVC syndrome.

Infection-related superior vena cava syndrome
Tuberculosis, histoplasmosis, and the infectious sequela fibrosing mediastinitis are uncommon causes of SVC syndrome in the USA, but still occur.

Malignancy-related superior vena cava syndrome
Lung cancer and non-Hodgkin lymphoma together cause about 95% of cancer-related SVC syndrome. About 2–4% each of patients with lung cancer or non-Hodgkin lymphoma develop SVC syndrome during their illness. Puzzlingly, Hodgkin lymphoma rarely causes SVC syndrome despite it often affecting the mediastinal lymph nodes.

Thrombosis-related superior vena cava syndrome
Placement of intravenous catheters in the large vessels is believed to be causing an increasing proportion of cases of SVC syndrome, although precise numbers are hard to come by because the absolute risk for any given catheter placement is extremely low (e.g. hundreds of thousands of central venous lines are placed in the USA each year). Many cases of line-related thrombosis causing SVC occur in hypercoagulable cancer patients.

Collateral vessels can dilate and proliferate in response to a slow obstruction of flow through the SVC, resulting in a compensated state for weeks before symptoms develop.

What to look out for in suspected superior vena cava syndrome
Facial edema is the most common symptom of SVC syndrome. This can be subtle; a patient may describe feeling bloated or ‘puffy’. Venous distension in the neck may be present on examination.

In patients with malignancy, dyspnea, cough, chest and shoulder pain, and hoarseness are more commonly noted compared with ‘benign’ compression. Dyspnea may be worse when leaning forward or lying down. Arm swelling is another common symptom of SVC syndrome.
What to do for superior vena cava syndrome
Although SVC syndrome has been traditionally regarded as a medical emergency, authors imply it should perhaps be reclassified most often as an urgency, with time for deliberation and testing to guide thoughtful decision-making. Before rushing the patient with 'typical' SVC syndrome to radiation therapy, consider that the resulting tissue necrosis could make a biopsy uninterpretable and seriously compromise the diagnosis and management of cancer, if present. (This assumes that frank airway obstruction or cerebral edema are not present — two situations in which SVC syndrome is a true emergency and immediate radiation therapy and/or stent placement are essential.)

Diagnosing the underlying cause of SVC syndrome is essential, whenever possible, because many causes of SVC syndrome are benign. A contrast-enhanced computed tomography (CT) scan of the chest is the most useful imaging study. Authors advise the careful use of selected invasive diagnostic procedures such as cytology of sputum and/or bronchial washings, thoracentesis for pleural effusions, and needle biopsy of any palpable lymph nodes. They do not mention bone marrow biopsy, but some would say suspicion for lymphoma should make this a consideration. Standard physician thinking has been that intrathoracic or transthoracic needle biopsies in patients with SVC syndrome generally carry an unacceptable risk for life-threatening bleeding, but each patient's situation should be considered individually.

Specific interventions employed for superior vena cava syndrome include

Endovascular stents
Self-expandable stents are highly effective at relieving the symptoms of SVC syndrome. Over 90% of patients report symptom relief after stent placement, and the technical success rate of placement is greater than 95%. Multiple stents may need to be placed in series (so-called ‘kissing stents’). Stents may even be placed in a SVC that is totally occluded or contains thrombus; catheter-directed thrombolysis, balloon angioplasty, or mechanical thrombectomy may be required before stent placement.

SVC stents have the advantage of not requiring a diagnosis before implementation. Complication rates of placement are 3–7%, but potentially catastrophic (infection, pulmonary embolus, stent migration, bleeding, or perforation of the SVC). SVC stents should therefore be reserved for patients who require urgent or emergent intervention due to symptoms. Most other patients can be managed more conservatively — for example, with chemotherapy and/or radiation, if malignancy is the cause of SVC syndrome.

Short-term anticoagulation is provided at many centers after SVC stent placement. Whether long-term anticoagulation is needed or helpful after stent placement not due to SVC thrombus is unknown. Some authors have recommended warfarin for months, whereas others suggest antiplatelet therapy alone.

Chemotherapy
Initial chemotherapy is the treatment of choice for SVC syndrome because of small-cell lung cancer, non-Hodgkin lymphoma, or germ cell cancers. Radiation therapy is not used alone in these patients and could possibly be counterproductive.

Patients with non-small-cell lung cancer with SVC syndrome do not respond well to chemotherapy and are usually managed with radiation therapy and/or endovascular stent.

Radiation therapy
Most patients with SVC syndrome due to cancer have radiation sensitive tumors. Radiation therapy can result in rapid improvement in patients with SVC syndrome due to lung cancer, in less than 72 h usually. Some patients may require weeks to respond to radiation, and about 20% of patients with SVC syndrome do not achieve symptomatic benefit from radiation therapy.

Catheter-directed thrombolytic therapy
Catheter-directed thrombolytic therapy has been used on a case-by-case basis to treat obstruction of the SVC due to thrombus. Anecdotal reports suggest effectiveness, but the true benefits and risks in SVC syndrome due to thrombus are unknown.

Glucocorticoids
Glucocorticoids may be helpful in patients with lymphoma or thymoma or other steroid responsive malignancies. Steroids are not recommended for use in patients with SVC syndrome due to lung cancer or other causes. Corticosteroids are commonly used prophylactically to reduce swelling during radiation therapy, but this is a separate indication (and without evidence of benefit).

Diuretics
There is no evidence to suggest that diuretics are beneficial in treating SVC syndrome, although they are commonly used.

Cancer-associated hypercalcemia
Hypercalcemia has been reported to occur in 10–20% of patients with malignancies. Malignancy is one of the most common causes of hypercalcemia. Certain cancers are more likely to cause hypercalcemia compared with
Others. The most common cancers that are associated with the development of hypercalcemia are squamous cell lung cancer, squamous cell head and neck cancers, breasts cancer, multiple myeloma, T-cell lymphomas, renal cell cancer, and ovarian cancer.

Hypercalcemia may be associated with bone metastases in patients with solid tumors (e.g. metastatic breast cancer). Increased bone resorption by osteoclasts leads to hypercalcemia. The increased bone resorption in this setting may be mediated by prostaglandins or other factors. In addition, tumor cells may be able to resorb bone directly.

Hypercalcemia is also associated with hematologic malignancies such as multiple myeloma or T-cell lymphomas. Again, hypercalcemia in these cases results from increased bone resorption by osteoclasts, mediated by lymphokines.

In recent years, hypercalcemia associated with solid tumors without bone metastases (e.g. squamous cell lung or head and neck cancers) has been studied most widely. Hypercalcemia in these cases is due to a systemic humoral factor(s) that is produced by the tumor, the so-called humoral hypercalcemia of malignancy. Recent investigations have identified parathyroid hormone-related protein as a probable mediator of humoral hypercalcemia of malignancy. Parathyroid hormone-related protein may act in conjunction with other factors (e.g. transforming growth factor α, tumor necrosis factor, interleukin-1) to cause the effects seen in humoral hypercalcemia.

The proximal cause of hypercalcemia in all of these situations is increased bone resorption. However, the kidneys help to maintain calcium homeostasis by increasing urinary calcium excretion when bone resorption increases. Changes in renal handling of calcium, then, are important in precipitating hypercalcemia in patients with increased bone resorption. Normal calcium reabsorption in the proximal renal tubule is linked with sodium reabsorption and with volume status. Hypercalcemia is associated with a decreased effect of ADH on the renal tubules, leading to dehydration. Dehydration leads to a decrease in GFR, increasing sodium and thus calcium reabsorption and worsening the hypercalcemia. Other factors such as vomiting may also contribute to precipitating or maintaining hypercalcemia.

Normal total serum calcium is about 8.5–10.5 mg/dl. About 40% is bound to proteins, mainly albumin. Fifteen percent is complexed to anions, and 45% is the free, ionized, active form. Formulae are available for correcting calcium concentrations for changes in albumin. These are supposed to estimate ionized, active calcium, although the correlation with measured ionized calcium is questionable. However, ionized calcium is usually not measured, and the formulae, based on albumin, are frequently used [e.g. corrected serum calcium = \((4−\text{albumin}) \times 0.8\) + measured serum calcium].

Clinical manifestations of hypercalcemia include the following: GI-related manifestations: nausea, vomiting, constipation; neurologic manifestations: weakness, lethargy, confusion, coma; and renal manifestations: polyuria, thirst. Symptoms may depend on the rate of rise of calcium — for example, slow, gradual increases may be less symptomatic compared with abrupt increases. Progressive hypercalcemia can lead to death. Prompt treatment is initiated in patients who are symptomatic and/or whose calcium is very high (e.g. \(≥13\) mg/dl). Other patients are treated, but perhaps less urgently. Remember, also, that certain drugs can contribute to hypercalcemia (e.g. thiazides, lithium).

**Treatment**

The first line of treatment for cancer-associated hypercalcemia is hydration with saline. Hydration repletes volume and increases calcium excretion. Promotion of sodium diuresis leads to calciuresis as noted above. Hydration over 2 days (2–8 l/day, depending on hydration status, of 0.9% NaCl) can decrease serum calcium by approximately 2 mg/dl. Note that unless other treatment is initiated, or the underlying malignancy treated, calcium will rise again.

Furosemide may be used to prevent fluid overload from hydration (e.g. in patients with CHF). Furosemide also has a calciuric effect and has been suggested as a treatment in addition to, or following, hydration. Reports of successful lowering of calcium with furosemide involved very high doses along with large volumes of fluid, strict electrolyte monitoring and replacement, and intensive care monitoring. Outside of this setting, dehydration from furosemide can offset any calciuric benefit, and its use should probably be reserved for patients who cannot tolerate hydration, as noted above.

Bisphosphonates: today, bisphosphonates are probably the most frequently used calcium-lowering agents. They (etidronate, pamidronate) prevent osteoclastic bone resorption, and they may directly inhibit osteoclasts. Etidronate can also impair bone formation. For prompt response, bisphosphonates are given intravenously. Pamidronate is more potent compared with etidronate, and is probably used more often, although its clear superiority is not well documented. The recommended dose of pamidronate is 60–90 mg, intravenous. With
either bisphosphonate, calcium decreases in about 48 h and may fall to normal over the next 2–3 days. Although commonly recommended for administration over 24 h, pamidronate has been safely administered by short infusion (e.g. 0.5–3 h), making it attractive for outpatient use. Bisphosphonates are relatively free of side effects. There are reports of elevations of serum creatinine with etidronate in large doses. The clinical importance of mild reversible elevations is not clear. Because of the reports, it is recommended to avoid the use of etidronate in patients with serum creatinine greater than 5, and to decrease the dose when creatinine is 2.5 or greater. Clinically, however, bisphosphonates may be safe to use even before patients are completely rehydrated (e.g. while their creatinine may still be elevated).

Oral etidronate has been recommended for maintenance of normocalcemia. Its efficacy is less well established than that of parenteral bisphosphonates. Doses up to 20 mg/kg/day have been used. Although inhibition of bone formation is a potential concern, many patients with cancer-associated hypercalcemia have limited survival, and will be unlikely to suffer long-term consequences.

Plicamycin (mithramycin) is commonly used to treat cancer-associated hypercalcemia after hydration. The dose is 25 mcg/kg and should be reduced in patients with renal dysfunction (e.g. by 50%). Plicamycin may be given as an intravenous bolus or infusion. Most side effects of plicamycin are associated with higher or repeated doses (e.g. 25–50 mcg/kg/day’5). These side effects include thrombocytopenia, coagulopathy, and hepatitis. The 25 mcg/kg dose given once and perhaps repeated in 48–72 h if necessary is well tolerated. Although calcium is lowered to normal levels in majority of patients, the duration of normocalcemia is variable. When plicamycin provides normocalcemia for 7 days or more, it can also be a useful agent for maintaining lowered calcium.

Calcitonin is also used to lower serum calcium. It works within several hours and may be useful in lowering calcium acutely. Calcitonin may also be used in patients with renal insufficiency or before rehydration. Resistance develops quickly to calcitonin, and although some investigators suggest that steroids prolong the effectiveness, others have not found that to be the case. Calcitonin requires frequent parenteral administration (intravenous or SQ). These latter factors make calcitonin a less than optimal choice for maintenance of normocalcemia.

Finally, cisplatin has been used to treat hypercalcemia associated with certain malignancies. It may provide several weeks of normocalcemia. However, it should not be used in patients with renal insufficiency. Cisplatin should only be given to patients who have been well hydrated.

Maintenance of normocalcemia may be achieved with intermittent administration of some of the agents described above to lower calcium initially (e.g. plicamycin, pamidronate). Maintenance with oral etidronate was discussed above. Oral phosphate is also used to maintain normocalcemia, provided patients are not hyperphosphatemic. Neutral phosphate capsules should be emptied and mixed with liquid. The starting dose of phosphate is about 1 g/day in divided doses. Diarrhea frequently impairs dose escalation and/or compliance, thus minimizing effectiveness.

Malignant pericardial effusions
Introduction
Malignant pericardial effusions (MPEs) are a rare complication of advanced cancer, but are associated with high morbidity and mortality. This fast fact discusses the diagnosis and management of MPEs.

Epidemiology and prognosis
Approximately 10% of patients with cancer develop cardiac metastases, with ~75% of these affecting the epicardium. Only a third of these, however, will develop clinically significant MPEs. Lung and breast cancers are the most common causes. MPEs are associated with a poor prognosis. Studies suggest a median survival of 2–3 months after a MPE is diagnosed, with a mean survival of 5 months for solid tumors and 20 months for hematologic malignancies.

Physiology and symptoms
The pericardial space is normally filled with less than 50 ml of serous fluid. As this volume increases due to epicardial or pericardial metastases or lymphatic obstruction, both right and left ventricular failure can occur due to inadequate filling. Signs and symptoms include peripheral and pulmonary edema, chest
discomfort, cough, shortness of breath, and orthopnea. Severity of symptoms depends on the volume of the MPE as well as the rapidity of its accumulation; severe cases can present with cardiac tamponade and shock. An echocardiogram is indicated whenever an MPE is suspected. Not only does it confirm the presence of an effusion but also its findings can dictate whether or not urgent treatment is indicated (e.g., if signs of tamponade are evident). A diagnostic pericardiocentesis or pericardial biopsy is sometimes needed to confirm the cause of the effusion.

Treatment options

1. **Systemic chemotherapy or radiotherapy** are effective for chemosensitive or radiosensitive tumors such as previously untreated breast cancer and many lymphomas. Reaccumulation rates for both modalities are about one-third overall, depending on the patient's overall course and response to therapy.

2. **Pericardiocentesis** results in immediate symptom relief in most patients; however, the effusion may rapidly reaccumulate in many patients, requiring repeat pericardiocentesis (within 1–2 weeks in some series).

3. **Pericardial sclerosis** involves instilling a sclerosing agent with the intention of scarring the pericardium to the epicardium, preventing reaccumulation of the MPE. Multiple agents have been studied, including doxycycline, minocycline, and bleomycin. Success rates (no reaccumulation at 30 days) are about 70–90%. Longer term success rates have not been defined because of the poor survival of study patients. The major side effects are chest pain (50–70%), cardiac arrhythmias, and fever. In head-to-head comparisons with doxycycline, bleomycin has been shown to have fewer side effects and to lead to shorter hospitalizations.

4. **Surgical decompression** therapies range from less invasive (balloon pericardiostomy, subxiphoid or thoracoscopic pericardectomy) to more extensive (open thoracotomy with pericardial stripping). A pericardial ‘window’ (which allows ongoing drainage of fluid externally or internally such as into the pleural cavity) is often created. Case series have suggested that reaccumulation rates with surgical therapies are low (<15% up to 10 months out).

Decision-making

The treatment of MPEs depends on how urgently treatment is needed, the likelihood of the tumor responding to antineoplastic treatments, and the anticipated survival of the patient. A multidisciplinary approach to decision-making, involving input from medical and radiation oncology, cardiology, and thoracic surgery is recommended. Simple pericardiocentesis may be appropriate for patients with short prognoses (<1 month), particularly if their MPE is not expected to reaccumulate in their remaining life-span. A symptomatic patient with no signs of tamponade and a chemotherapy-sensitive tumor such as untreated breast cancer may receive a durable response from a pericardiocentesis for symptom relief, followed by chemotherapy. Patients with longer prognoses (>1 month) who are expected to reaccumulate their MPEs will likely benefit most from sclerosis or surgical decompression; there is no clear evidence currently suggesting that one strategy is superior to the other. Symptom-directed care without specific intervention for the MPE is an appropriate option for patients with very short prognoses and for those who decline more invasive treatments.

Malignant spinal cord compression

Malignant spinal cord compression (MSCC) is an uncommon condition that affects people with certain cancers that have spread to the bones in the spine, or have started in the spine.

MSCC happens when cancer cells grow in, or near to, the spine and press on the spinal cord and nerves. This causes swelling and a reduction in the blood supply to the spinal cord and nerve roots. The symptoms of spinal cord compression are caused by the increasing pressure (compression) on the spinal cord and nerves.

Any type of cancer can spread to the bones of the spine (vertebrae), which may lead to spinal cord compression. It is more common in certain cancers including breast, lung, or prostate and in individuals who have lymphoma or myeloma.

Symptoms

1. Back or neck pain: the first symptom is usually any unexplained back or neck pain, which may be mild to begin with but becomes severe. The pain may feel like a ‘band’ around the chest or abdomen and can radiate over the lower back, into the buttocks, or legs. The pain can also spread down the arms. Quite often this pain is worse when lying down and it may affect sleeping.

2. Numbness or pins and needles in toes and fingers, or over the buttocks.

3. A new feeling of being unsteady on your feet, having difficulty climbing stairs or walking, or your legs giving way.

4. Difficulty controlling your bladder, passing very little urine, or passing none at all.

5. Constipation or problems controlling your bowels.
Cancer-related medical emergencies

These symptoms can also be caused by a number of other conditions. It is very important to let the doctor know presence of any of these symptoms so that they can be investigated.

The earlier MSCC is diagnosed, the better the chances are of treatment being effective.

Diagnosis

*Magnetic resonance imaging scan*

This scan uses magnetism instead of X-rays to build up a detailed picture of areas of the body. The scanner is a powerful magnet, so individuals may be asked to complete and sign a checklist to make sure it is safe for them.

Before undergoing the scan, individuals are asked to remove any metal belongings including jewellery. Some people are given an injection of dye into a vein in the arm. This is called a contrast medium and can help the images from the scan to show up more clearly. During the test, individuals are asked to lie very still on a couch inside a long cylinder (tube) for about 30 min. Some people feel a bit claustrophobic during the scan. Earplugs or headphones are given as it is noisy.

*Computed tomography scan*

A CT scan takes a series of X-rays, which build up a three-dimensional picture of the inside of the body. The scan takes 10–30 min. CT scans use small amounts of radiation, which is unlikely to harm individuals undergoing the scan or anyone they come into contact with.

They may be asked not to eat or drink for at least 4 h before the scan.

They may be given a drink or injection of a dye, which allows particular areas to be seen more clearly. For a few minutes, this may make them feel hot all over. It is important to let the doctor know allergies to iodine or presence of asthma, because individuals with such conditions could have a more serious reaction to the injection.

Having an MRI or CT scan is painless; however, individuals may find lying on a hard surface for a long time uncomfortable. Individuals can ask for a painkiller before the scan if required.

*Bone scan*

This scan does not diagnose MSCC but may be performed to check whether there are any abnormal areas inside the bone.

Rarely, MSCC is the first symptom of cancer. The doctor may recommend a biopsy of the spine to give an exact diagnosis.

Treatment

Treatment should be started as soon as possible after diagnosis, with the aim of minimizing permanent damage to the spinal cord. Treatment will also help to reduce pain by shrinking the tumor and relieving the pressure on the nerves. The damage to the spinal cord means that some individuals will have some paralysis at the time of diagnosis. This may be permanent in some people.

The choice of treatment depends on several factors including the type of cancer, the area of the spine affected, and general fitness. The most common treatment is radiotherapy, although surgery and chemotherapy are also used sometimes.

Treatment usually involves a combination of the following.

*Assessing mobility*

The doctor usually advises the patient to lie flat on the back until tests have shown whether the individual has a spinal cord compression or not. This is to reduce movement of the affected area of the spine and to prevent an increase in symptoms.

If the tests confirm the presence of spinal cord compression, the doctor and physiotherapist decide what movement is safe for the individual and explain the do’s and don’ts.

During and after treatment, individuals will have regular physical examinations with the doctor and physiotherapist, when they will carry out a detailed check of the nervous system. This includes examining range of movement, muscle strength, co-ordination, and sensation to touch, which helps them to see any improvement in symptoms.

*Collars and braces*

Some individuals may be given a collar or brace to wear that can help to support their neck or spine, which the physiotherapist will discuss with the patient.

*Steroids*

Steroids are chemicals naturally produced in the body that help control and regulate how the body works. High doses of a steroid called dexamethasone are usually started immediately if spinal cord compression is suspected. The steroid helps reduce pressure and swelling around the spinal cord and can quickly relieve symptoms such as pain. The dose is gradually reduced over time and then stopped depending on the improvement of symptoms and after starting other treatments such as radiotherapy and surgery.
Radiotherapy
Radiotherapy is the use of high-energy rays to destroy cancer cells. It is the most common way to treat spinal cord compression. It is usually used on its own, or occasionally alongside other treatments such as surgery. It is given by directing radiotherapy rays at the tumor from outside the body, known as external radiotherapy. Radiotherapy is usually given as a short course of treatment. This can range from one single treatment to one treatment a day for 2 weeks. It may be given for up to 4 weeks for myeloma and lymphoma. Radiotherapy will be started as soon as possible after MSCC is diagnosed.

Surgery
Surgery is only suitable to treat a small number of people for their spinal cord compression. This depends on several factors, including the type of tumor, where it is situated, and how unstable the spine may be.

The aim of surgery is to remove as much of the tumor as possible and relieve pressure within the spinal canal.

Surgery may involve removing several parts of the vertebrae, as well as removing as much of the tumor as possible, without weakening the spine. The common surgical techniques used in this situation are called anterior stabilization and debulking of tumor, or decompression laminectomy.

This surgery may also involve stabilizing the spine further by means of metal rods or bone grafts. The doctor or nurse will explain the operation in more detail if surgery is appropriate.

If some of the tumor cannot be removed by surgery, or if the tumor comes back after initial treatment, radiotherapy is sometimes given.

Chemotherapy
Chemotherapy is the use of anticancer (cytotoxic) drugs to destroy cancer cells. It is occasionally used to treat spinal cord compression. It may be used for tumors that are sensitive to chemotherapy, such as lymphoma or small-cell lung cancer.

Chemotherapy and hormonal therapy can also be used after radiotherapy/surgery for certain cancers, such as breast and prostate cancers.

Coping with symptoms
Pain control
In case of pain, the doctor or nurse discuss ways of controlling pain. Different drugs may be given to help with pain, and these will be assessed regularly to make sure they are effective. Bisphosphonate drugs can be used to treat pain and weakened vertebrae in breast cancer and myeloma. They can also be used in prostate cancer if painkillers are ineffective.

Loss of mobility
Mobility may be affected by changes in muscle strength and ability to feel and control the movement in muscles. The physiotherapist will help individuals to adjust to these changes. An occupational therapist can give practical advice and supply aids to help the individual to be as independent as possible.

Bladder changes
The doctor and nurse monitor how well the bladder is working, and a thin flexible tube (catheter) may be used to help drain urine from the bladder in patients having problems in passing urine.

Bowel changes
Medication may be given to help with constipation or to help patients having difficulty controlling bowel.

After treatment have finished
Spinal cord compression can affect people differently. The care required after treatment depends on the result of treatment and level of mobility. Before leaving the hospital, the staff should organize any care the patient might require when at home.

Individuals who have lost the ability to walk or have lost movement before treatment, may not get this back. Further care may be available at cancer center, local hospital, or hospice. This involves a team of healthcare professionals who work closely with the patients and their family to organize a plan of care and rehabilitation to suit your needs.

Acknowledgements
Conflicts of interest
None declared.

References
Cancer-related medical emergencies


Chronic obstructive pulmonary disease in treated pulmonary tuberculous patients
Mohamed W. Zakaria, Heba A. Moussa

**Background/Aim** To detect the prevalence of chronic obstructive pulmonary disease (COPD) as a sequel of treated pulmonary tuberculosis (PTB).

**Materials and methods** A total of 50 adults, 28 men and 22 women, with a definite diagnosis of PTB and complete antituberculous therapy, with subsequent presentation of exertional dyspnea and/or cough, and expectorations for which no other alternative cause was found, were included in our study. All the patients underwent full history taking, full clinical examination, chest radiography, erythrocyte sedimentation rate, prebronchodilator and postbronchodilator forced vital capacity (FVC%), and forced expiratory volume (FEV%, %) in the first second of FEV/FVC%.

**Results** Pulmonary function testing showed 22 patients (44%) with irreversible obstructive pattern denoting chronic obstructive pulmonary disease (COPD), seven patients had restrictive ventilatory defect, and three patients had mixed obstructive and restrictive pattern. Of those 22 patients with irreversible obstructive pattern (COPD), 11 patients (50%) had mild obstruction, nine patients (40.9%) had moderate obstruction, and two patients (9.1%) had severe obstruction. There is a positive correlation between dyspnea and post-tuberculous COPD patients, and a negative correlation between cough and post-tuberculous COPD patients. There is no correlation between the duration since the completion of antituberculous therapy and development of COPD.

**Conclusion** COPD can be a sequel of PTB and should be overlooked, especially in those patients complaining of dyspnea even in the absence of any history of smoking. Post-tuberculous COPD as a cause of COPD in nonsmokers should be now more recognized in countries where the prevalence of PTB is still high.

**Keywords:** chronic obstructive pulmonary disease, post-tuberculous COPD, pulmonary tuberculosis

Chest Diseases Department & TB Outpatient Clinic, Faculty of Medicine, Kasr El Aini Hospital, Cairo University, Cairo, Egypt

Correspondence to Mohamed W. Zakaria, MD, Chest Diseases Department & TB Outpatient Clinic, Faculty of Medicine, Kasr El Aini Hospital, Cairo University, 5, Makrize Street, Zamalek, Cairo 11211, Egypt

Tel: 02 2735 4973;
e-mail: mw_khalil@hotmail.com

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Introduction

Chronic obstructive pulmonary disease (COPD) is estimated to affect 65 million people worldwide. It is currently the third leading cause of death, accounting for approximately three million deaths annually. Of the total number of deaths, 90% are in low-income and middle-income countries where the prevalence of pulmonary tuberculosis (PTB) remains high [1].

A relationship between PTB and the development of COPD has been suggested in several reports. However, a serious limitation is the confounding caused by concurrent exposure to risk factors such as tobacco smoking, dust and biomass fuel, and childhood respiratory illnesses, and a lack of diagnostic precision when distinguishing COPD from other forms of structural lung disease (e.g. bronchiectasis) found in patients who had PTB [2].

Chronic obstructive airway disease as a complication of PTB has been restudied recently in many regions of the globe [3,4]. In the executive summary of the 2006 update of the Global initiative for chronic obstructive lung disease (GOLD) guidelines [5], the role of tuberculosis (TB) in the development of chronic airway obstruction (CAO) has been recognized. According to the GOLD Workshop summary, chronic bronchitis or bronchiolitis and emphysema can occur as complications of PTB [6].

Aim of the study

The aim of this study was to detect the prevalence of COPD as a sequel of treated PTB.

Materials and methods

A total of 50 adults, 28 men and 22 women from TB clinic of Chest Diseases Department, Cairo University, previously diagnosed as having PTB based on clinical suspicious, chest radiography, and a positive sputum examination for acid fast bacilli by Ziehl Neelson, who had a complete antituberculous therapy, with subsequent presentation of chronic exertional dyspnea and/or cough and expectorations for which no other alternative cause was found, were included in our study.

Those patients having a probability of reactivated TB, having a history of current or previous smoking or occupational exposure, asthmatics, and cases of
interstitial lung disease and ischemic heart disease were excluded.

Patients were subjected to:

1. Full history taking.
2. Full clinical examination.
3. Chest radiography and erythrocyte sedimentation rate.
5. Prebronchodilator and postbronchodilator forced vital capacity (FVC%), forced expiratory volume in the first second (FEV₁%) and FEV₁/FVC %.

Prebronchodilator and postbronchodilator FVC%, FEV₁%, and FEV₁/FVC% were recorded in each case through simple spirometry on ZAN Messgeraete, 1999 GmbH (Schlimphofer Strasse 14, Oberthulba, 97723, Germany). Stages and pattern of COPD were recorded; classification of the severity of airflow limitation was done as per revised GOLD 2013 [7]. This was carried out in the Chest Department of Kasr El Aini Hospital, from February 2013 to March 2014.

Data were statistically described in terms of mean ± SD, median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was made using Student’s $t$-test for independent variables. Correlation between various variables was carried out using Spearman’s rank correlation equation for non-normal variables. $P$-value less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (SPSS Inc., Chicago, Illinois, USA) version 15 for Microsoft Windows (California, USA).

### Results

This study included 50 patients, 28 men and 22 women, their age ranging from 23 to 63 years old, with a mean age of 40.70 years. All patients successfully completed their antituberculous chemotherapy from a period ranging from 5 to 18 years with a mean of 10 years ago.

A total of 39 patients complained of dyspnea, 22 patients complained of cough, and 16 patients complained of both dyspnea and cough.

Pulmonary function testing showed 22 patients (44%) with irreversible obstructive pattern denoting COPD, seven patients had restrictive ventilatory defect, and three patients had mixed obstructive and restrictive pattern (Table 1).

Of those 22 patients with irreversible obstructive pattern (COPD), 11 patients (50%) had mild obstruction, nine patients (40.9%) had moderate obstruction, and two patients (9.1%) had severe obstruction, as per revised GOLD classification of 2013 [7] (Table 2).

Table 3 shows a positive correlation between dyspnea and pulmonary functions.

Table 4 shows no correlation between cough and pulmonary functions.

Table 5 shows no correlation between the duration since the completion of antituberculous therapy and development of COPD.

### Discussion

Our study found that of the 50 symptomatic patients,
22 patients (44%) who successfully completed their antituberculous regimen, presenting mainly with dyspnea with or without cough, developed COPD, denoting that COPD can be a sequel of treated PTB.

Lee and Chang [8] found that CAO is a common finding owing to TB-destroyed lung. Patricio Jiménez et al. [9] found that CAO is a common sequel with TB.

PLATINO study, a latest large population-based multicenter study, carried out in five Latin American countries (n = 5571 participants) included patients on the criteria of a past diagnosis of PTB by a physician and performed spirometry in the field. It included only those patients presenting to the hospital with dyspnea. Along with the exclusion of other possible confounding factors, smokers and patients with age more than 65 years were also excluded; it was found that FEV₁ is reduced compared with FVC in most cases [10]. However, another previous study had found that, after 15 years’ follow-up of 40 patients, there was a higher yearly decline in FVC compared with FEV₁ [11].

Kim et al. [12] conducted a study to assess the impact of PTB on the prevalence of COPD, and found that the prevalence of COPD increased from 3.7 to 5% by including participants with a history of TB treatment.

COPD can occur as one of the chronic complications of PTB, and the obstructive ventilatory defect appears more common among various pulmonary function derangements [13].

Verma et al. [14] concluded that there is indeed an important contribution of TB to airflow obstruction (AFO), linking two of the most common ailments in the world. For many persons with TB, microbiological cure is just the beginning, not the end of their illness. The prevention and adequate treatment of TB would reduce the burden of AFO in all countries, especially the developing countries. However, the exact abnormality that results from tuberculous infection has to be considered in detail with future studies, and a better understanding of the pathophysiology of airflow limitation may point the way to therapeutic strategies for control of symptoms in these patients.

Allwood et al. [2] confirms an association between a past history of TB and the presence of CAO. This association is independent of cigarette smoking and biomass fuel exposure. The mechanisms underlying the development of AFO and its natural history and response to treatment require further study. AFO may progress after the completion of PTB treatment. In view of the large number of patients with PTB worldwide, and the rising incidence of COPD globally, the contribution of PTB as a contributory cause in the pathogenesis of COPD is important both to epidemiologists and health-care providers.

In our study, we could not find a correlation between the duration since the completion of antituberculous therapy and development of COPD. Willcox and Ferguson [15] found that the obstructive changes become pronounced after 10 years of follow-up in treated cases and correlated with the residual scarring on chest radiograph, regardless of the findings on original chest radiographs.

Obstructive airway disease has many causes. TB, which can be a cause of this, has not been studied in detail. Even the organizations, such as GOLD and GINA, authority figures in COPD and asthma, respectively, have not recognized or treated PTB as an etiological factor, which again shows that post-pulmonary tuberculous obstructive airway disease is a clinical entity in its infancy. Post-tubercular impairment can be manifested as reversible or irreversible obstructive airway disease, mixed defect, or as pure restrictive defects [14].

COPD can be a sequel of PTB and should be overlooked, especially in those patients complaining of dyspnea even in the absence of any history of smoking. Post-tuberculous COPD as a cause of COPD in nonsmokers should be now more recognized in countries where the prevalence of PTB is still high.

**Acknowledgements**

**Conflicts of interest**

None declared.

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Evaluation of serum troponin I in patients with acute exacerbations of chronic obstructive pulmonary disease
Neveen Hasaneen\textsuperscript{a}, Ayman Abd Elrahman\textsuperscript{a}, Mohamed El Mahdy\textsuperscript{a}, Osama El Shaer\textsuperscript{b}, Mohamed Hassan\textsuperscript{c}, Mahmoud M. El-Habashy\textsuperscript{d}

Introduction
Chronic obstructive pulmonary disease is a common, preventable, and treatable disease. Troponin I is a component of the contractile proteins present in all muscles. The amino acid sequence of cardiac troponin I (cTnI) contains a section that is unique to cardiac muscle.

Aim
The aim of the study was to evaluate the incidence of cTnI elevation in patients with acute exacerbation of chronic obstructive pulmonary diseases (AECOPDs) and study the possible association of the level of cTnI with the severity of AECOPD, need for assisted ventilation, and length of hospital stay.

Patients and methods
This study was performed on 30 patients with AECOPD admitted to the Chest Department and Respiratory ICU at Benha University Hospital. On admission, all patients were subjected to full medical history taking and full clinical examination. We examined the patients for signs and symptoms of right ventricular (RV) failure. Echocardiography was performed for every patient. Serum troponin I levels (upon admission and 24 h later) were evaluated.

Results
The study showed 21 (70%) of 30 patients with positive troponin I versus nine (30%) with negative troponin I. There was a nonsignificant statistical difference among all studied AECOPD patients as regards smoking habits, as 89% of troponin I-negative patients were smokers versus 81% of troponin I-positive patients. When assessed on the basis of pulmonary function tests, 75% of troponin I-negative patients were found to be in moderate stage. 53% of troponin I-positive patients were in moderate stage, and 33% of troponin I-positive patients were in severe stage. There was a significant statistical difference in troponin elevation as regards pulmonary hypertension (71% of cTnI-positive patients vs. 11% of cTnI-negative patients), RV strain (90% of cTnI-positive patients vs. 33% of cTnI-negative patients), and tricuspid regurge (52% of cTnI-positive patients) but a nonsignificant difference as regards left ventricular dysfunction among all studied AECOPD patients.

Conclusion
cTnI in AECOPD patients is mostly positive in tachypneic, tachycardiac, hypoxemic, and hypercapnic patients with more severe pulmonary hypertension and RV dysfunction.

Positive cTnI in AECOPD patients may suggest exacerbation severity, the need for mechanical ventilation (MV), and longer duration of hospitalization. 

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Keywords: acute exacerbation of chronic obstructive pulmonary disease, cardiac troponin I, mechanical ventilation

\textsuperscript{a}Departments of Chest, \textsuperscript{b}Clinical and Chemical Pathology, \textsuperscript{c}Cardiology, Benha University, Benha, \textsuperscript{d}Department of Chest, Menoufia University, Shebin Elkom, Egypt

Correspondence to Mahmoud M. El-Habashy, MD, Department of Chest, Menoufia University, Shebin Elkom, Egypt
Tel: 00201112143143; e-mail: habashylic@yahoo.com

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Introduction
Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients. COPD is the fourth leading cause of death in the world [1].

Exacerbation of COPD is an event in the natural course of the disease characterized by a change in the patient’s baseline dyspnea, cough, and/or sputum beyond day-to-day variability sufficient to warrant a change in management [2]. Exacerbations affect the quality of life and prognosis of patients with COPD. Hospital mortality of patients admitted for a hypercarbic COPD exacerbation is ~10%, and the long-term outcome is poor. Mortality reaches 40% at 1 year in those needing mechanical support, and all-cause mortality is even higher (up to 49%) 3 years after hospitalization for a COPD exacerbation [3].

The spectrum of cardiovascular complications associated with COPD is clearly broad. Right ventricular (RV) dysfunction and pulmonary vascular disease are common in COPD and progress with time. Other cardiac diseases found frequently in patients with COPD, including coronary artery disease and arrhythmias, present a unique challenge for clinicians, as the combination of both pulmonary and cardiac disease appears to be additive with regard to morbidity and mortality [4].

The cardiovascular alterations are extremely complex. During an episode of acute exacerbation, the increased
work and oxygen cost of breathing, the increase in left ventricular afterload related to the more negative intrathoracic pressure, the worsening of pulmonary hypertension, and the presence of hypoxemia and hypercapnia may all contribute to the development of cardiac injury [5].

Cardiac biomarkers, such as cardiac troponins, were initially developed for the evaluation of patients with myocardial ischemia and congestive heart failure. The elevated levels of serum cardiac troponins have also been documented in RV dysfunction. In RV failure, cardiac troponins are suspected to be elevated secondary to RV ischemia or microinfarction resulting from increased wall tension, metabolic demand, and reduced coronary perfusion with or without atherosclerosis [6–8]. The release of cardiac troponin from the myocyte to the blood can be due to reversible or irreversible cell damage [9].

Troponin I is a component of the contractile proteins present in all muscles. The amino acid sequence of cardiac troponin I (cTnI) contains a section that is unique to cardiac muscle. The cTnI assay measures these cardiospecific components to provide a highly specific marker for cardiac muscle cell injury. It has no cross-reactivity with the two skeletal muscle isoforms. cTnI is a highly sensitive and long-lasting marker of cardiac injury. Measurements of cTnI concentrations in renal failure, in myopathic states, and after acute skeletal muscle injury have shown normal concentrations in the absence of cardiac injury [10].

**Aim**

The aim of the study was to evaluate the incidence of cTnI elevation in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD) and study the possible association of the level of cTnI with severity of AECOPD, need for assisted ventilation, and length of hospital stay.

**Patients and methods**

This study was performed on 30 patients with AECOPD admitted to the Chest Department and Respiratory ICU at Banha University Hospital.

COPD and AECOPD were diagnosed according to the global initiative for chronic obstructive lung disease 2011 (GOLD, 2011) [1].

**Exclusion criteria** [11]

Patients were excluded from the study if they had concomitant diseases such as:

(1) Ischemic heart disease, previous myocardial infarction, heart trauma (including contusion, ablation, pacing, implantable cardioverter defibrillator firings including atrial defibrillators, cardioversion, endomyocardial biopsy, and cardiac surgery.

(2) Aortic valve disease and hypertrophic obstructive cardiomyopathy with significant left ventricular hypertrophy.

(3) Malignant hypertension.

(4) Postoperative noncardiac surgery patients.

(5) Renal impairment (patients with elevated creatinine>2 mg/dl are excluded).

(6) Hypothyroidism and hyperthyroidism.

(7) Infiltrative diseases, including amyloidosis, hemochromatosis, sarcoidosis, and scleroderma.

(8) Acute neurological disease, including cerebrovascular accident and subarachnoid bleeding.

**Methods**

On admission, the following examinations were carried out on all patients:

(1) Full medical history from the patient (if possible) or his relatives: history of smoking (current, ex, or nonsmoking), history of chest symptoms (cough, expectoration, dyspnea, and wheeze), history of previous intubation and/or ventilator support, prior evidence of cor pulmonale with or without congestive heart failure, comorbidities, and drug therapy.

(2) Full clinical examination (general and local).

(3) Plain chest and heart radiography (posteroanterior, anteroposterior, and/or lateral).

We searched for any of the following to detect RV failure [12]:

(a) Dilatation of the proximal pulmonary arteries with abrupt tapering of the distal branches.

(b) Filling of the retrosternal space secondary to RV enlargement.

(c) Inferior vena cava and azygous vein dilatation.

(d) Increased curvature of the right-heart border secondary to right atrial dilatation seen on anteroposterior or posteroanterior view.

(4) Pulmonary function test:

Measurements of forced expiratory volume in the first second (FEV₁) for assessment of severity of disease were obtained from previous recorded measurements from chest outpatient clinics before admission or from their hospital records; seven patients out of all studied patients had no record for pulmonary functions.

Patients were classified according to their postbronchodilator FEV₁ into mild (FEV₁≥80%
predicted), moderate (50% ≤ FEV₁ < 80% predicted), severe (30% ≤ FEV₁ < 50% predicted), and very severe (FEV₁ < 30% predicted) [9].

(5) Echocardiography (ECHO):

ECHO findings associated with RV failure were the following [12]:

(a) RV dilatation and hypokinesis.
(b) RV hypertrophy.
(c) Change to a more concentric RV morphology.
(d) Paradoxical septal motion.
(e) Impaired LV diastolic function.
(f) Right atrial enlargement.
(g) Tricuspid regurgitation.
(h) Pulmonary artery hypertension as estimated by the modified Bernoulli equation.
(i) Pulmonary artery dilatation.
(j) Lack of inspiratory collapse of the inferior vena cava.
(k) Pericardial effusions.

(6) Laboratory investigations:

(a) Complete blood count.
(b) Serum electrolytes (Na, K).
(c) Serum troponin I (upon admission and 24 h later).

Results

The results of this study showed the following:

(1) There was a nonsignificant statistical difference among all studied AECOPD patients as regards age, as the mean age in the troponin I-positive group was 55 versus 52 years in the troponin I-negative group. Also there was no significant statistical difference as regards sex, as the study included two female patients.

(2) It was found that smoking does not affect cTnI, irrespective of the degree of smoking (Table 1).

(3) With respect to the relationship between FEV₁ and troponin, 33% of cTnI-positive patients were in very severe stage, 53% were in severe stage, and 14% were in moderate stage, revealing significant statistical difference in cTnI elevation among all studied patients with respect to the severity of disease (Table 2 and Fig. 1).

(4) The current work revealed significant positive correlation as regards pCO₂, significant negative correlation as regards pO₂, SO₂%, and pH, and nonsignificant correlation as regards HCO₃⁻ (Table 3).

(5) P-pulmonale, RV strain, pulmonary hypertension, and tricuspid regurgete were considerably affected upon cTnI positivity (Table 4).

Table 1 Relationship between smoking habit and troponin level (ng/ml) among all studied acute exacerbation of chronic obstructive pulmonary disease patients at admission

<table>
<thead>
<tr>
<th>Smoking</th>
<th>Troponin [n (%)] (ng/ml)</th>
<th>Test of significance</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.01 (n = 9)</td>
<td>≥0.01 (n = 21)</td>
<td></td>
</tr>
<tr>
<td>None (n = 2)</td>
<td>1 (11.1)</td>
<td>1 (4.8)</td>
<td>1.614</td>
</tr>
<tr>
<td>Ex-smokers (n = 3)</td>
<td>0 (0.0)</td>
<td>3 (14.2)</td>
<td></td>
</tr>
<tr>
<td>Smokers (n = 25)</td>
<td>8 (88.9)</td>
<td>17 (81.0)</td>
<td></td>
</tr>
<tr>
<td>Moderate smokers</td>
<td>4 (50.0)</td>
<td>5 (29.4)</td>
<td>1.307</td>
</tr>
<tr>
<td>(n = 9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heavy smokers</td>
<td>4 (50.0)</td>
<td>12 (70.6)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 Severity of disease (FEV₁ %) and its impact upon troponin level (ng/ml) among acute exacerbation of chronic obstructive pulmonary disease patients at admission

<table>
<thead>
<tr>
<th>Severity of disease by PFTs</th>
<th>Troponin [n (%)] (ng/ml)</th>
<th>Test of significance</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.01 (n = 8)</td>
<td>≥0.01 (n = 15)</td>
<td></td>
</tr>
<tr>
<td>Moderate (n = 8)</td>
<td>6 (75.0)</td>
<td>2 (13.3)</td>
<td>Fisher exact 0.009 (HS) test = 9.33</td>
</tr>
<tr>
<td>Severe (n = 10)</td>
<td>2 (25.0)</td>
<td>8 (53.3)</td>
<td></td>
</tr>
<tr>
<td>Very severe (n = 5)</td>
<td>0 (0.0)</td>
<td>5 (33.4)</td>
<td></td>
</tr>
</tbody>
</table>

FEV₁, forced expiratory volume in the first second; HS, highly significant; PFT, pulmonary function test.

Table 3 Arterial blood gases parameters among all studied acute exacerbation of chronic obstructive pulmonary disease patients and its impact upon troponin level (ng/ml) at admission

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Troponin (mean ± SD) (ng/ml)</th>
<th>Test of significance</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;0.01 (n = 9)</td>
<td>≥0.01 (n = 21)</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.39 ± 0.03</td>
<td>7.29 ± 0.05</td>
<td>5.53</td>
</tr>
<tr>
<td>pCO₂</td>
<td>49.78 ± 6.83</td>
<td>62.05 ± 6.54</td>
<td>4.65</td>
</tr>
<tr>
<td>pO₂</td>
<td>80.33 ± 5.63</td>
<td>61.98 ± 6.89</td>
<td>6.96</td>
</tr>
<tr>
<td>SO₂</td>
<td>89.89 ± 2.15</td>
<td>83.57 ± 4.04</td>
<td>4.40</td>
</tr>
<tr>
<td>HCO₃⁻</td>
<td>29.22 ± 1.99</td>
<td>28.33 ± 3.86</td>
<td>0.65</td>
</tr>
</tbody>
</table>

Fig. 1

Severity of disease (FEV₁ %) and its impact upon troponin level (ng/ml) among acute exacerbation of chronic obstructive pulmonary disease patients at admission. FEV₁, forced expiratory volume in the first second.
(6) As regards the need for MV, cTnI positivity was more prominent among patients who were ventilated rather than among those who not need MV (Table 5).
(7) As longer the duration of hospitalization the greater the severity of the disease and exacerbation, duration of hospitalization was significantly different among cTnI-positive patients (13.9 ± 4.87) and cTnI-negative patients (7.89 ± 2.67) (Table 6).

Discussion
In the present study, the mean age of patients with positive cTnI was 55.57 ± 7.36 years and the mean age of patients with negative cTnI was 52.56 ± 6.52 years, with no significant difference. This is in agreement with the results of Baillard et al. [5] who found no significant difference between positive and negative cTnI patients as regards age in their study.

In contrast, Harvey and Hancox [13] reported a significant difference in the mean age of cTnI-positive patients compared with cTnI-negative patients.

Also in our study there was no significant statistical difference among AECOPD patients as regards sex. This is in agreement with the results of Harvey and Hancox [13] and Deveci et al. [14]. Aksay et al.[15], however, reported contrasting findings. They found a significant difference in sex among AECOPD patients. This finding could be attributed to the large number of female patients included in their study (59%), with most of them being diagnosed with pulmonary embolism (PE).

As regards smoking habit, there was no significant statistical difference in cTnI elevation among nonsmokers and smokers (Table 1). This may be due to the number of nonsmokers included in the study (two patients). This is in agreement with the studies by Baillard et al. [5] and Deveci et al. [14], who excluded the effect of smoking on cTnI levels among all studied patients. These results suggest that smoking has no effect on cTnI level in AECOPD patients.

As regards the severity of disease on the basis of FEV1, (Table 2 and Fig. 1), there was a significant statistical difference in troponin levels among all studied AECOPD patients when evaluated with pulmonary function tests, as 75% of troponin I-negative patients were in moderate stage, 53% of troponin I-positive patients were in severe stage, and 33% of troponin I-positive patients were in very severe stage.

In our study arterial blood gases parameters showed a significant statistical difference in troponin positivity in relation to pH, pCO2, pO2, and SO2, but no significant difference in relation to HCO3 (Table 3). Baillard et al. [5] reported a significant statistical difference in troponin positivity in relation to pCO2, pO2, and SO2, but no significant difference in relation to pH and HCO3. Harvey and Hancox [13] demonstrated a significant role of O2 saturation, pCO2, and pH on cTnI positivity. This could be attributed to the differences in the criteria of selection, the number of patients included, and the severity of AECOPD. Aksay et al. [15] agreed as regards oxygen saturation.

ECHO findings showed a significant statistical difference as regards RV strain (90% of cTnI-positive patients vs. 33% of cTnI-negative patients), pulmonary hypertension (71% of cTnI-positive patients vs. 11% of cTnI-negative patients), and tricuspid regurgite (52%...
of cTnI-positive patients) (Table 4). These findings are in agreement with those of Aksay et al. [15] who revealed a significant effect of RV dysfunction on cTnI elevation, and those of Harvey and Hancox [13], who suggested that the severity of acute exacerbation may lead to cardiac damage and troponin release. Potential mechanisms of cardiac injury include the following: acute elevation of pulmonary arterial pressure secondary to hypoxic vasoconstriction with subsequent RV distension (similar to the proposed mechanism of cTnI release in pulmonary embolism), tachyarrhythmia such as atrial fibrillation, and cardiac damage mediated by sepsis and/or metabolic stress due to hypoxia and acidosis. Seyhan et al. [16] found a strong correlation between RV dysfunction and cTnI in a group of AECOPD patients.

Baillard et al. [5] did not report a significant effect of either RV dysfunction upon cTnI or cor pulmonale. They stated that the reason for cTnI elevation is difficult to determine, because the cardiovascular alterations are complex. During episodes of exacerbation, the increased work and oxygen cost of breathing, the increase in left ventricular afterload related to the more negative intrathoracic pressure, the worsening of pulmonary hypertension, and the presence of hypoxemia and hypercapnia may all contribute to the development of cardiac injury.

In our study it was found that there was no significant statistical difference between patients with left ventricular dysfunction and patients without left ventricular dysfunction with respect to cTnI positivity. In contrast, Render et al. [17] and Connors et al. [18] reported left ventricular dysfunction in 30% of patients admitted for AECOPD.

In addition, MacIntyre and Huang [19] found that elevation of troponins (especially troponin I) was associated with increased severity of exacerbation. However, troponin T and pro-brain natriuretic peptide are elevated in patients with acute left heart failure and may be used to exclude left ventricular dysfunction as the cause of AECOPD.

As regards the need for MV, cTnI positivity was more prominent among patients who were ventilated versus those who did not need MV (Table 5). This finding is in agreement with those of Aksay et al. [15] who reported that there was a significant statistical difference in cTnI positivity between patients who needed mechanical ventilation and those who did not.

As regards the duration of hospitalization (Table 6), a significant difference was seen in cTnI positivity in relation to duration of hospitalization: cTnI positivity was more prominent in patients with longer duration of hospitalization. This could be attributed to the greater severity of the disease, exacerbation, the need for ICU admission, and the need for MV.

These findings are in agreement with those of Harvey and Hancox [13] who found that patients with greater number of hospital days were more cTnI-positive compared with those with shorter duration. The same findings were made by King et al. [20], who found a significant effect of length of hospitalization on cTnI elevation, and by Martins et al. [21] who found a significant effect of hospital length of stay upon cTnI elevation.

Conclusion

(1) cTnI in AECOPD patients is mostly positive in tachypneic, tachycardic, hypoxemic, and hypercapnic patients with more severe pulmonary hypertension and RV dysfunction.

(2) Positive cTnI in AECOPD patients may suggest exacerbation severity, the need for MV, and longer duration of hospitalization.

Acknowledgements

Conflicts of interest

None declared.

References


Evaluation of serum troponin I
Hasaneen et al.


Introduction

Although chronic obstructive pulmonary disease (COPD) is primarily a respiratory disease, systemic complications contribute considerably toward the prognosis. Most of these systemic complications, including weight loss, skeletal muscle dysfunction, osteoporosis, and atherosclerosis, are considered age-related abnormalities [1].

Telomere attrition in circulating white blood cells has been proposed as a marker for cumulative oxidative stress and inflammation and, therefore, as an indicator of the pace of biological aging [2]. Telomeres are DNA sequences and associated proteins that cap and stabilize the ends of linear chromosomes, thereby maintaining genome integrity and stability. Telomere length (TL) is not only related to the basic biology of aging as a trigger of cellular senescence but also reflects the balance between oxidative stress and antioxidant defense mechanisms [3].

The existing hypothesis for the pathogenetic mechanism of COPD is explained in terms of proteases, oxidants, and inflammation, whereas a new hypothesis is explained in terms of apoptosis, proliferation, and senescence. The two hypotheses can be integrated into a single hypothesis by linking senescence and inflammation [4].

Aim of the work

The aim of this work is to measure TL in patients with COPD and to study its relation to demographic data, spirometric indices, and arterial blood gases parameters.

Participants and methods

This case–control study was carried out at Al-Zahraa University Hospital on 31 age-matched men; they were divided into two groups.

(1) Group I (control group): It included 11 healthy lifelong nonsmoker volunteers. None of them had any symptoms suggestive of any disease and their spirometric indices and arterial blood gas values were in the normal range.

(2) Group II (COPD group): It included 20 COPD patients with symptoms of chronic airflow limitation and fulfilled the spirometric criteria set out by the GOLD 2011 guideline. The patients were included only if they had a stable course of disease with regular follow-up during the preceding 1 year and no hospitalization for COPD-related illness during the preceding 6 months. All of them had irreversible/partially reversible obstruction of airflow. COPD patients had a postbronchodilator FEV₁/FVC% of less than 70%. They had an increase in FEV₁ of less than 200 ml or less than
12% of baseline value 20 min after two puffs of inhaled salbutamol (100 μg) administered by a metered-dose inhaler. Most patients were using medications to treat COPD, including β2-agonists (salbutamol or formoterol), theophylline, and inhaled corticosteroids (budesonide); none of them was using oral steroids or long-term oxygen therapy.

Individuals known to have infective or interstitial lung diseases, bronchial asthma, cardiac, hepatic, renal, gastrointestinal, metabolic or endocrine diseases, malignancy, and inflammatory diseases such as diabetes mellitus were excluded from the study.

The study was approved by the ethical committee of Al-Azhar University. An informed written consent was obtained from all participants before their enrollment into the study.

All participants were subjected to the following studies: detailed assessment of history and complete clinical examination were performed, and age, BMI, pack-years of smoking (current smokers and ex-smokers), and mean arterial blood pressure (MAP) were recorded. The BODE (Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity) index score was calculated [5]. Dyspnea was assessed using the modified medical research council dyspnea scale (mMRC scale), whereas exercise was assessed by the 6-min walk test, which was carried out according to the ATS [6].

Spirometry was carried out using spirometry Spirosift 5000 manufactured for Fukuda Denshi USA, INC. 7102-A 180th Avenue Northeast Redmond, WA, 98052 by Nippon Systemhouse CO., LTD; made in Japan. Spirometric indices were calculated using the best of three technically satisfactory trials in accordance with the recommendations of the ATS.

Telomere length measurement
Fasting venous blood samples (5 ml) were drawn into EDTA-containing tubes in the morning (08:00–09:00 a.m.) and were stored at −70°C. DNA was extracted from white blood cells. Leukocyte TL was measured using the quantitative real-time method described by Cawthon [7], which measures the relative TL by determining the ratio of telomere repeat copy number (T) to the single-copy gene (S) number (T/S ratio) in experimental samples relative to a reference sample. The target gene in our study was the telomere and the reference gene was the acidic ribosomal phosphoprotein PO (36B4).

The TL of peripheral blood leukocytes were standardized to the reference single-copy gene (S) to yield a T/S ratio using the comparative C<sub>i</sub> method (T/S = 2<sup>ΔC<sub>i</sub></sup> ).

The ΔC<sub>i</sub> value for each sample was determined by calculating the difference between the C<sub>i</sub> value of the target gene and the C<sub>i</sub> value of the endogenous reference gene [7].

Statistical presentation and analysis of the study data were carried out using Statistical Package for the Social Sciences (SPSS) version 17. Parametric data were expressed as mean ± SD and nonparametric data were expressed as number and percentage of the total. An unpaired Student t-test was used to compare between two groups in quantitative data according to the computer program SPSS for Windows. The analysis of variance test was used for comparison when there were more than two groups in quantitative data. The linear correlation coefficient was used to detect the correlation between two quantitative variables in one group. P value greater than 0.05 was considered nonsignificant, P value less than 0.05 was considered significant, and P value of 0.01 or less was considered highly significant.

Results
Figures 1–8 indicate that the TL ratio in COPD patients shows a statistically significant positive correlation with FVC%, FEV<sub>1</sub>%, FEF<sub>25–75</sub>%, SpO<sub>2</sub>%, pH, and PaO<sub>2</sub>. Moreover, TL ratio showed a significant negative correlation with the BODE index; among BODE index parameters, it was negatively correlated with the dyspnea score.

TL was not correlated with age, smoking/year, smoking duration, MAP, vital capacity, FEV<sub>1</sub>/FVC%, PaCO<sub>2</sub>, HCO<sub>3</sub>, BMI, and six-min walk distance (6MWD).

In addition, TL was significantly shorter in patients with very severe COPD (FEV<sub>1</sub> < 30) than those with severe COPD (FEV<sub>1</sub> > 30) (P = 0.00).

Discussion
There is a growing realization that COPD involves several processes present in aging and cellular senescence [8]. Some have suggested that COPD is a disease of accelerated aging [9].

In the current study, peripheral blood leukocytes were assessed for TL not only because they were readily available, easily obtained, and processed, but also because they reflect the amount of stress on immune cells because of cigarette smoke and/or other environmental stresses [10]. Several studies have shown that TL in peripheral blood mononuclear cells is representative of that of many tissues; the intraindividual correlation between TL in different tissues is high [11].
The real-time PCR approach was chosen for TL measurement as a method based on PCR requires a lesser amount of DNA and can be completed in a short time. In addition, this method targets only the telomeric region and does not include the subtelomeric region as the TL restriction fragments method does [7]. For practical reasons, quantitative PCR has become the favored technique in telomere research over the past few years [12]. We have chosen the 36B4 gene as a single-copy gene for normalization because it has already been validated for gene–dosage studies [7].

Patients with diseases other than COPD were excluded from the study as many diseases were associated with TL shortening. Also, COPD patients who were receiving systemic steroids were excluded from the study because of the immune modulating effect of steroids [13]. Exposure of human T lymphocytes to cortisol is associated with a significant reduction in telomerase activity [14].

In the current study, the COPD patients and control participants selected were men to avoid TL variation with sex. Many studies confirmed that in adulthood the age-adjusted TL is shorter in men than in women [15–18]. TL in adults may have potential differences because of sex differences and exposures to oxidative stress [19]; also, it may be attributed to potential telomerase upregulation by estrogens [20].

In the current study, there was no significant correlation between TL and BMI in both groups (P > 0.05). McGrath et al. [18] and Lee et al. [9] did not find a significant relationship between TL and BMI.

TL showed no significant correlation with MAP. Jeanclos et al. [21] reported that TL correlated inversely

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**Fig. 1**

Correlation between telomere length (T/S ratio) and FVC% in the COPD group. COPD, chronic obstructive pulmonary disease; FVC, forced vital capacity.

**Fig. 2**

Correlation between telomere length and FEV1% in the COPD group. COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 s.

**Fig. 3**

Correlation between telomere length and FEF25–75% in the COPD group. COPD, chronic obstructive pulmonary disease; FEF, forced expiratory flow.

**Fig. 4**

Correlation between telomere length and SpO2% in the COPD group. COPD, chronic obstructive pulmonary disease.
with pulse pressure. This difference may be explained by the fact that all participants in our study had normal blood pressure.

TL was significantly shorter in COPD [1.1 ± 1.127 (0.001–4.427)] in comparison with the control group [4.352 ± 2.611 (1.0–8.143)] (Table 1). Thériault et al. [22] and Mui et al. [23] found that COPD patients had significantly shorter TL compared with healthy controls. Savale et al. [2] reported decreased TL in peripheral leukocytes from COPD patients compared with both healthy nonsmoker and smoker participants. Houben et al. [24] documented that TL was significantly shorter in peripheral blood lymphocytes of COPD patients than controls. Morlá et al. [25] found shorter TL in circulating lymphocytes from smoker COPD compared with healthy controls. Tomita et al. [26] found reduced TL of alveolar macrophages (AM) from bronchoalveolar of smokers than nonsmokers, whereas there was no difference between healthy smokers and smokers with COPD and shorter TL in smokers (with and without COPD) than nonsmokers. Tsuji et al. [27] reported that TL in alveolar type II cells and endothelial cells was significantly shorter in patients with emphysema than in asymptomatic nonsmokers, but no difference was detected between COPD and non-COPD smokers (Tables 2 and 3).

We studied TL in smoker COPD and healthy controls and found that TL was significantly shorter in smokers (COPD) [1.1 ± 1.127 (0.001–4.427)] than in nonsmoker controls [4.352 ± 2.611 (1.0–8.143)] (Table 1). TL was shorter in current smokers (0.631 ± 0.416) compared with ex-smokers (1.484 ± 1.385); the difference was statistically nonsignificant, but when compared with healthy controls, it showed significant shortening (Table 4). However, TL was not correlated with cigarette smoke exposure (pack-
Table 1 Comparison of all variables between both groups

<table>
<thead>
<tr>
<th>Indices</th>
<th>Control (n = 11)</th>
<th>COPD (n = 20)</th>
<th>t-test</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic data</td>
<td></td>
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<tr>
<td>Age (years)</td>
<td>50.0 ± 7.0</td>
<td>53.6 ± 6.5</td>
<td>-1.44</td>
<td>0.16</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.5 ± 3.2</td>
<td>26.1 ± 3.9</td>
<td>-0.47</td>
<td>0.63</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>92.7 ± 7.1</td>
<td>93.1 ± 6.4</td>
<td>-0.17</td>
<td>0.86</td>
</tr>
<tr>
<td>Spirometric indices</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VC%</td>
<td>90.2 ± 4.5</td>
<td>39.0 ± 14.4</td>
<td>11.37</td>
<td>0.00*</td>
</tr>
<tr>
<td>FVC%</td>
<td>93.3 ± 4.5</td>
<td>38.7 ± 15.5</td>
<td>11.26</td>
<td>0.00*</td>
</tr>
<tr>
<td>FEV₁ %</td>
<td>93.6 ± 5.7</td>
<td>27.0 ± 11.8</td>
<td>17.44</td>
<td>0.00*</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>84.0 ± 3.4</td>
<td>56.9 ± 9.0</td>
<td>9.47</td>
<td>0.00*</td>
</tr>
<tr>
<td>FEF25–75 %</td>
<td>85.5 ± 6.4</td>
<td>15.1 ± 8.7</td>
<td>23.05</td>
<td>0.00*</td>
</tr>
<tr>
<td>ABG parameters</td>
<td></td>
<td></td>
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<tr>
<td>SpO₂ %</td>
<td>96.6 ± 1.2</td>
<td>95.0 ± 1.8</td>
<td>2.43</td>
<td>0.02*</td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>95.3 ± 2.1</td>
<td>78.0 ± 9.1</td>
<td>6.11</td>
<td>0.00*</td>
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<tr>
<td>PaCO₂ (mmHg)</td>
<td>40.5 ± 3.4</td>
<td>41.2 ± 5.2</td>
<td>-0.38</td>
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<tr>
<td>pH</td>
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<td>7.3 ± 0.0</td>
<td>1.01</td>
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<tr>
<td>HCO₃⁻ (mEq/l)</td>
<td>25.0 ± 1.5</td>
<td>24.7 ± 2.8</td>
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<td>0.71</td>
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<tr>
<td>TL</td>
<td>4.35 ± 2.6</td>
<td>4.10 ± 1.12</td>
<td>4.85</td>
<td>0.00*</td>
</tr>
</tbody>
</table>

ABG, arterial blood gas; COPD, chronic obstructive pulmonary disease; FEF, forced expiratory flow; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; MAP, mean arterial blood pressure; SpO₂, oxygen saturation; VC, vital capacity; *Significant difference.

Table 2 Smoking status in the COPD group

<table>
<thead>
<tr>
<th>Smoking status</th>
<th>Current smokers [n (%)]</th>
<th>Ex-smokers [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>9 (45)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>Pack-year in COPD patients</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pack-year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>37.5–120.0</td>
<td>74.8 ± 30.9</td>
</tr>
<tr>
<td>Current smoker</td>
<td>30.0–80.0</td>
<td>49.4 ± 17.9</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease.

year smoking) (P = 0.87). Although smoking status was not associated with a significant difference in TL, the TL from COPD patients, who all had significant smoking history (on average more than 10 pack-years), was significantly shorter than that of the control participants of the same age. These data suggest that previous cigarette exposure or COPD accelerates telomere attrition, leading to short telomeres. Similar results have been reported by many investigators; Houben et al. [24] concluded that shorter TL was not related to smoking exposure in COPD. Mui et al. [23] found no association between TL and pack-year, and no difference was found between current and ex-smokers. However, Valdes et al. [28] recorded a dose-dependent TL correlation with smoking, and each pack-year smoked was equivalent to an additional five base pair loss of TL. Their results emphasize the proaging effects of cigarette smoking. McGrath et al. [18] reported significantly shorter TL in healthy smokers than healthy nonsmokers. They did not observe an association between smoking status (current vs. former; never vs. ever) and TL among control participants. Similarly, Morlá et al. [25] have reported previously that TL was reduced in peripheral blood lymphocytes in smokers with and without COPD; they observed a dose–response relationship between cumulative lifetime exposure to tobacco smoking and TL. Lee et al. [9] found no significant difference in TL between the quitter group and the smoker groups (sustained quitters vs. intermittent quitters and sustained quitters vs. continuous smokers); however, a significant difference existed when adjusted for age. TL of the control group was significantly longer than all three smoker groups. Tomita et al. [26] reported evidence that smoking induces shortening of TL in AMs from both young and old individuals. Their findings suggested that smoking might induce AM senescence and COPD might be associated with premature aging. Tsuji et al. [27] reported no significant differences in TL between patients with emphysema and asymptomatic smokers. Shen et al. [29] reported that TL was associated inversely with pack-years of smoking among controls. The significant relationship found between a history of smoking and TL reported in some studies, but not in others, including our study, may be because of differences in smoking history, age, and stages of COPD.

In the present study, no significant correlation was found between TL and years of smoking; however, Shen et al. [29] found a significant positive interaction between TL and years of smoking. McGrath et al. [18]
reported that age-adjusted TL was five base pair shorter for every pack-year smoked and observed a significant correlation between TL and pack-years of smoking. Hou et al. [30] reported that TL tended to decrease with increasing pack-years of cigarette smoking. Several factors may explain this discrepancy, such as different white blood cells that were studied, the fact that our study and that of Morlá et al. [25] included only men, and the relatively small population sizes of both studies.

In the present study, TL was shorter in COPD patients than in the healthy controls (Table 1); among COPD patients, it was shorter in those with FEV₁% less than 30% than those with FEV₁% greater than 30%, and it was correlated positively with FVC%, FEV₁%, and FEF₂₅₋₇₅%. The same results were obtained by Tsuji et al. [27] as they reported that TL in type II pneumocytes and endothelial cells was correlated positively with FEV₁%. Schulz et al. [31] reported that FEV₁%, FVC, but not flow rates, were correlated positively with TL. Mui et al. [23] reported a strong, but nonsignificant, correlation between TL and FEV₁% in COPD, whereas a significant positive relationship was found between TL and FEV₁%/FVC in COPD, but no association was found between TL and FVC% in COPD. However, Savale et al. [2] found no relationship between TL and FEV₁%, and FVC, and reported no significant difference in TL between patients with FEV₁ less than or greater than 50%. Lee et al. [9] found no significant relationship between TL and FEV₁%. This discrepancy may be explained by the different stages of airflow limitation, which was severe to very severe in our study and moderate to severe in Savale et al. [2] and mild to moderate in Lee et al. [9].

In the current study, there was a significant positive correlation between TL and SpO₂, pH, and PaO₂, whereas PaCO₂ showed an inverse nonsignificant correlation (Figs. 4–6); the same results were obtained by Savale et al. [2], who found a strong positive correlation of TL with both PaO₂ and SpO₂ as well as a negative correlation with PaCO₂.

In the current study, TL was not correlated with age (P > 0.05). The same result was obtained by Lee et al. [9], Shen et al. [29], and McGrath et al. [18]; they found no significant relationship between TL and age. However, many studies observed that TL shortened linearly with age [2,15,24,28,32]. Morlá et al. [25] found that TL significantly decreased with age in smokers, but no correlation was found in never-smokers. The exact reason for this discrepancy is unclear; it may be explained by the fact that smoking also reduces TL and attenuates the relationship between chronological age and TL and the narrow age spectrum in our study. It may also be because TL is considered to be a biomarker of biological age rather than chronological age [33].

In the current study, in COPD, there was a significant negative correlation between TL and the BODE index (r = −0.594; P = 0.006); among the BODE components, the dyspnea score was correlated negatively with TL (P = 0.011) (Figs. 7 and 8). Savale et al. [2] reported no relationship between TL and the BODE index; among the BODE components, 6MWD was correlated positively with TL. Mui et al. [23] found no significant relationship between TL and BMI.

The present study has some limitations that deserve comments. First, the sample size of the present study is relatively small. Second, all patients had severe to very severe COPD; thus, the relationship of TL across the full range of COPD severity is unknown.

Conclusion and recommendations
The results of this study support the link between TL shortening and COPD, which confirms accelerated cellular senescence in COPD.

TL was correlated positively with airflow limitations and it may be related to impaired physical activities in COPD patients. Early smoking cessation for all COPD patients to decrease the rate of cellular senescence is mandatory. Further study of TL involving a large number of patients and different stages of COPD to assess the effect of disease severity is required. A cohort study to detect the rate of telomere attrition in COPD and its relation to morbidity and mortality is required.

Acknowledgements
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Conflicts of interest
There are no conflicts of interest.

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Prevalence and predictors of chronic obstructive pulmonary disease among high-risk Egyptians
Azza F. Said\textsuperscript{a}, Ashraf A. Ewis\textsuperscript{b}, Ahmad A. Omran\textsuperscript{c}, Mohamed E. Magdy\textsuperscript{a}, Micheal F. Saleeb\textsuperscript{d}

\textbf{Introduction} Chronic obstructive pulmonary disease (COPD) prevalence, morbidity, and mortality vary across countries and across different groups within countries with a direct relation to the prevalence of tobacco smoking. Other risk factors for COPD include genetic factors, longstanding asthma, outdoor air pollution, second-hand smoke exposure, biomass smoke, indoor air pollution, occupational exposures, and tuberculosis [1]. The prevalence and burden of COPD are projected to increase in the coming decades because of continued exposure to COPD risk factors and the changing age structure of the world’s population. As these factors are rapidly increasing in developing countries, COPD will become a major health problem, exerting a huge demand on economic and healthcare resources in developing countries [2].

In Egypt, although COPD is a rising significant health problem, data on its prevalence, morbidity, and mortality are still lacking and have to be estimated [3]. Because currently available treatments have minimal impact on disease progression, a strategy for early diagnosis of COPD is a critical priority. Early implementation of spirometry for individuals at risk may identify the disease in its early stages [1].

In 2001, the Global Initiative for Chronic Obstructive Lung Disease committee was the first to publish a consensus statement propagating the use of a fixed \( \text{FEV}_1 / \text{FVC} < 0.70 \) value and fixed \( \text{FEV}_1 \) values to classify severity [4]. The choice of a fixed cutoff point for the GOLD-COPD definition was made for generalization and simplification [5]. However, more recently the GOLD committee recognized that using a fixed value of less than 0.70 may lead to potential overdiagnosis of COPD in the elderly as the \( \text{FEV}_1 \) value decreases more quickly with age than the FVC [6]. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) proposed using a threshold below the lower limit of normal adjusted for age instead of a fixed criterion...
for FEV<sub>1</sub>/FVC [7]. They defined the LLN as the fifth percentile of reference values drawn from the Third National Health and Nutrition Examination Survey (NHANES-III) cohort [8]. Calculation of LLN is based on multiple regression calculations and may be subject to considerable variability around the median and is affected by sex and race [9], and a value of FEV<sub>1</sub>/FVC below the LLN of an age-matched healthy reference group is considered abnormal and consistent with a diagnosis of COPD [10,11].

**Aim of the work**
The first objective of this study was to identify the prevalence of COPD among high-risk individuals using GOLD and FEV<sub>1</sub>/FVC < LLN definitions, with estimation of the accuracy of using the FEV<sub>1</sub>/FVC < LLN for diagnosis of COPD. The second aim was to detect predicting factors for COPD diagnosis.

**Patients and methods**
A total of 363 randomly selected individuals at high risk for COPD were studied from January 2011 to September 2013. This study was approved by the ethical committee of the Faculty of Medicine, Minia University. Informed consent was obtained from all participants. They were divided into three groups:

**Group I:** This group included 176 individuals aged 40 years or older with a smoking history of at least 10 pack-year (current or ex-smoker). They were relatives or visitors of patients admitted to Mallawy Chest Hospital, Minia Government, Egypt.

**Group II:** This group involved 107 workers who were engaged in construction and/or brick manufacturing.

**Group III:** This group comprised 80 randomly selected women with a history of exposure to biomass fuel in a poorly ventilated dwelling from two villages (Tahna El-Gabal and El-Arean) of Minia City.

Individuals with a history of known chronic cardiopulmonary diseases and those with collagen vascular diseases were excluded.

All participants were subjected to the following:

1. A questionnaire including age, sex, smoking status, presence of chronic cough, chronic sputum production, chest wheezing, and shortness of breath; grading of dyspnea using a modified medical research council (MMRC) dyspnea scale.
2. General examination, including measurements of body weight, height, and BMI.
3. Local chest examination.

4. Spirometry was performed on those with one or more positive symptoms in the respiratory questionnaire using a calibrated digital hand-held spirometer (TED, SPANSH). The best of three measurements was obtained while the patients were in the seated position. Values were obtained while the participant exerted his or her maximum effort were used so as to avoid any expected error in diagnosis. Results were obtained for FVC, FEV<sub>1</sub>, ratio of FEV<sub>1</sub>/FVC (FEV<sub>1</sub>/FVC%), forced expiratory flow at 25–75% of vital capacity, and peak expiratory flow. The absolute values and the percentages of spirometric parameters predicted from the participant’s age, sex, and height were calculated. Individuals who had FEV1/FVC < 70% and FEV1 < 80% predicted with FVC ≥ 80% were asked to perform a postbronchodilator spirometry test 20 min after two puffs of 200 µg salbutamol.

A postbronchodilator FEV<sub>1</sub>/FVC < 70% of predicted established the diagnosis of ‘GOLD-COPD’ [4]. Values of FEV<sub>1</sub>/FVC < LLN in an age-matched healthy reference group were considered abnormal and consistent with a diagnosis of ‘LLN-COPD’ [10,11].

From several LLN equations provided we selected LLN prediction equations as per the study by Hankinson et al. [8]. LLN equations for FEV<sub>1</sub>/FVC% specific for sex, ethnicity, and age were derived from the NHANES-III database for ages 8–80 years.

\[
\text{LLN of FEV}_1/\text{FVC for males} = 78.38 - 0.206 \times \text{age},
\]

\[
\text{LLN of FEV}_1/\text{FVC of females} = 81.01 - 0.212 \times \text{age}.
\]

Free software with documentation for all ethnic groups is now available and was also used in this study [12].

COPD patients who were diagnosed under both definitions were further examined by means of a chest radiograph, complete blood count, C-reactive protein (CRP) levels, and sputum culture on chocolate agar media.

**Statistical analysis**
Statistical analyses were performed using the statistical package for social sciences (SPSS) program, version 16. Differences in the mean of quantitative variables were analyzed using parametric tests (the independent sample t-test, one-way analysis of variance test), and differences between categorical variables were analyzed using the χ²-test. For all tests, the values of P-value less than 0.05 were regarded as statistically significant.

**Results**
A total of 363 individuals with high risk for COPD participated in the study and they were divided into
three groups. Group I (176, 48.5%) comprised smokers of male sex and their mean age was 51.2 years with a smoking history of at least 10 pack-years. Group II included 107 (29.5%) individuals; 55 (51.8%) were construction workers and 52 (48.2%) were brick manufacturers and 91.6% of them were current smokers. Group III comprised 80 (22%) women with a positive history for biomass exposure. They were exposed to high levels of indoor air pollution due to biomass cooking or heating in their houses for at least 20 years (Table 1).

Tables 2, 3, and 4 show the prevalence of COPD on the basis of GOLD and prebronchodilator and postbronchodilator FEV\(_1\)/FVC < LLN criteria as 9.6, 17.4, and 8.9%, respectively. The prevalence of COPD was not significantly different among the studied groups on either GOLD or LLN criteria (P = 0.7, 0.2, and 0.58, respectively).

On determining the accuracy of FEV\(_1\)/FVC < LLN for the diagnosis of COPD, we considered GOLD as the gold standard ‘Reference test’ for diagnosis of COPD and compared FEV\(_1\)/FVC < LLN with that of GOLD and found that 33 of 35 participants had COPD on the basis of both criteria, giving a sensitivity of 94.3%. Second, on using the postbronchodilator value of FEV\(_1\)/FVC < LLN, it was found that 31 of 35 participants had COPD on the basis of both criteria, resulting in a sensitivity of 88.6%. On assessment of specificity of prebronchodilator FEV\(_1\)/FVC < LLN, it was found that 298 out of 328 did not have COPD on the basis of either criteria, yielding a specificity of 90.8%. However, for postbronchodilator FEV\(_1\)/FVC < LLN, it increased to 99.7% (327 out of 328 participants had no COPD on the basis of either criteria) (Table 5).

The GOLD-COPD was graded using postbronchodilator % of predicted FEV\(_1\) values: GOLD 1 (mild), FEV\(_1\) ≥ 80%; GOLD 2 (moderate), FEV\(_1\) < 80% predicted but ≥ 50% predicted; GOLD 3 (severe), FEV\(_1\) < 50% predicted but ≥30% predicted; and GOLD 4 (very severe), FEV\(_1\) < 30% predicted [10]. According to the severity criteria of GOLD, the prevalence of GOLD 1 (mild), GOLD 2 (moderate), GOLD 3 (severe), and GOLD 4 (very severe) COPD was 3, 69, 17, and 11%, respectively (Fig. 1). Moderate grade (GOLD 2) was the most frequently seen (24 out of 35 patients, 69%) with closely related distribution among the three studied groups (nine patients in group I, eight in group II, and seven in group III). In

### Table 1 Descriptive data of all participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (n = 176)</th>
<th>Group II (n = 107)</th>
<th>Group III (n = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Range</td>
<td>40–74</td>
<td>24–67</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>51.2 ± 7</td>
<td>49.4 ± 7.8</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>176 (62.2)</td>
<td>107 (37.8)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Current smoker</td>
<td>166 (94.4)</td>
<td>98 (91.6)</td>
</tr>
<tr>
<td></td>
<td>Ex-smoker</td>
<td>10 (5.6)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td></td>
<td>Nonsmoker</td>
<td>0 (0.6)</td>
<td>6 (5.6)</td>
</tr>
<tr>
<td>BMI</td>
<td>&lt;18.5</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>18.5–24.9</td>
<td>138 (47.9)</td>
<td>96 (33.3)</td>
</tr>
<tr>
<td></td>
<td>25–29.9</td>
<td>37 (52.1)</td>
<td>11 (15.5)</td>
</tr>
<tr>
<td></td>
<td>≥30</td>
<td>1 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Range</td>
<td>19.4–30.4</td>
<td>19.8–29.4</td>
<td>16.6–30.4</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>23.6 ± 1.7</td>
<td>23.3 ± 1.6</td>
</tr>
</tbody>
</table>

Data are represented as n [%], whereas for age and BMI, it is presented as range and mean ± SD.

### Table 2 Prevalence of COPD among the studied groups as defined by GOLD criteria

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (n = 176)</th>
<th>Group II (n = 107)</th>
<th>Group III (n = 80)</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>15 (8.5)</td>
<td>11 (10.3)</td>
<td>9 (11.2)</td>
<td>35 (9.6)</td>
<td>0.7</td>
</tr>
<tr>
<td>Non-COPD</td>
<td>161 (91.5)</td>
<td>96 (89.7)</td>
<td>71 (88.8)</td>
<td>328 (90.4)</td>
<td></td>
</tr>
</tbody>
</table>

Data are represented as n [%]; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

### Table 3 Prevalence of COPD among the studied groups by prebronchodilator FEV\(_1\)/FVC < LLN

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (n = 176)</th>
<th>Group II (n = 107)</th>
<th>Group III (n = 80)</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>28 (15.9)</td>
<td>16 (15)</td>
<td>19 (23.8)</td>
<td>63 (17.4)</td>
<td>0.2</td>
</tr>
<tr>
<td>Non-COPD</td>
<td>148 (84.1)</td>
<td>91 (85)</td>
<td>61 (76.2)</td>
<td>300 (82.6)</td>
<td></td>
</tr>
</tbody>
</table>

Data are represented as n [%]; COPD, chronic obstructive pulmonary disease; LLN, lower limit of normal.

### Table 4 Prevalence of COPD among the studied groups by postbronchodilator FEV\(_1\)/FVC < LLN

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (n = 176)</th>
<th>Group II (n = 107)</th>
<th>Group III (n = 80)</th>
<th>Total</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>COPD</td>
<td>13 (7.4)</td>
<td>10 (9.4)</td>
<td>9 (11.2)</td>
<td>32 (8.9)</td>
<td>0.58</td>
</tr>
<tr>
<td>Non-COPD</td>
<td>163 (92.6)</td>
<td>97 (90.6)</td>
<td>71 (88.8)</td>
<td>331 (91.1)</td>
<td></td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; LLN, lower limit of normal.

### Table 5 Diagnostic accuracy of FEV\(_1\)/FVC < LLN

<table>
<thead>
<tr>
<th>Variables</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive predicted value (%)</th>
<th>Negative predicted value (%)</th>
<th>Accuracy (%)</th>
<th>Error %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prebronchodilator FEV(_1)/FVC &lt; LLN</td>
<td>94.3</td>
<td>90.8</td>
<td>52.4</td>
<td>99.3</td>
<td>91.2</td>
<td>8.8</td>
</tr>
<tr>
<td>Postbronchodilator FEV(_1)/FVC &lt; LLN</td>
<td>88.6</td>
<td>99.7</td>
<td>96.9</td>
<td>98.8</td>
<td>98.6</td>
<td>1.4</td>
</tr>
</tbody>
</table>

LLN, lower limit of normal.
contrast, all four (11%) patients with COPD grade 4 (very severe) were from group I.

Discussion
This study was designed to detect the prevalence of COPD among high-risk individuals on the basis of GOLD and LLN definitions. Using the GOLD definition, the prevalence of COPD was found to be 9.6% (Table 2). Estimates of prevalence from industrialized countries range widely, reflecting both true differences as well as differences in the definition of COPD and the diagnostic tools used in the surveys, and whether spirometry was used to confirm the diagnosis. Most studies find a prevalence of 10–15% in the population above 35–40 years of age [13–17]. An international survey (BREATH Study) [18] in a large sample of individuals aged 40 years and above in 12 countries of the MENA region showed that 3.6% of individuals fulfilled the epidemiological definition of COPD. Most studies estimated the prevalence of COPD in general population samples and not among those at high risk only. Hill et al. [19] detected the prevalence of COPD among patients at risk in primary care (age ≥40 years with a smoking history of 20 pack-years) to be 20.7%. Another study by Zielinski and Bednarek [20] found that spirometric signs of airway obstruction were found in 24.3% of individuals at high risk for COPD (smokers who were >39 years old with a smoking history of >10 pack-years).

The prevalence of COPD was higher in this study when the prebronchodilator FEV$_1$/FVC < LLN definition was used (Table 3) compared with the GOLD definition (17.4 vs. 9.6%, respectively) and closer to that of GOLD on using postbronchodilator FEV$_1$/FVC < LLN (8.9%) (Table 4). This could be attributed to the fact that the LLN definition could diagnose obstructive airway diseases other than COPD, such as asthma, as in 28 of 63 patients on LLN definition the postbronchodilator values of FEV$_1$/FVC were more than 70% predicted.

This study revealed that both occupational exposure and biomass fuel use contribute to the presence of COPD as a risk factor to a similar extent as smoking ($P > 0.05$).

There is an evidence-based review that presents an overview of studies comparing the FEV$_1$/FVC < LLN with FEV$_1$/FVC < 0.70 in diagnosing spirometry-based COPD [21]. The majority of studies concluded that using the FEV$_1$/FVC < 0.70 approach resulted in a greater prevalence of COPD, which was often interpreted as ‘overdiagnosing COPD’. All these studies were performed in western countries and almost uniformly did not include postbronchodilator values as recommended by GOLD-COPD.

In accordance with our results, Aggarwal et al. [22] found an overall lower prevalence rate when applying FEV$_1$/FVC < 0.70 instead of the LLN (23.6 and 28.2%, respectively). This study was performed in India and was composed of 56.1% men of a mean age of 48.2 years. Another study in Lebanon [23] found that the prevalence of COPD as per GOLD was 9.7% [95% confidence interval (CI) 8.5–10.9%] and as per LLN was 12.5% (95% CI 11.2–13.9%).

However, all previous studies on LLN and GOLD compared the two methods without application of a reference test. Without a reference, however, it is impossible to determine which method performs better [24].

Although the LLN might be a statistically more sound method of diagnosing airflow obstruction compared with the fixed ratio, it has not been clinically validated for want of a gold standard. Longitudinal studies of outcomes comparing the two methods of defining cutoffs have been equivocal [25].

On determining the accuracy of FEV$_1$/FVC < LLN for the diagnosis of COPD, we found that the sensitivity of prebronchodilator FEV$_1$/FVC < LLN was higher than the postbronchodilator value (94.3 and 88.6%, respectively). The positive and negative predicted values and accuracy of prebronchodilator FEV$_1$/FVC < LLN were 52.9, 99.3, and 91.2%, respectively, whereas that of postbronchodilator values were 96.9, 98.8, and 98.6%, respectively. In contrast, specificity of postbronchodilator FEV$_1$/FVC < LLN was nearly 100% (99.7%) (Table 5).
Kato et al. [26] found that $\text{FEV}_1/\text{FVC} < \text{LLN}$ had a sensitivity of 65.0% and specificity of 100% for the diagnosis of COPD. Güder et al. [27] used the consensus of an expert panel as a reference standard for COPD, which is accepted as the best alternative in the absence of a true reference standard. They found that the sensitivity and specificity of GOLD for the diagnosis of COPD as compared with the reference test were 85.4 and 79.1%, respectively. They also found the sensitivity and specificity of $\text{FEV}_1/\text{FVC} < \text{LLN}$ to be 55.1 and 96.2%.

COPD is and remains a clinical diagnosis, and therefore a panel decision on its absence or presence by taking into account all relevant clinical factors, such as age, respiratory complaints, smoking history, etc. is the classical approach. The fixed $\text{FEV}_1/\text{FVC} < 0.70$ criterion and the LLN should subsequently be compared with the panel diagnosis of COPD and the sensitivity/specificity evaluated [21].

Regarding the classification of the severity of COPD by GOLD using postbronchodilator values of $\text{FEV}_1$, we found that grade II (moderate) and grade III (severe) were higher than the other grades of COPD (68.6 and 17.1%, respectively) (Fig. 1). The prevalence of early COPD is high and varies significantly between countries. In the BOLD study, the prevalence of GOLD stage I COPD ranged from 1% in the Philippines to 16% in Austria, whereas that of GOLD stage II COPD ranged from 5% in Germany to 12% in South Africa [13]. Distribution of COPD stage in COPD patients in Lebanon was as follows: 17.6% mild (stage I), 58.3% moderate (stage II), 20.3% severe (stage III), and 3.8% very severe (stage IV) [23]. Another study in Copenhagen revealed that 6.2% of patients had mild COPD, 9.2% had moderate COPD, and 2.0% had severe or very severe COPD [28]. Deveci et al. [29] performed a study in Turkey and found that the majority of COPD cases were at stages I and II (22.6 and 66%, respectively). Unfortunately, in the current study, grade I (mild COPD) had the lowest frequency (2.9%) and all cases of grade 4 were found among group I participants only.

It is clear from our study and from other studies conducted in the Middle East that moderate grade of COPD is more frequent than other grades.

On considering the predicting factors for COPD using GOLD criteria, it was found that age 50 years, 12.5 pack-years, and chest wheezes were the highest independent factors for the presence of COPD (Table 6). As per the LLN criteria, we found that current smokers, ex-smokers, 12.5 pack-years, and chest wheezes were also high-risk factors (Table 7). Minas et al. [30] found that male sex ($P = 0.001$), older age ($P < 0.001$), a smoking habit of more than 10 pack-years ($P < 0.001$), and the presence of respiratory symptoms, mainly cough, sputum production, dyspnea, and wheezing ($P < 0.001$), were the most significant factors related to the presence of COPD.

### Table 6 Regression analysis for prediction of COPD by GOLD definition

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>$P$-value</td>
</tr>
<tr>
<td>Age (¬50 years)</td>
<td>2.42 (1.16–5.03)</td>
<td>0.02</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.25 (0.65–2.79)</td>
<td>0.7</td>
</tr>
<tr>
<td>Occupation</td>
<td>1.23 (0.54–2.97)</td>
<td>0.4</td>
</tr>
<tr>
<td>Biomass fuel</td>
<td>1.36 (0.57–3.25)</td>
<td>0.6</td>
</tr>
<tr>
<td>Smokers+ex-smokers</td>
<td>0.91 (0.87–0.94)</td>
<td>0.1</td>
</tr>
<tr>
<td>Pack-year (12.5)</td>
<td>2.38 (0.99–5.72)</td>
<td>0.047</td>
</tr>
<tr>
<td>Chest wheezes</td>
<td>4.80 (1.57–14.74)</td>
<td>0.021</td>
</tr>
<tr>
<td>Expectoration</td>
<td>0.72 (0.20–2.58)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

CI, confidence interval; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; OR, odds ratio.

### Table 7 Regression analysis for prediction of COPD by $\text{FEV}_1/\text{FVC} < \text{LLN}$

<table>
<thead>
<tr>
<th>Variables</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>$P$-value</td>
</tr>
<tr>
<td>Age (¬50 years)</td>
<td>1.34 (0.78–2.32)</td>
<td>0.16</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.69 (0.92–3.11)</td>
<td>0.8</td>
</tr>
<tr>
<td>Occupation</td>
<td>0.93 (0.48–1.81)</td>
<td>0.11</td>
</tr>
<tr>
<td>Biomass fuel</td>
<td>1.65 (0.86–3.17)</td>
<td>0.12</td>
</tr>
<tr>
<td>Smokers+ex-smokers</td>
<td>1.68 (0.21–13.62)</td>
<td>0.048</td>
</tr>
<tr>
<td>Pack-year (12.5)</td>
<td>2.09 (1.06–4.13)</td>
<td>0.03</td>
</tr>
<tr>
<td>Chest wheezes</td>
<td>2.26 (0.76–6.76)</td>
<td>0.002</td>
</tr>
<tr>
<td>Expectoration</td>
<td>0.43 (0.17–1.10)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

CI, confidence interval; COPD, chronic obstructive pulmonary disease; LLN, lower limit of normal; OR, odds ratio.
et al. [31] revealed a statistically significant association between COPD and age of 55 years and above (odds ratio 10.9, 95% CI 3.8–30.1, \( P < 0.001 \)) and between COPD and pack-years of 20 or more (odds ratio 3.2, 95% CI 1.2–8.5, \( P = 0.016 \)) in current smokers as positive predictors for COPD.

The chronic inflammation in COPD, orchestrated by multiple inflammatory cells and mediators in the airways and lung tissues, is induced by inhalation of noxious gases and particulate matter. This persistent inflammatory response in the lung is also associated with a significant systemic inflammatory response yielding adverse clinical outcomes, the so-called systemic effects of COPD. Although the origin of systemic inflammation present in COPD remains poorly understood, it is clearly established that some inflammatory markers are raised in systemic circulation. Of the blood-based biomarkers, CRP has shown the greatest promise [32].

In patients with COPD, increased CRP levels are associated with poor lung function, reduced exercise capacity, and worse quality of life. It is also a significant predictor of all-cause mortality [33]. CRP increase in COPD patients may be either due to the disease itself causing systemic inflammation or due to related factors such as ischemic heart disease and cigarette smoking [34].

In the present study we assessed CRP among patients with COPD and it was found that the number of patients with positive CRP was significantly higher than the number of patients with negative CRP (57.1 vs. 42.9%, respectively, \( P = 0.009 \)) on the basis of the GOLD definition (Table 8).

The lower airways have until recently been considered a sterile environment, and in airway diseases such as bronchiectasis and COPD the isolation of bacteria such as Hemophilus influenzae and pseudomonas species in sputum samples by culture is not uncommon. Although these pathogens are often associated with exacerbations, they are also often present during stable phase of the airways disease, indicating chronic colonization [35,36].

Sputum microbiology was assessed in this work among COPD patients and we found that COPD patients by GOLD definition had a significantly higher proportion of Gram-negative organisms in sputum culture compared with other microorganisms (Table 9). In accordance with this result, Bari et al. [37] found that the prevalence of lower airway bacterial colonization in outpatients with stable COPD is high and is mainly due to Gram-negative bacilli like Pseudomonas.

### Table 8 CRP among COPD patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>CRP+</th>
<th>CRP−</th>
<th>Z</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD-COPD ( (n = 35) )</td>
<td>20 (57.1)</td>
<td>15 (42.9)</td>
<td>2.36</td>
<td>0.009</td>
</tr>
<tr>
<td>LLN-COPD ( (n = 63) )</td>
<td>35 (55.6)</td>
<td>28 (44.4)</td>
<td>0.85</td>
<td>0.196</td>
</tr>
</tbody>
</table>

Data are represented as \( n \) [%]; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LLN, lower limit of normal; \( P < 0.05 \), significant.

### Table 9 Sputum culture results among COPD patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Gram- positive</th>
<th>Gram- negative</th>
<th>Mixed organism</th>
<th>Z</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOLD-COPD ( (n = 35) )</td>
<td>11 (31.4)</td>
<td>17 (48.6)</td>
<td>7 (20)</td>
<td>1.89</td>
<td>0.029</td>
</tr>
<tr>
<td>LLN-COPD ( (n = 63) )</td>
<td>24 (38)</td>
<td>21 (33.5)</td>
<td>18 (28.5)</td>
<td>1.16</td>
<td>0.124</td>
</tr>
</tbody>
</table>

Data are represented as \( n \) [%]; COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LLN, lower limit of normal; \( P < 0.05 \), significant.

Certain limitations need to be considered in the interpretation of our findings. First, our work was carried out only on high-risk individuals and not on general population samples. Second, we used reference equations for FEV\(/FVC < LLN from the USA that may not ideally apply to our population. This may result in biased outcomes because of nonavailability of population-specific reference equations in our locality. Although a free software is now available for different races, its accuracy with respect to the reference equations has not been established. The other limiting factor was the small sample of individuals assessed.

The main strength of the present study is the inclusion of risk factors other than smoking in the evaluation of COPD prevalence, as well as the use of postbronchodilator values of FEV\(/FVC in the LLN definition.

### Conclusion

This study showed that the prevalence of COPD among high-risk Egyptians by GOLD and LLN criteria was 9.6 and 17.4%, respectively. The present study showed a higher prevalence of grade 2 (69%) and grade 3 (17%) and lower prevalence of grade 1 (3%) COPD. Prebronchodilator FEV\(/FVC < LLN had a high sensitivity and specificity for COPD diagnosis. The postbronchodilator LLN definition is superior in ruling out the presence of COPD as a good negative test.

Age 50 years, pack-years of 12 or more, and chest wheezing were strong predictors of COPD; therefore, spirometry in high-risk groups, especially if they had these predictors, can help detect COPD in early stages.

Increasing awareness of COPD in the general population and specifically among high-risk individuals can aid in the early diagnosis of this disease.
Our results highlight COPD as a major public health problem in Egypt and call for more research to be directed toward preventive measures and efforts.

Acknowledgements
Conflicts of interest
There are no conflicts of interest.

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Evaluation of nasal optiflow device in the management of chronic obstructive pulmonary disease patients with acute exacerbations

Adel M. Saeed\textsuperscript{a}, Khaled M. Wagih\textsuperscript{a}, Nasra A. Hussein\textsuperscript{b}

\textbf{Background} A new form of therapy that provides humidified high-flow oxygen through a nasal cannula has been introduced recently as an alternative in the treatment of spontaneously ventilating patients with high oxygen requirements.

\textbf{Objective} The aim of the study was to evaluate the efficacy of a nasal optiflow device in the management of chronic obstructive pulmonary disease (COPD) patients with acute exacerbations in comparison with a conventional venturi mask.

\textbf{Patients and methods} Forty-five COPD patients with respiratory failure type II admitted to the RICU at Abbasia Chest Hospital were recruited and divided into two groups: group 1 included 20 randomly selected COPD patients with acute exacerbations connected to a venturi mask; group 2 included 25 randomly selected COPD patients with acute exacerbations connected to nasal high flow (NHF) oxygen with an optiflow system. All patients were subjected to full history taking, thorough clinical examination, and routine laborator\textsuperscript{a}y investigations with chest X ray (CXR) and repeated analyses of arterial blood gases (ABGs).

\textbf{Results} No statistically significant difference was observed between the two groups with respect to baseline ABG variables (on admission). In both methods (NHF and venturi mask) there was statistically significant improvement in ABG variables in the form of raised pH, PO\textsubscript{2}, and O\textsubscript{2} saturation and reduced PCO\textsubscript{2} when compared with baseline ABG values. Although there was no significant difference in weaning results between the two groups, there was significant decline in PCO\textsubscript{2} in the NHF group. There was no significant difference in the outcome and end result between the two groups; successful weaning was achieved in 70\% of patients in the venturi group and in 64\% of the NHF group, whereas failure was reported in 30\% of patients in the venturi group and in 36\% in the NHF group.

\textbf{Conclusion} The nasal optiflow device is highly expensive compared with the venturi mask, although both are approximately equally successful in the treatment of COPD patients with respiratory failure type II.\textsuperscript{1}

\textbf{Keywords:} chronic obstructive pulmonary diseases, nasal high flow, respiratory failure type II, venturi mask

\textsuperscript{1}Pulmonary Medicine Department, Faculty of Medicine, Ain Shams University, \textsuperscript{a}Chest Department, Abbasia Chest Hospital, Cairo, Egypt

Correspondence to Khaled M. Wagih, MD, 28 Othman Ebnaffan Street, Heliopolis, Cairo 1736, Egypt
Tel: +20 100 124 0282; fax: 0226202814; e-mail: khaledwagih1970@hotmail.com

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Introduction

Respiratory failure may be acute or chronic. Acute hypercapnic respiratory failure develops over minutes to hours, whereas chronic respiratory failure develops over several days or longer \cite{1}.

The major treatment for respiratory failure is oxygen therapy, which can be used for a variety of purposes in both chronic and acute patient care. Oxygen is essential for cell metabolism, as tissue oxygenation is essential for all normal physiological functions \cite{2}.

Nasal high flow (NHF) is a new respiratory care therapy that aims to meet or exceed the patient’s normal inspiratory demand by creating minimal air dilution \cite{2}.

It can more accurately deliver prescribed oxygen concentrations at high flows, providing both versatility and continuity of care as patients wean or their condition becomes more acute. This greater flexibility eliminates the need to switch between oxygen delivery systems \cite{3}.

It has other benefits as well, such as flushing of the anatomical dead space of the upper airway by the high incoming gas flows. This creates a reservoir of fresh gas available for each and every breath, minimizing the rebreathing of CO\textsubscript{2} \cite{4}.

In addition, the NHF can deliver optimal humidity, which emulates the balance of temperature and humidity that occurs in healthy lungs, maintaining mucociliary clearance. This is important for patients with secretion problems, such as those with chronic obstructive pulmonary disease (COPD). By delivering optimal humidity, drying of the airway is reduced, which maintains the function of the mucociliary transport system, clearing secretions more effectively and reducing the risk of respiratory infection \cite{5}.

Aim

The aim of this study was to evaluate the efficacy of a nasal optiflow device in the management of COPD patients with acute exacerbations in comparison with a conventional venturi mask (VM).

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Evaluation of nasal optiflow device
Saeed et al.

The optiflow device
This system basically works with an air oxygen blender allowing from 21 to 100% FIO₂ and generates a flow rate up to 60 l/min, but most patients in our study are put on a flow rate of 10 l/min and FIO₂ ranging between 35 and 60%. The gas is heated and humidified through an active heated humidifier and delivered through a single limb heated inspiratory circuit (to avoid heat loss and condensation) to the patient through a nasal cannula of large diameter [8].

The study endpoint was weaning success, need for intubation and mechanical ventilation, and occurrence of complications (Fig. 1).

Statistical analysis
The collected data were revised, coded, tabulated, and analyzed with an IBM computer using statistical package for the social sciences (SPSS, version 12; SPSS Inc., Chicago, Illinois, USA). Data were presented and appropriately analyzed according to the type of data obtained for each parameter.

Descriptive statistics
(1) The mean ± SD, median, and minimum and maximum values (range) were determined for quantitative variables.
(2) Qualitative variables were presented as number and percentage.

Analytical statistics
(1) The χ₂-test was used to compare qualitative variables between two groups.
(2) The unpaired t-test was used to compare quantitative variables in parametric data (SD < 50% mean).
(3) The paired t-test was used to compare quantitative variables in the same group.
(4) The Spearman correlation coefficient test was used to rank variables positively or inversely [9].

Patients and methods
The study was conducted on 45 patients diagnosed with COPD according to GOLD [6], who presented with acute exacerbations and were admitted to the respiratory ICU in Abbasia Chest Hospital during the period between February 2014 and August 2014. All patients were diagnosed (on the basis of clinical and arterial blood findings) as having respiratory failure type II necessitating oxygen therapy and were classified into two groups:

(1) First group included 20 randomly selected COPD patients with acute exacerbations connected to a VM.
(2) Second group included 25 randomly selected COPD patients with acute exacerbations given NHF oxygen by means of an optiflow system.

Inclusion criteria were as follows:
To be included in the study the participants had to be COPD patients with acute exacerbations, with respiratory failure, admitted to the respiratory ICU.

Exclusion criteria were as follows:
(1) Presence of other chest diseases such as bronchial asthma, pulmonary tuberculosis, interstitial lung diseases, pulmonary embolism, and pneumonia.
(2) Presence of any organ failure such as cerebrovascular stroke, heart failure, hepatic cell failure, and renal failure.
(3) Having a disturbed conscious level.

All patients were subjected to the following:
(1) Full history taking, including of their relatives.
(2) Clinical examination, including:
   (a) General and local chest, cardiac, abdominal, and neurological examination.
   (b) Routine laboratory investigations.

These included:
(1) Random blood sugar.
(2) Serum electrolytes.
(3) Kidney and liver function tests.
(4) Complete blood picture.
(5) Plain chest radiography.
(6) ECG.
(7) Repeated arterial blood gases (ABGs).

Venturi mask
This comes in a kit that includes five to seven interchangeable air entrainment devices used to achieve an inspired oxygen concentration between 24 and 60%, depending on the manufacturer, and flow ranging between 2 and 15 l/min [7].

(a) Nasal optiflow device. (b) Venturi mask.
Results

This study was conducted on 45 COPD patients who presented with acute exacerbation necessitating oxygen therapy. Patients were classified into two groups; the first group included 20 patients connected to a VM, whereas the second group included 25 patients connected to NHF oxygen by means of an optiflow device.

There was no statistically significant difference between the two studied groups as regards general data. The mean age of the VM group was 60.7 years (about 75% of patients were male and 25% were female), whereas the mean age of the NHF group was 60 years (about 92% of patients were male and 8% were female) (Table 1).

There were no statistically significant differences between the studied groups as regards general examination for blood pressure, cyanosis, jaundice, pulse, lower limb (LL) edema, and neck veins.

No statistically significant differences were found between the studied groups as regards blood gases at admission, on the basis of the unpaired t-test (Table 2).

No statistically significant differences were found between the studied groups as regards blood gases on day 1 on the basis of the unpaired t-test (Table 3).

PH was seen to be increased and PCO$_2$ to be reduced, whereas PO$_2$ and SO$_2$ were increased, with highly significant statistical difference, on the paired t-test (Table 4).

pH, PO$_2$, SO$_2$, HCO$_3^-$, and base excess (BE) were raised with highly significant statistical difference, whereas PCO$_2$ was reduced with statistically significant difference, on using the paired t-test (Table 6).
Table 5 Comparison between the results at admission and on day 1 as regards blood gases in the nasal high flow group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Admission</th>
<th>Day 1</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.30 ± 0.05</td>
<td>7.33 ± 0.05</td>
<td>3.727</td>
<td>&lt;0.001 (HS)</td>
</tr>
<tr>
<td>PCO₂</td>
<td>72.5 ± 12</td>
<td>69.4 ± 11</td>
<td>1.7</td>
<td>&gt;0.05 (NS)</td>
</tr>
<tr>
<td>PO₂</td>
<td>33.7 ± 7.7</td>
<td>61 ± 5.6</td>
<td>10</td>
<td>&lt;0.001 (HS)</td>
</tr>
<tr>
<td>HCO₃</td>
<td>34.4 ± 4</td>
<td>35.4 ± 5</td>
<td>1.2</td>
<td>&gt;0.05 (NS)</td>
</tr>
<tr>
<td>BE</td>
<td>7.6 ± 1.5</td>
<td>9.2 ± 1.8</td>
<td>1.5</td>
<td>&gt;0.05 (NS)</td>
</tr>
<tr>
<td>SO₂</td>
<td>0.57 ± 0.13</td>
<td>0.88 ± 0.1</td>
<td>9.7</td>
<td>&lt;0.001 (HS)</td>
</tr>
</tbody>
</table>

HS, highly significant.

Variable Title

Table 6 Comparison between the results at admission and on day 2 in the venturi mask group

<table>
<thead>
<tr>
<th>Variables</th>
<th>Admission</th>
<th>Day 2</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.28 ± 0.07</td>
<td>7.35 ± 0.07</td>
<td>4.858</td>
<td>&lt;0.001 (HS)</td>
</tr>
<tr>
<td>PCO₂</td>
<td>80.3 ± 10</td>
<td>72 ± 7</td>
<td>2.4</td>
<td>&lt;0.05 (S)</td>
</tr>
<tr>
<td>PO₂</td>
<td>38.1 ± 8</td>
<td>60.3 ± 5</td>
<td>8</td>
<td>&lt;0.001 (HS)</td>
</tr>
<tr>
<td>HCO₃</td>
<td>34.5 ± 7</td>
<td>38.8 ± 4</td>
<td>2.2</td>
<td>&lt;0.05 (S)</td>
</tr>
<tr>
<td>BE</td>
<td>8.6 ± 2.3</td>
<td>13.5 ± 6</td>
<td>3.4</td>
<td>&lt;0.001 (HS)</td>
</tr>
<tr>
<td>SO₂</td>
<td>0.62 ± 0.3</td>
<td>0.88 ± 0.2</td>
<td>7.8</td>
<td>&lt;0.001 (HS)</td>
</tr>
</tbody>
</table>

HS, highly significant; S, significant.

pH was seen to be increased, PCO₂ to be reduced, and SO₂, PO₂, and base excess (BE) to be increased with statistically significant difference on using the paired t-test (Table 7).

PCO₂ was found to be higher in the VM group with statistically significant difference between the two groups on using the unpaired t-test; there was no significant difference as regards other variables (Table 8).

PCO₂ was found to be reduced, whereas pH, PO₂, BE, and SO₂ were found to be increased, with statistically significant difference on using the paired t-test (Table 9).

PCO₂ was found to be reduced with statistically significant difference, whereas pH, PO₂, and SO₂ were found to be increased with highly statistically significant difference, on using the paired t-test (Table 10).

No statistically significant difference was found between the two groups as regards blood gases 1 h after weaning on a nasal prong, on using the unpaired t-test (Table 11).

No statistically significant difference was found between the two groups as regards the outcome, on using the χ²-test. In the VM group 14 (70%) patients were successfully weaned on a nasal prong, whereas five (25%) patients were mechanically ventilated and one (5%) patient was put on noninvasive mechanical ventilation; two (10%) patients from those ventilated patients died. In the NHF group 16 (64%) patients were successfully weaned on a nasal prong, whereas five (20%) patients were mechanically ventilated and four (16%) were put on noninvasive mechanical ventilation. One (4%) patient from those ventilated died (Table 12).
A highly significant statistical difference was found between the two groups regarding the duration of stay in the ICU on using the unpaired \( t \)-test. The mean duration was longer in the VM group (3.1 ± 1.25 days) compared with the NHF group (1.52 ± 1.1 days) (Table 13).

No significant correlation was found between FIO\(_{2}\) and flow of \( O_2 \) of the VM versus blood gases on the Spearman correlation test (Table 14).

No significant correlation was found between FIO\(_{2}\) and flow of \( O_2 \) of NHF versus blood gases on the Spearman correlation test (Table 15).

**Discussion**

Recently, a new therapy that provides humidified high-flow oxygen through a nasal cannula (HFNC) has been introduced as an alternative for the treatment of spontaneously ventilating patients with high oxygen requirements [3].

Our study was conducted in the respiratory ICU of Abbasia Chest Hospital and included 45 patients admitted with an acute exacerbation of COPD with respiratory failure, who were divided into two groups: the first group included 20 patients who were connected to a VM, whereas the second group included 25 patients who were connected to NHF oxygen by means of an optiflow device.

The first group included 16 male and four female patients with a mean age of 60.7 ± 7 years, but the second group included 23 male and two female patients with a mean age of 60 ± 5 years, with no statistically significant difference between the two groups regarding age and sex. This result was in agreement with that of Charles *et al.* [10] who reported a mean age of 69.4 ± 9.2 years in their study. Lenglet *et al.* [11] reported a median age of 64 (46–84.7) years in their study.

Similar results were also seen in other studies such as those by Sztrymf *et al.* [12] and Roca *et al.* [13], who reported mean ages of 59 (38–73) and 57 (40–70) years, respectively.

The mean age in this study was higher than that in the study by Bräunlich *et al.* [14], who reported a mean age of 18–64 (32.8 ± 13.6) years. This difference may be because of the different diagnosis of patients [COPD and interstitial pulmonary fibrosis] in the study by Bräunlich and colleagues.

In the current study, an analysis of the ABGs during conventional oxygen therapy (VM) showed that the mean pH was significantly increased from 7.28 (7.28 ± 0.07) to 7.40 (7.40 ± 0.07), PaO\(_2\) was increased significantly from 38.1 (38.1 ± 8) to 62.6 (62.6 ± 7), and \( O_2 \) saturation was increased significantly from 62 (0.62 ± 0.3) to 91 (0.91 ± 0.02)%, whereas PaCO\(_2\) was significantly reduced from 80.3 (80.3 ± 10) to 66.8 (66.8 ± 11). During NHF, the analysis of ABGs showed that the mean pH was increased significantly from 7.30 (7.28 ± 0.05) to 7.39 (7.39 ± 0.04), PaO\(_2\) was increased significantly from 33.7 (33.7 ± 7.7) to 60.79 (60.79 ± 15.9), and \( O_2 \) saturation was increased significantly from 57 (0.57 ± 0.13) to 89 (0.89 ± 0.02)%; PaCO\(_2\) was reduced significantly from 72.5 (72.5 ± 12) to 55.6 (55.6 ± 0.7). Thus, it is clear that PaCO\(_2\) was significantly reduced in the NHF group, whereas PaO\(_2\) was significantly increased.

**Table 12 Comparison between both groups as regards outcome**

<table>
<thead>
<tr>
<th>Variables</th>
<th>N (%)</th>
<th>Test</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>VM (n = 20)</td>
<td>NHF (n = 25)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Outcome details | |          |
|-----------------|------------------|
| Nasal prong     | 14 (70)          | 16 (64)          | Fisher exact test |
| Mechanical ventilation | 5 (25)          | 5 (20)          |
| Noninvasive mechanical ventilation | 1 (5)          | 4 (16)          |
| Death           | 2 (10)           | 1 (4)           |
| Weaning outcome | Failed           | 6 (30)           | Fisher exact test |
|                 | Success          | 14 (70)          |        |

NHF, nasal high flow; VM, venturi mask.

**Table 13 Comparison between both groups as regards the duration of stay in the ICU**

<table>
<thead>
<tr>
<th>Variables</th>
<th>VM (n = 20)</th>
<th>NHF (n = 25)</th>
<th>( T )</th>
<th>( P )</th>
</tr>
</thead>
</table>

| Duration ICU | 3.1 ± 1.25 | 1.52 ± 1.1 | 4.533 | <0.001 (HS) |

HS, highly significant; NHF, nasal high flow; VM, venturi mask.

**Table 14 Correlation between FIO\(_{2}\) and flow with arterial blood gas parameters in the venturi mask group**

<table>
<thead>
<tr>
<th>Variables</th>
<th>FIO(_{2})</th>
<th>Flow</th>
<th>( R )</th>
<th>( P)-value</th>
<th>( R )</th>
<th>( P)-value</th>
</tr>
</thead>
</table>

| Average pH | -0.176     | 0.459 | -0.256 | 0.277 |
| Average PCO\(_{2}\) | 0.242 | 0.304 | 0.358 | 0.121 |
| Average PO\(_{2}\) | 0.182     | 0.443 | 0.400 | 0.080 |
| Average HCO\(_{3}\) | 0.104     | 0.664 | 0.094 | 0.692 |
| Average BE | 0.052     | 0.828 | 0.058 | 0.808 |
| Average SO\(_{2}\) | 0.034     | 0.887 | 0.170 | 0.474 |

**Table 15 Correlation between FIO\(_{2}\) and flow with arterial blood gas parameters in the nasal high flow group**

<table>
<thead>
<tr>
<th>Variables</th>
<th>FIO(_{2})</th>
<th>Flow</th>
<th>( R )</th>
<th>( P)-value</th>
<th>( R )</th>
<th>( P)-value</th>
</tr>
</thead>
</table>

| Average pH | -0.279     | 0.176 | 0.03  | 0.885 |
| Average PCO\(_{2}\) | 0.072 | 0.732 | 0.245 | 0.238 |
| Average PO\(_{2}\) | 0.14     | 0.504 | 0.137 | 0.512 |
| Average HCO\(_{3}\) | -0.049    | 0.814 | 0.388 | 0.056 |
| Average BE | -0.14     | 0.503 | 0.369 | 0.07 |
| Average SO\(_{2}\) | -0.01     | 0.962 | -0.057 | 0.788 |

NHF, nasal high flow; VM, venturi mask.
significantly higher in the VM group than in the NHF group. In contrast, there was no significant difference between the two groups with respect to pH, PO₂, and O₂ saturation. These results were in agreement with those of Makowski et al. [15], who evaluated the efficacy of a NHF device and enrolled 55 (75.93%) patients; 42 patients with respiratory failure type I and 13 (24.07%) patients with respiratory failure type II. They reported that NHF was associated with significant decline in PCO₂ only after 3 days ($P < 0.05$), with significant improvement in O₂ saturation, PaO₂, and significantly increased pH ($P < 0.05$).

Sztrymf et al. [16] reported significant increase in PaO₂ in 38 patients with acute respiratory failure after 1 h with NHF in comparison with baseline ($141 \pm 106$ vs. $95 \pm 40$ mmHg, respectively; $P = 0.009$).

Peters et al. [17] studied 50 ICU patients with hypoxemic respiratory distress using NHF (including 12 COPD patients) with pH more than 7.28 and CO₂ less than 65 mmHg and found a significant increase in mean O₂ saturations from 89.1 to 94.7% ($P < 0.001$).

These results were in agreement with those of Lenglet et al. [11], whose study was conducted on 17 patients with acute respiratory failure to evaluate the efficacy of NHF in Emergency Department of University Hospital (France). They found that PaO₂ increased significantly from 61 (56–74) to 129 (96–194) mmHg, and O₂ saturation increased significantly from 90 (88.5–94) to 97 (92.5–100)% ($P < 0.001$). However, in contrast to our study there were no significant changes between the baseline value and that after using NHF with regard to pH [7.40 (7.35–7.44) vs. 7.42 (7.35–7.44), respectively] and PaCO₂ [40 (34.5–47) vs. 40 (35.5–46) mmHg, respectively]. This difference might be because all patients in the study by Lenglet and colleagues had respiratory failure type I.

Parke et al. [18] evaluated NHF oxygen versus usual oxygen therapy and demonstrated that mean PaCO₂ was significantly lower in the NHF group (NHF 39.75 mmHg group vs. 41.25 mmHg usual care, $P = 0.03$); however, in contrast to our study, O₂ saturation was higher in the usual oxygen therapy group compared with the NHF group in 340 postcardiac surgical patients over 14 months in the cardiothoracic and vascular ICU (New Zealand). This difference might be because of the unrecognized oxygen devices used other than NHF.

Similar findings were obtained by Bräunlich et al. [14] in a study conducted in University Hospital of Leipzig (Germany). They found that NHF was associated with significant fall in PCO₂, from 55.65 ± 0.81 to 50.48 ± 0.69 mmHg in 20 COPD patients and from 51.54 ± 0.7 to 47.93 ± 0.53 mmHg in 20 interstitial pulmonary fibrosis patients with hypercapnia.

In contrast to our study, there was no significant change between the NHF and VM groups as regards O₂ saturation. Sarkisian-Donovan et al. [19] reported that NHF was associated with significantly increased O₂ saturation, from 88 (78–95) to 97 (90–100)% ($P = 0.000004$), when compared with traditional oxygen therapy (VM or nonrebreathing mask) in 29 patients with respiratory insufficiency. This difference may be due to unclear variable adjustment of flow and FIO₂ or frequent displacement of the mask.

Taft et al. [20] compared NHF oxygen versus conventional oxygen therapy (including nasal cannula, VM, face mask, and nonrebreathing mask) in 49 patients with impending respiratory failure and found that NHF was associated with significant improvement in oxygenation, as O₂ saturation on conventional oxygen therapy increased to 88.9 ± 4.98 versus 96.5 ± 2.78% on NHF oxygen ($P < 0.001$). This difference may be because most patients had respiratory failure type I.

Roca et al. [21] compared NHF oxygen with a conventional VM in 10 ICU patients with respiratory failure. An analysis of ABG after 30 min on oxygen therapy revealed the following values between VM and HFNC, respectively: mean pH 7.40 (7.37–7.46) versus 7.43 (7.37–7.48); PaO₂ 107 (69–145) versus 195 (177–243); PaCO₂ 39 (33–47) versus 38 (34–46); HCO₃⁻ 23.5 (20.3) versus 23.5 (21.7–29.0); and O₂ saturation 96 (91–98) versus 99 (98–99). There was no statistical difference in PCO₂ ($P = 0.718$); NHF was associated with significant increase in O₂ saturation ($P = 0.012$), but this study was similar to ours in that there was no statistical difference in pH ($P = 0.168$). This difference may be explained by the relatively small number of patients upon whom this study was conducted (only 10 patients). Idone et al. [22] conducted a study on 35 patients (18 NHF and 17 VM) needing high-flow oxygen in Università Cattolica del Sacro Cuore (Roma, Italy) to compare NHF with VM and noted that oxygen desaturations were more frequent with VM. This difference was explained by intolerance and frequent displacement of the VM in their study.

Also, Antonicelli et al. [23], whose study was conducted on 75 postextubated critically ill patients to compare NHF (40 patients on NHF) with VM (35 patients on VM) in ‘Agostino-Gemell’ University Hospital (Rome,
Italy), reported that PO₂ was higher in the NHF group than in the VM group (317 ± 78 vs. 253 ± 84 at 24 h; \( P < 0.01 \)). Oxygen desaturations were more frequent with the VM than with NHF, but PaCO₂ was similar in the two groups, with no statistical difference. This difference was explained by the fact that discomfort and interface displacement were more frequent with VM than with NHF in their study (70 vs. 30% patients; \( P < 0.01 \)).

The study by Riesen et al. [24], which enrolled 14 patients with hypoxic respiratory failure to compare NHF oxygen with conventional oxygen therapy via a VM or noninvasive ventilation (NIV) in University Hospital Tübingen (Germany) using a FIO₂ of 0.6, reported that there was significant increase in PO₂ that was highest under NIV (129 ± 38 mmHg), followed by NHF (101 ± 34 mmHg; \( P < 0.01 \) vs. NIV) and finally VM (85 ± 21 mmHg), with no significant difference in PCO₂. However, similar to our study, there was no significant difference in pH between the three groups. This difference might be because patients had respiratory failure type I.

Also in contrast to our study is that by Sztrymf et al. [12], who reported that NHF was associated with a significant increase in oxygen saturation as measured by pulse oximetry [93.5 (90–98.5) vs. 98.5 (95.5–100)%; \( P = 0.0003 \)], significantly increased PaO₂ [from 65.5 (53.5–83.5) to 114.5 (72.5–192) mmHg; \( P = 0.001 \)], and moderately increased PaCO₂ [from 39.5 (32.5–42.5) to 43 (36–46.5) mmHg; \( P = 0.005 \)]. However, it is similar to ours in that there was no significant change in pH in 20 patients with acute respiratory failure in the ICU on comparing NHF oxygen with conventional oxygen therapy. This difference may be because of the ineffectiveness of unrecognized oxygen therapy and because patients might have had respiratory failure type I.

In the current study, failure in weaning was seen in six (30%) patients in the first group (VM); five (25%) patients required mechanical ventilation and one (5%) patient required noninvasive mechanical ventilation (NIV). Among them two (10%) patients died. In the second group (NHF), failure in weaning was seen in nine (36%) patients; five (20%) patients required mechanical ventilation and four (16%) patients required noninvasive mechanical ventilation. Among them one (4%) patient died. Successful weaning was seen in 14/20 (70%) patients of the first group (VM) and in 16/25 (64%) patients in the second group (NHF), with no significant difference between the two groups.

These results were in agreement with those of Sztrymf et al. [16], in whose study nine of 38 (23.5%) patients failed on NHF and required invasive mechanical ventilation.

In addition, in the study by Sztrymf et al. [12] six of 20 (30%) patients were intubated and three patients died in the ICU (mortality rate 15%).

But these results were better than those of Lenglet et al. [11], in whose study in university hospital's emergency department 10/17 (59%) patients were successfully weaned from HFNC; however, seven (41%) patients required invasive mechanical ventilation and six (35%) patients died. This difference might be explained by the uncooperation and intolerance of patients in their study.

Also Roca et al. [21] found that 50% (5/10) of the patients using nasal optiflow devices required intubation. This difference may be because of the relatively small number of patients upon which this study was based.

In the study by Sarkisian–Donovan et al. [19] and Taft et al. [20] no patients using high-flow oxygen therapy required noninvasive or invasive ventilation. This difference may be because our patients had respiratory failure type II and were prone to developing severe hypercapnia and respiratory acidosis or to have a disturbed conscious level and hence require intubation and mechanical ventilation.

As regards the duration of stay in the ICU, in our study a significantly long duration was seen in the VM group [3.1 (3.1 ± 1.25) days] compared with the NHF group [1.52 (1.52 ± 1.1) days].

The length of ICU stay in this study is nearly similar to that seen in the study by Peters et al. [17], who found that the median duration of stay among patients with NHF was 1.25 (range 0.8–6) days. Our results were also similar to those of Sztrymf et al. [12], who saw a median duration of stay among patients on NHF of 1.04 (0.7–5) days or 26.5 (17–121) h.

The length of stay of patients on NHF in the study by Sztrymf et al. [16] was longer than that of our study, with a mean duration of 2.8 (2.8 ± 1.8) days with a maximum of 7 days. This difference may be because of the severe condition of the patients included in their study.

The length of stay of patients with NHF was 0.6 (0.17–1.4) days or 13.5 (4–34.5) h in the study by Lenglet et al. [11]. This difference may be because their study was conducted in the emergency department.

In the current study, the most important complication in patients with NHF was the intolerance to NHF, which was seen in four (16%) patients due to the heavy circuit of the device and high temperature of the
humidifier (37°C, 44 mg/l). The other complications that occurred with both devices, which were the causes of failure and intubation, were similar, and included disturbed conscious level, elevated CO₂ retention, progressive hypoxia, and greater respiratory distress, with no statistically significant differences between the two groups.

These findings are similar to those of Sarkisian-Donovan et al. [19], who reported that one patient required a reduction in the temperature of the device to 36°C.

Roca et al. [13] reported that one patient found the gas temperature to be too high.

These findings were in contrast to those of Richard et al. [25] whose study was conducted on 20 patients with respiratory failure in the University Department of Respiratory Medicine, St Vincent’s Hospital (Ireland). They found that two patients refused the VM because of discomfort and intolerance to the mask. This difference may be explained by the optimal humidity associated with NHF.

Idone et al. [22] reported that there was an improvement in discomfort with NHF, particularly with respect to dryness of the mouth. Oxygen desaturation and interface displacement requiring an intervention were more frequent with the VM. This difference may be attributed to the optimal humidity associated with NHF.

In this study, there was no significant correlation between FIO₂ and flow of O₂ versus the change in blood gases in the VM group or in the NHF group.

The result in this study was in contrast to those of Bräunlich et al. [14] who conducted their study in the University of Leipzig (Germany) on 16 COPD patients and found that PCO₂ decreases with NHF rate, as high-flow nasal prong leads to improved PCO₂ in comparison with low-flow nasal prong. It was suggested that PCO₂ improvement was more likely to be caused by constant flushing of the upper respiratory tract.

Therefore, in the present study, despite the high cost, heavy circuit, and the need for periodic examination, the nasal optiflow device achieved a success rate of 64% in the management of COPD patients with respiratory failure type II, which is approximately similar to that of the VM, which achieved a success rate of 70%.

(2) The nasal optiflow device is not indicated for patients with unstable COPD or for patients with acute hypercapnia and pH of less than or equal to 7.25 because of the higher probability of NHF failure.

(3) The nasal optiflow device is highly costly compared with the VM because of its high price and the need for periodic examination of the device by an experienced engineer and the need for changing the oxygen sensor every 2 years. This high cost makes it unsuitable for a poor country like Egypt, especially as its success rate is almost similar to that of the VM, which is cheaper.

The main benefit in the clinical use of NHF is the effective humidification, although it is associated with a variable degree of inadequate tolerance due to heaviness of its circuit and high temperature of the humidification (37°C, 44 mg/l).

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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12 Sztymf B, Messika J, Mayot T, Lenglet H, Dreyfuss D, Ricard JD. Impact of high-flow nasal cannula oxygen therapy on intensive care unit patients
Study of serum C-reactive protein level and sputum eosinophils in patients with bronchial asthma
Abdelsadek H. Al-Aarag\textsuperscript{a}, Abeer M. Rawy\textsuperscript{a}, Mona M. EL-Behissy\textsuperscript{b}, Marwa M. Abdelraheem\textsuperscript{a}

\textbf{Background} Asthma is a chronic inflammatory disorder of the airways in which many cells play a role, in particular mast cells, eosinophils, and lymphocytes. It is a major chronic airway disorder that poses a serious public health problem worldwide. C-reactive protein (CRP) is used mainly as a marker of inflammation.

\textbf{Aim of the work} This study aims to clarify the relationship between serum CRP, sputum eosinophils, and the degree of airway inflammation in asthmatic patients (stable or in exacerbation) for use as a prognostic marker in detecting the severity of the disease.

\textbf{Participants and methods} The study was carried out on 60 patients who were admitted to the chest department, Benha University Hospital. They were divided into two groups: 40 patients with bronchial asthma (20 patients with controlled asthma and 20 patients with exacerbated asthma) and 20 apparently healthy individuals. Patients and controls were subjected to a full assessment of history and clinical examination. Spirometry, serum CRP level, and sputum eosinophil count were measured in asthmatic patients and in healthy control individuals.

\textbf{Results} Serum CRP was significantly increased in 85\% of patients with acute exacerbation, whereas only 30\% of patients with controlled asthma showed increased serum CRP. Its level was markedly increased during exacerbation. The sputum eosinophil count was highly increased in the exacerbated asthma group and 25\% of patients in the controlled asthma group. There was a negative correlation between CRP, forced expiratory volume in the first second (FEV\textsubscript{1}), FVC, and FEV\textsubscript{1}/FVC and a highly significant positive correlation with sputum eosinophils.

\textbf{Conclusion} There is an association between airway inflammation in bronchial asthma and increased level of CRP and sputum eosinophils. \textit{Egypt J Broncho} 2015 9:43–47 © 2015 Egyptian Journal of Bronchology.

\textbf{Keywords:} bronchial asthma, C-reactive protein, forced expiratory volume in the first second, sputum eosinophils

\textsuperscript{a}Departments of Chest, \textsuperscript{b}Clinical and Chemical Pathology, Faculty of Medicine, Benha University, Banha, Egypt

Correspondence to Abeer M. Rawy, MD, Department of Chest, Faculty of Medicine, Benha University, Banha, Egypt
Tel: 00201001756638; e-mail: abeer Rawy@yahoo.com

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Introduction
Asthma is an inflammatory disorder of the airways that involves several inflammatory cells and multiple mediators that result in characteristic pathophysiological changes. The airway inflammation in asthma is persistent even though symptoms are episodic [1]. Two main mechanisms have been identified that underlie airway obstruction in experimental asthma. The first, type I hypersensitivity, is principally an antibody-mediated reaction. The second mechanism that contributes toward airway obstruction, type IV hypersensitivity, also crucially involves Th2 cells [2].

Eosinophils are present in increased numbers in the airways, and release basic proteins that may damage airways epithelial cells. They may also play a role in the release of growth factors and airway remodeling [3,4]. Two-thirds of patients with mild to moderate asthma are reported to have increased sputum eosinophils [5]. Blood eosinophilia is known to be an indirect marker of airway inflammation in asthma [6].

C-reactive protein (CRP) is one of the acute-phase reactants whose levels increase in response to inflammation; thus, it is a marker of airway inflammation. Its synthesis by the liver is regulated to a large extent by the proinflammatory cytokine interleukin-6 [7,8]. Increased CRP levels have been associated with many conditions such as cardiovascular diseases, obesity, smoking, and diet/nutritional state [9]. It is a powerful predictor of adverse cardiovascular events. Respiratory impairment is also associated with cardiovascular events [8,10]. Al-Aarag \textit{et al.} [11] reported elevated levels of CRP in chronic obstructive pulmonary disease patients without clinically relevant ischemic heart diseases (IHD) and independent of cigarette smoking. CRP is associated negatively with indices of pulmonary function and associated positively with sputum eosinophils in steroid-naive asthmatics, but not in those treated with steroids [11]. The association between asthma and CRP is by no means clear. A recent population-based study showed associations of increased levels of serum CRP with a high frequency of bronchial hyperresponsiveness (BHR) [12,13].
The aim of this study was to clarify the relationship between serum CRP and sputum eosinophils in asthmatic patients, either stable or in exacerbation, and also its relation to the respiratory impairment measured by pulmonary function tests (PFT) for use as a prognostic marker in detecting the severity of the disease.

**Patients and methods**

This study was carried out on 60 individuals, 20 men and 40 women. They were divided into 40 patients with bronchial asthma and 20 healthy individuals as a control group. The patients were admitted in the chest department of Benha University Hospital in the period between March 2011 and March 2012. They were divided into three groups: group I included 20 patients with controlled bronchial asthma, two men and 18 women. Their ages ranged from 20 to 40 years, mean age 36.1 ± 7.50 years. Group II included 20 patients with bronchial asthma on exacerbation, six men and 14 women, ranging in age from 20 to 45 years, mean age 32.8 ± 8.89 years. Group III included 20 healthy individuals, 12 men and eight women, ranging in age from 25 to 48 years, mean age 36.1 ± 7.32 years.

According to GINA 2011 [14], controlled asthma was defined as the need for rescue medications twice or less a week (short-acting β2-agonists), no limitation of daily activity, no nocturnal symptoms, twice or less a week, daytime symptoms, and forced expiratory volume in the first second (FEV1)% greater than 80% predicted. There were no exacerbations and no use of systemic steroids in the previous 12 months. Acute asthma exacerbation was defined as dyspnea and wheezing with or without increased coughing [15]. Patients were excluded if they were smokers, had respiratory infection within the month preceding the study, a rheumatologic illness, malignancy, diabetes, heart failure, a history of venous embolisms, coronary heart disease, and liver or kidney diseases (diseases that may result in elevation of CRP levels) [16].

The diagnosis and classification of asthma were performed according to GINA guidelines (2011) [14]. Informed consent was obtained from all the patients before enrollment. They all underwent a full clinical examination, pulmonary function tests (FEV1 before and after salbutamol inhalation), sputum and blood sampling for sputum eosinophil count, and measurement of serum CRP. Normal volunteers were also enrolled in the study as healthy controls. None of them had any history of lung or allergic disease and were not using any medication. They had a normal lung function test (FEV1 >80%). All participants were submitted to a full assessment of history, clinical examination, chest radiography (posteroanterior view), pulmonary function tests, assessment of serum CRP, sputum for eosinophils and others (echocardiography, complete blood count, liver and kidney function tests, and fasting blood sugar).

Pulmonary function tests were performed using Sensor-medics V max series, 2130 spirometer, V6200 Autobox, 6200DL. (Sensor Medics Corporation, 22705 Savi Ranch Parkway Yorba Linda, 92887-4645 California, USA). Short-acting bronchodilators were stopped at least 8 h before the test. Dynamic spirometry was performed by measurement of FEV1% predicted according to the standards of the European Respiratory Society [17]. The highest value of FEV1 of three forced expiratory maneuvers was used.

**Blood sampling**

Fresh serum samples (stable 7 days at 2–8°C or 3 months at −20°C) were centrifuged in the presence of fibrin before testing. The CRP-latex agglutination test was used for the qualitative and semiquantitative detection of the CRP in human serum. Latex particles coated with IgG anti-human CRP were agglutinated when mixed with samples containing CRP. The CRP-latex sensitivity was calibrated to the Reference material CRM 470/RPPHS.

**Sputum induction and processing**

Sputum was collected either spontaneously or induced with hypertonic saline nebulization from all participants. Before sputum induction, patients inhaled 200 µg of salbutamol to minimize bronchoconstriction during the induction procedure. Sputum was induced by inhalation of a 3% hypertonic saline solution for 5 min (DeVilbiss 65 ultrasonic nebulizer; DeVilbiss, Somerset, Pennsylvania, USA), and the participants were encouraged to cough and expectorate sputum into sterile containers between each dose of nebulized saline. This procedure continued until an adequate sample containing more than 0.5 ml visible mucoid material was obtained. If a satisfactory sputum sample was not obtained at the time the FEV1 had decreased more than 20% compared with the baseline values occurred or if troublesome symptoms appeared, the procedure was stopped [17]. Nebulization with 4.5% saline was continued for 4-min periods once the FEV1 had returned to within 10% of the baseline.

Sputum was selected from saliva and was treated by adding four volumes of 0.1% dithiothreitol (DTT-sputolysin 10%; Calbiochem Corp., La Jolla, California, USA) and mixed by rotating for 30 min at 37°C, followed by four volumes of PBS. The suspension was filtered through a 60 mm nylon gauze (Millipore,
North Ryde, New South Wales, Australia) and the total cell count of leukocytes and viability was determined. The cell suspension was centrifuged at 200 g for 10 min and the supernatant was aspirated and stored at −70°C. The cell pellet was resuspended in PBS to obtain a concentration of 1 × 10^6 cells/ml and 70 ml was placed in cups of a Shandon III cytocentrifuge (Shandon Cytospin, Sewickey, Pennsylvania, USA) for slide preparation. An adequate sample is defined as less than 50% squamous cells. The eosinophil and neutrophil counts are then expressed as a percentage of the total cell count as it is more accurate than the absolute count [18].

Statistical analysis
The values were reported as mean ± SD. For statistical analysis between two groups, the χ²-test was used. The levels of each marker were compared between the study groups and the control group using SPSS computer package. (SPSS Inc., 233 South Wacker Drive, 11th Floor, Chicago, USA). P values of less than 0.05 were considered significant (Rosner, 1988) [19].

Results
Patients’ demographic and laboratory data are presented in Table 1.

CRP was significantly higher (P < 0.001) in asthmatic patients compared with the control group. Overall, 30% of the patients in the controlled asthma group and 85% of patients with exacerbated asthma had increased levels of CRP, whereas the healthy group had normal levels of CRP. There was a highly significant difference in CRP between the three groups Tables 2 and 3.

Sputum eosinophils were found in all cases of asthma during exacerbation, whereas only five of patients with stable controlled asthma had positive eosinophils in their sputum. None of the healthy control participants had eosinophils in their sputum as shown in Table 4.

Pulmonary function tests: it was found that FEV₁, FVC, and FEV₁/FVC were significantly decreased in all patients with asthma exacerbation in relation to the stable asthma group and the healthy group (Table 5). There were highly significant positive correlations between CRP and leukocytosis, erythrocyte sedimentation rate (ESR), a significant positive correlation between CRP and both eosinophils% and peak expiratory flow (PEF), and a highly significant negative correlation between CRP and FEV₁ and FVC. No significant negative correlation was found between CRP and FEV₁/FVC (Table 6).

Discussion
It is well known that CRP increases during infection and autoimmune disorders [19]. A positive relationship has been reported between elevated CRP levels and current asthma [20,21], respiratory impairment [22], and BHR [23]. In recent years, there have been some reports on the measurements of serum levels of Hs-CRP as a useful tool for the detection of systemic inflammation in asthma [24–26].

Eosinophil inflammation is a hallmark feature of asthma [27]. Eosinophils play a crucial role in the pathogenesis and course of asthma as most allergic and nonallergic asthmatic patients, including those of mild asthma, have a bronchial eosinophilia and there is a significant association between eosinophils and severity of asthma as well as BHR [28].

For this reason, several studies were carried out to determine the relationship between asthmatic patients, CRP, and sputum eosinophils [20–30].

In the present study, high serum levels of CRP were related strongly to asthma exacerbation, whereas lower levels of CRP were observed in stable asthma. The difference in CRP was very significantly higher during exacerbation than in stable asthma patients and control individuals. These results were in agreement with other

Table 1 Patients’ demographic data

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age (years) (mean ± SD)</th>
<th>Sex (male/female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled asthma</td>
<td>36.1 ± 7.50</td>
<td>2/18</td>
</tr>
<tr>
<td>Exacerbated asthma</td>
<td>32.8 ± 8.89</td>
<td>4/16</td>
</tr>
<tr>
<td>Healthy participants</td>
<td>36.1 ± 7.32</td>
<td>12/8</td>
</tr>
</tbody>
</table>

Table 2 Percentage of positive C-reactive protein in the groups studied

<table>
<thead>
<tr>
<th>CRP</th>
<th>N (%)</th>
<th>P-value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High CRP (&gt;6 mg/l)</td>
<td>Normal CRP (0–6 mg/l)</td>
<td>Total</td>
</tr>
<tr>
<td>Controlled asthma group (N = 20)</td>
<td>6 (30)</td>
<td>14 (70)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Exacerbated asthma group (N = 20)</td>
<td>17 (85)</td>
<td>3 (15)</td>
<td>20 (100)</td>
</tr>
<tr>
<td>Total asthma</td>
<td>23 (57.5)</td>
<td>17 (42.5)</td>
<td>40 (100)</td>
</tr>
<tr>
<td>Healthy group (N = 20)</td>
<td>0 (0)</td>
<td>20 (100)</td>
<td>20 (100)</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; HS, highly significant.
These results support the concept that exacerbated asthma is always associated with increased inflammatory response, which increases the level of CRP in these patients.

These results were also in agreement with Mojtaba et al. [29], who showed that CRP levels in asthma patients were significantly higher than those in normal individuals. These results were supported by other authors, such as Takemura et al. [24] and Fujita et al. [25], who reported that measurement of serum CRP was a useful tool for the detection of systemic inflammation in asthma. Razi et al. [30] reported that serum CRP levels measured by high-sensitivity assays increased in acute asthma and may be used as a diagnostic tool for the detection and monitoring of inflammation in these patients.

In the current study, there was a highly significant difference in sputum eosinophil% between the three groups and the eosinophilic count was correlated strongly to asthma exacerbation compared with the stable asthma group and the healthy control group. This result was in agreement with the results of other studies [31,32]. The observation of increased numbers of eosinophils was a feature of asthma for many decades. Eosinophils and their granule products, including Charcot Leyden crystals were a hallmark of spontaneously induced sputum and were plentiful in the airways in post-mortem specimens [32]. Subsequent studies have confirmed this association [33].

In the current study, spirometry was performed for patients during asthma exacerbation, patients with stable asthma, and in normal individuals; there were significant differences in spirometric data between the three groups. There was a highly significant negative correlation between asthma severity and PFT measured by FEV\(_1\), FVC, and FEV\(_1\)/FVC. These results were in agreement with those of Mojtaba et al. [29], who showed that spirometry markers such as FEV\(_1\), and FVC or FEV\(_1\)/FVC in asthma patients were significantly lower than those in normal individuals.

Also, there was a highly significant negative correlation between PFT (the same parameters) and serum CRP. These results were in agreement with those of Alobaidi et al. [8], who found that FEV\(_1\) was significantly inversely correlated with serum CRP in all asthmatic patients whether in a stable or an exacerbation state. Many studies found that increasing serum CRP in asthmatic patients was associated with significantly impaired lung functions indicated by decrease in FEV\(_1\), FVC, and FEV\(_1\)/FVC, which also support the results of the current study [24, 25, 30, 36–38].

### Conclusion and recommendations

There is an association between airway inflammation in bronchial asthma and systemic inflammation. CRP is markedly increased in asthmatic patients, especially during exacerbation. Increases in CRP levels were associated with a steeper decrease in FEV\(_1\) and impaired other pulmonary function parameters. CRP showed

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### Table 3 C-reactive protein (mg/l) in the groups studied

<table>
<thead>
<tr>
<th>CRP</th>
<th>Range</th>
<th>Mean ± SD</th>
<th>P value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled asthma group (N = 20)</td>
<td>0–22</td>
<td>15.33 ± 2.4</td>
<td>≤0.001</td>
<td>HS</td>
</tr>
<tr>
<td>Exacerbated asthma group (N = 20)</td>
<td>0–90</td>
<td>55.36 ± 12.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy group (N = 20)</td>
<td>0–6</td>
<td>2.1 ± 0.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; HS, highly significant.

### Table 4 Sputum eosinophil percentage in the groups studied

<table>
<thead>
<tr>
<th>Eosinophil (%)</th>
<th>Range</th>
<th>Mean ± SD</th>
<th>Number of cases</th>
<th>F test</th>
<th>P value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controlled asthma group (N = 20)</td>
<td>0–16</td>
<td>12.1 ± 2.99</td>
<td>5</td>
<td>8.362</td>
<td>0.009</td>
<td>HS</td>
</tr>
<tr>
<td>Exacerbated asthma group (N = 20)</td>
<td>0–70</td>
<td>49.36 ± 10.3</td>
<td>20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group III (n = 20)</td>
<td>Negative</td>
<td>–</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HS, highly significant.

### Table 5 PFT findings in all groups

<table>
<thead>
<tr>
<th>PFT</th>
<th>FEV(_1)</th>
<th>FVC</th>
<th>FEV(_1)/FVC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>Predicted (%)</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>Controlled asthma group (N = 20)</td>
<td>2.63 ± 0.96</td>
<td>72.6 ± 8.62</td>
<td>3.52 ± 0.63</td>
</tr>
<tr>
<td>Exacerbated asthma group (N = 20)</td>
<td>1.12 ± 0.41</td>
<td>47.6 ± 12.1</td>
<td>2.41 ± 0.28</td>
</tr>
<tr>
<td>Healthy group (N = 20)</td>
<td>2.53 ± 0.63</td>
<td>86.3 ± 6.65</td>
<td>3.99 ± 0.74</td>
</tr>
</tbody>
</table>

| F test | 13.36 | 2.632 | 0.635 |
| P value | 0.001 | 0.015 | 0.225 |
| Significance | HS | S | NS |

HS, highly significant; NS, nonsignificant; S, significant.
Table 6 Correlation coefficient (r) of CRP with age, sex, pulmonary functions, ESR, total leukocytic count, and eosinophil% in all the groups studied (n = 60)

<table>
<thead>
<tr>
<th>Patients variables</th>
<th>CRP</th>
<th>P value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.253</td>
<td>0.410</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.324</td>
<td>0.658</td>
<td>NS</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>-0.852</td>
<td>0.001</td>
<td>HS</td>
</tr>
<tr>
<td>ESR</td>
<td>-0.811</td>
<td>0.001</td>
<td>HS</td>
</tr>
<tr>
<td>FEV₁</td>
<td>0.563</td>
<td>0.001</td>
<td>HS</td>
</tr>
<tr>
<td>FVC</td>
<td>0.510</td>
<td>0.001</td>
<td>HS</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>0.017</td>
<td>0.201</td>
<td>NS</td>
</tr>
<tr>
<td>PEF</td>
<td>-0.314</td>
<td>0.004</td>
<td>S</td>
</tr>
<tr>
<td>Eosinophil%</td>
<td>0.320</td>
<td>0.002</td>
<td>S</td>
</tr>
</tbody>
</table>

CRP, C-reactive protein; HS, highly significant; NS, nonsignificant; S, significant.

A highly significant positive correlation with sputum eosinophils. The degree of sputum eosinophilia correlates with the disease severity in asthma. It is recommended to use serum CRP as a sensitive marker and a diagnostic tool for the detection and monitoring of airway inflammation in patients with bronchial asthma.

Acknowledgements

Conflicts of interest

None declared.

References

Measurement of exhaled nitric oxide in healthy Egyptian population: normal ranges and factors affecting
Abeer M. Rawy

**Background** Nitric oxide is an important regulatory mediator throughout the body. Naturally, the diagnostic applicability of fraction of exhaled nitric oxide (FeNO) depends on the availability of reference values that adequately take into account the major factors affecting FeNO. FeNO values are strongly influenced by several intraindividual factors, including age, atopy, high immunoglobulin E, height, weight, sex, and smoking habits. This study aimed to address the normal ranges of FeNO in healthy Egyptian adults and its relation to other personal factors.

**Materials and methods** A total of 211 healthy Egyptian individuals were selected from pulmonary outpatient clinics and the Chest Department of University Hospital during the period between January 2014 and September 2014. Pulmonary function tests, FeNO measurement, and laboratory tests were carried out. The participants' demographic data were also recorded.

**Results** There was significant negative correlation between measured FeNO and age, weight, BMI, and smoking index. A positive correlation was found between FeNO and height. Female participants had significantly lower levels of FeNO (20.4 ± 9.9) compared with male nonsmokers (28.2 ± 12.4).

**Conclusion** FeNO is affected by sex, BMI, weight, height, and current smoking. The reference ranges for FeNO in healthy Egyptian adults were similar to those of the Caucasian population. In general, values of more than 50 parts per billion (ppb) in male participants and 40 ppb in female participants are considered abnormal in Egyptian populations. *Egypt J Broncho* 2015 9:48–54 © 2015 Egyptian Journal of Bronchology.

**Keywords:** BMI, Egyptians, fractional exhaled nitric oxide, healthy, sex, smoking index

Department of Chest, Faculty of Medicine, Benha University, Egypt
Correspondence to Abeer M. Rawy, MD, Department of Chest, Faculty of Medicine, Benha University, Egypt
Tel: 00201001756638; e-mail: abeer_rawy@yahoo.com

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Measurement of exhaled nitric oxide Rawy 49

is of potential use in clinical practice, there is a need to establish a reference for different populations to aid in the interpretation of measured values. Furthermore, ATS/ERS has encouraged investigators to publish physiological normal values for healthy populations of various racial backgrounds to enable an individual’s results to be compared with data from a racially similar population [4]. In the Arab population, there are only two studies that have been published on normal values of FeNO [22,23].

The aim of this study was to identify factors that influence the FeNO values of healthy Egyptian adults in different age groups, as well as establish a reference range for FeNO in Egyptians and study its applicability and reliability in similar populations compared with other studies conducted in the nearby countries and other values published worldwide.

Materials and methods
Study population and design
This study was carried out in pulmonary outpatient clinic in association with chest department of university hospital in the period between January and September 2014 and it was approved by the local ethics committee. A total of 300 healthy adults from the community were invited to participate in this study, but only 211 accepted to participate, whereas 89 refused. All individuals who accepted to participate in this study were included, and a written informed consent was obtained from each person. Individuals who refused to participate in this study were excluded. Other exclusion criteria included a history or manifestations of atopic diseases (such as allergic asthma, atopic dermatitis, allergic rhinitis, and food allergy), acute respiratory tract infection in the last 4 weeks, and chronic respiratory illness (such as chronic obstructive pulmonary disease, interstitial lung disease, and bronchiectasis, etc.). Individuals who had obstructive abnormality in spirometry defined by forced expiratory volume in first second/forced vital capacity (FEV$_1$/FVC) less than 0.7 or those on current use of inhaled or systemic steroid were also excluded. The participants were asked to answer structured questionnaires on medical history and allergic symptoms. A thorough clinical examination, chest radiography, spirometry, and other laboratory tests were performed. Individuals who fulfilled the inclusion criteria underwent FeNO.

Fraction of exhaled NO measurement
FeNO was measured using an online electrochemical nitric oxide monitor (NIOX MINO; Aerocrine, AB Solna, Sweden) according to 2005 ATS/ERS guidelines [4], with a sensitivity of one parts per billion (ppb). This nitric oxide analyzer has been approved by the US Food and Drug Administration for clinical use. The participants were asked about current medication or food intake that could interfere with the FeNO measurement results. In addition, they were instructed to avoid smoking, exercise, and ingestion of food, water, or caffeine at least 4 h before testing. All tests were performed at the same time of the day between 13:00 and 16:00 h daily to minimize possible circadian effects. The procedure was started by asking the individuals to exhale completely to empty their lungs outside the analyzer and then to inhale to total lung capacity through the mouthpiece and finally exhale into the device at a constant expiratory flow rate of 50 ml/s (±10%) over 10 s and a pressure of 10 cmH$_2$O according to the guideline recommendation [4]. Three acceptable and reproducible maneuvers (within 10% deviation) were performed. Final FeNO values were calculated as the arithmetic mean of these values. The NO analyzer was calibrated every 2 weeks using a certified calibration gas (Linde, Munich, Germany) according to the manufacturer’s recommendations. Ambient air pressure, temperature, humidity, and ambient NO levels were recorded for each measurement.

Pulmonary function tests
Before performing the test, ambient temperature and pressure were entered along with the patient data [age (years), weight (kg), height (cm), and sex] so that all results were calculated as percent-of-predicted (% predicted) except for FEV$_1$/FVC. Pulmonary function tests were performed using a Sensor-medics Vmax series, 2130 spirometer, V 6200 Autobox, 6200 DL (Sensor Medics Corporation, California, USA). Flow/volume loop was performed to all participants. Individuals with FEV$_1$/FVC less than 0.7 and FEV$_1$ less than 80% of predicted were excluded from the study. All individuals who were included in this study had to have normal spirometry.

Other laboratory tests
Complete blood count was performed to exclude acute infection and eosinophilia. Random blood sugar, liver function tests, and kidney function tests were performed to exclude chronic illness.

Statistical analysis
The data were analyzed using the statistical package for social sciences, version 11. Data were expressed as mean ± SD for continuous variables and as percentages for categorical variables. Comparisons between variables were performed using Student’s t-test for continuous variables. Frequency distribution and cumulative percentage were determined for FeNO.
We calculated Pearson's correlation coefficient to see the relation of FeNO with other parameters. Multiple linear regressions were carried out to find the predictor variables for FeNO. A $P$-value of 0.05 or less was considered statistically significant and all tests were two tailed.

Results
Baseline characteristics
Baseline demographic characteristics are presented in Table 1 with pulmonary functions tests and laboratory data. The study included 211 healthy Egyptian individuals (155 men and 56 women). There were 47 male participants who were smokers, whereas all female participants were nonsmokers. The mean age of men was 37.6 ± 13.1 and the mean age of women was 37 ± 14.1. The mean BMI in men was 30.2 ± 6.3 and the mean BMI in women was 31.4 ± 7.4. Pulmonary function tests, white blood cell, eosinophil count were all within normal values. Fraction of FeNO is also demonstrated in Table 1. The measured FeNO ranged between 6 and 50 ppb, with mean value of 25.5 ± 11.6 in men (28.2 ± 12.4 in nonsmokers and 19.4 ± 8.2 in smokers). In women the mean value of FeNO was 20.4 ± 9.9.

The cumulative percentage distribution based on different ranges of FeNO is shown in Table 2, and the distribution of FeNO based on different ranges of FeNO is shown in Fig. 1. There was a significant negative correlation between measured FeNO and age, weight, BMI, and smoking index (Table 3 and Fig. 2) but a positive correlation between FeNO and height was observed in all groups.

![Fig. 1](cumulative_percentage_distribution.png)

### Table 1 Demographic characteristics, pulmonary function tests, and laboratory data of all participants

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total number of men ($N = 155$)</th>
<th>Male nonsmokers ($N = 108$)</th>
<th>Male smokers ($N = 47$)</th>
<th>Women ($N = 56$)</th>
<th>Total number of participants ($N = 211$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean ± SD</td>
<td>37.6 ± 13.1</td>
<td>38.6 ± 13.4</td>
<td>34.7 ± 11.7</td>
<td>37 ± 14.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean ± SD</td>
<td>86.7 ± 19.6</td>
<td>86.1 ± 19.8</td>
<td>88.1 ± 19.4</td>
<td>76.1 ± 19</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>Mean ± SD</td>
<td>170 ± 7.5</td>
<td>168.8 ± 7.3</td>
<td>172.6 ± 7.5</td>
<td>155.5 ± 6.6</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Mean ± SD</td>
<td>30.2 ± 6.3</td>
<td>30.6 ± 6.9</td>
<td>29.8 ± 5.1</td>
<td>31.4 ± 7.4</td>
</tr>
<tr>
<td>Smoking index</td>
<td>Mean ± SD</td>
<td>61.7 ± 169.2</td>
<td>0</td>
<td>203.5 ± 515.1</td>
<td>0</td>
</tr>
<tr>
<td>FEV₁/FVC</td>
<td>Mean ± SD</td>
<td>88.6 ± 6.9</td>
<td>90.4 ± 8.4</td>
<td>82.6 ± 5.7</td>
<td>90 ± 7.9</td>
</tr>
<tr>
<td>FEV₁</td>
<td>Mean ± SD</td>
<td>85.2 ± 18.6</td>
<td>88.7 ± 14.5</td>
<td>80.3 ± 4.9</td>
<td>88.4 ± 13.4</td>
</tr>
<tr>
<td>FeNO (ppb)</td>
<td>Mean ± SD</td>
<td>25.5 ± 11.6</td>
<td>28.2 ± 12.4</td>
<td>19.4 ± 8.2</td>
<td>20.4 ± 9.9</td>
</tr>
<tr>
<td>WBCs</td>
<td>Mean ± SD</td>
<td>7.4 ± 2.0</td>
<td>6.4 ± 3.1</td>
<td>9.2 ± 2.4</td>
<td>8.0 ± 1.8</td>
</tr>
<tr>
<td>Eosinophil count</td>
<td>Mean ± SD</td>
<td>2.3 ± 1.2</td>
<td>2.9 ± 1.4</td>
<td>1.7 ± 0.9</td>
<td>1.7 ± 0.9</td>
</tr>
</tbody>
</table>

FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in first second; FVC, forced vital capacity; ppb, parts per billion; WBC, white blood cell.
Exhaled NO originates primarily in the airway epithelium, produced by inducible NO synthetase [17]. Because biological NO formation is a complex and energy-consuming process, airway NO formation is important in humans and, consequently, should be under tight biological control under normal circumstances. Its origin from the airway epithelium indicates that the total surface area of the airway mucosa will be an important determinant for exhaled NO [18]. Thus, it is logical that age and BMI were found to be important factors when evaluating FeNO values, as seen for other lung function parameters. In addition to individual-specific factors that affect the value of FeNO, several behavioral and environmental factors have been pointed out as influencing FeNO, such as allergen exposure [24], physical exercise [25,26], ozone exposure [27,28], and air pollution [29].

This study was carried out on 211 healthy Egyptian individuals, and results showed that FeNO values were significantly higher in men (25.5 ± 11.6 ppb) than in women (20.4 ± 9.9 ppb). These results matched with previous studies [30–34] in that the mean values of FeNO were higher in men than in women, but their measurements of FeNO were at lower levels (18.2 ± 10.6 in men and 12.1 ± 6.9 in women) than those in this study. This difference can be explained by the effect of environmental changes; all these studies were
conducted in the Far East region, whereas this study was conducted in the Caucasian middle east region. Moreover, those studies investigated populations with means of ages and BMI different than those in the current study.

For comparing the effect of sex on FeNO values in some of our areas, there were two studies conducted in nearby areas: one in Saudi Arabia and another in Tunisia. The study conducted in Kingdom of Saudi Arabia investigated only the FeNO in men and found the mean of FeNO to be 22.79 ± 8.13 ppb, which is close to that found in our study [23]. In Tunisia, the mean value of FeNO was at lower level compared with the current study and with no male-to-female differences (13.31 ± 4.55 in men and 13.84 ± 5.26 in women) [22]. Other studies conducted in different regions were in agreement with our study and showed higher level of FeNO in men than in women [9,11,20,35]. The sex-related differences of FeNO were explained by differences in the surface area of the airway epithelium, the major source of exhaled NO, and for which height is an important anthropometric correlate [20]. Moreover, genetic and hormonal factors also have a role in FeNO levels [36]. In fact, estrogen can activate the endothelial NO synthetase in human bronchiolar epithelial cells in vitro [37]. Moreover, relationship between estrogen/ progesterone levels and exhaled NO has recently been described [38].

As regards age, this study included individuals with age ranging between 18 and 60 years. The results showed that there was negative correlation between the mean of FeNO and age, with highly significant differences. This finding is accepted in adult population with ages between 18 and 60 years, but in children and elderly more than 60 years there were some differences. In the elderly, Gelb et al. [39] recently showed that FeNO and alveolar NO, but not bronchial NO flux, increased with age in adults, especially in those above 60 years. This is suggested to be because of the reduced lung diffusing capacity for NO (and carbon monoxide) seen in elderly, leading to less uptake of bronchial NO in the alveolar tract. There have been conflicting reports regarding the association between FeNO and age [32,40]. Potentially, this relationship is only detectable at very young ages and in advanced age, and it might be negligible during young adulthood. Possible explanations for an increase in FeNO with age could include diet [41], latent respiratory inflammation, or an increase in peripheral (alveolar) NO [39].

The present study identified a negative correlation of both weight and BMI with FeNO. This finding was supported by the findings of Maniscalco et al. [42] who observed that FENO is consistently reduced in severe obesity, and it is restored after weight reduction. This was explained by the effect of obesity on systemic oxidative stress, in part through increased production of reactive oxygen species in adipose tissue. It is hypothesized that the lung serves as a target organ for this oxidative stress. This is manifested as increased oxidation of airway NO into nitrate and reactive nitrogen species and hence the reduction of NO bioavailability and exhaled NO levels [23]. Some other studies showed no significant relationships between BMI and FeNO values [43–46].

Many studies investigated the effects of smoking on FeNO values in adults. There was consistent evidence that active smoking and acute cigarette smoke exposure lead to a transient decrease in FeNO levels in healthy and asthmatic adults [47,48]. In current study, there was a significant negative correlation between FeNO and smoking index with lower levels of FeNO in current smokers than in nonsmokers, which matched with the previous studies [47–49]. A record of smoking history is therefore necessary for the interpretation of results, and measurement is advised at least an hour after smoking.

As regards height, it is the only parameter that is positively correlated with FeNO in normal healthy participants. Olin et al. [40] noted that FeNO was clearly positively correlated with height in both men and women, which matched with the current study. This is probably because of the height-dependent increase in the total airway mucosal surface area that produces NO [50]. Therefore, height is the strongest independent predictor [51] for FeNO measurement.

Conclusion
FeNO is affected by sex, BMI, weight, height, and current smoking. In healthy Egyptian adults, women had lower levels of FeNO compared with male nonsmokers. In general, values of more than 50 ppb in men and 40 ppb in women are considered abnormal in Egyptian populations. FeNO measurement is a noninvasive tool, easy to perform, and it may add benefits in diagnostic tests in pulmonary diseases.

Acknowledgements
Conflicts of interest
None declared.

References


Olin AC, Rosengren A, Thelle DS, Lissner L, Bake B, Toren K. Height, age, and atopy are associated with fraction of exhaled nitric oxide in a large adult general population sample. Chest 2006; 130:1319–1325.


Factors predicting pulmonary hypertension in idiopathic pulmonary fibrosis patients

Samiaa H. Sadeka, Soheir M. Kasemb

Introduction

Idiopathic pulmonary fibrosis (IPF) is a disease characterized by progressive scarring of the lung tissue and a restrictive pattern of lung function with reduced gas exchange capacity [1]. Pulmonary arterial hypertension has been defined as a mean pulmonary artery pressure (mPAP) 25 mmHg or more at rest, with a normal pulmonary capillary wedge pressure [2]. The prevalence of pulmonary hypertension (PH) in patients referred for lung transplantation is 32–46% [3], but the overall prevalence of PH in IPF is lower than that in patients referred for transplantation [3]. In patients with IPF without PH, pulmonary function tests (PFTs) are used for the evaluation of severity and progression of disease [4]. Although respiratory failure is the most common cause of death in IPF, several comorbidities may also play a role; PH is the most important comorbidity with a prognostic role [5]. PH may reduce life expectancy in IPF to less than 1 year [5]. Studies using echocardiography for assessment of mortality in IPF showed that systolic pulmonary artery pressure (sPAP) more than 50 mmHg is associated with a median survival of 0.7 years; however, it is 4.1 years for an sPAP of 36–50 mmHg and 4.8 years for an sPAP of 35 mmHg or less [6].

Objectives

The aims of this work were to assess predictors of PH in IPF from both resting PFT and cardiopulmonary exercise testing (CPET) parameters and to determine cut-off values from resting PFT and CPET parameters to predict PH in IPF.

Patients and methods

The present study was carried out in the Department of Chest Diseases, Faculty of Medicine, Assiut University Hospital. Thirty-five patients with IPF were included in this study.

The diagnosis of IPF was made on the basis of the high resolution CT chest (HRCT) chest criteria according to ATS/ERS/JRS/ALAT, 2011 statement [7]. All patients were subjected to a full assessment of medical history, general and local chest examination, chest
radiograph posteroanterior chest radiograph (PA) view, HRCT chest, and spirometry.

Spirometry was performed using (Cosmed SrL, Quark PFT Ergo, P/N Co9035–12–99; Italy), where predicted values for FEV\textsubscript{1}, FVC, FEV\textsubscript{2}, FVC, and inspiratory capacity (IC) were calculated. Incremental CPET was performed using (Cosmed SrL, Quark PFT Ergo, P/N Co9035–12–99), where gas exchange values and exercise parameters were collected breath by breath, allowing measurement of minute ventilation (VE), tidal volume (VT), respiratory frequency (RF), oxygen uptake (VO\textsubscript{2}), end-tidal carbon dioxide (PETCO\textsubscript{2}), the anaerobic threshold, oxygen pulse (VO\textsubscript{2}/HR), ventilatory equivalent for carbon dioxide at anaerobic threshold, and the breathing reserve.

The level of dyspnea was assessed at the beginning of CPET and at VO\textsubscript{2} using the Borg Rating of Perceived Exertion Scale [8]. The Borg rating uses a scale from 0 to 10; the patient rates his/her perception of dyspnea, for example, scale 0 means no dyspnea, 3 means moderate dyspnea, scale 7 means severe dyspnea, but the patient can continue exercise, and scale 10 means maximum dyspnea such that the patient terminates exercise.

Lung volumes and diffusion capacity of the lung for carbon monoxide were determined using the single-breath method (D97723, Zan 300; Oberthulba, Germany, CO/CH\textsubscript{4} analyzer), where the total lung capacity (TLC) was calculated and predicted values for diffusing capacity for carbon monoxide (DLCO) adjusted for hemoglobin concentration were measured.

ABG in room air were obtained both at rest and at the end of exercise. A blood sample was obtained from the radial artery and analyzed using a blood gas analyzer (Rapid lab 850; CHIRON/Diagnostics Halstead, UK), with calculation of PaO\textsubscript{2}, SaO\textsubscript{2}, and PaCO\textsubscript{2}.

Two-dimensional Doppler echocardiography was performed using (Philips Invisor, 2002; Philips, USA). The mPAP was calculated from sPAP using the Chemla formula: mPAP = 0.61 × sPAP + 2 mmHg [9]. Patients were classified into two groups: PH patients, in whom mPAP was 25 mmHg or more, and a non-pulmonary-hypertension (NPH) group, in whom mPAP was less than 25 mmHg.

Statistical analyses
All PFT and exercise parameters are presented as mean percent predicted (%Pred) ±SD. The PH and NPH groups were compared in terms of resting PFT and CPET parameters using a \( t \) sample test, where \( P \) value less than 0.05 was considered significant. A receiver operating characteristic (ROC) curve was used to establish a cut-off value for prediction of PH in IPF patients.

Results
On comparing clinical and ABG parameters between PH and NPH groups, there were no significant differences in age and sex, dyspnea level, and arterial PaCO\textsubscript{2} both at rest and exercise, and VO\textsubscript{2} max was significantly higher in the PH group; however, arterial oxygen both at rest and exercise was significantly lower in the PH group (Tables 1 and 2).

Comparison between both groups for the resting PFT showed that PH patients had lower FEV\textsubscript{1}, FVC%, and IC%, whereas there was no significant difference in DLCO and TLC% (Table 3).

CPET patients with PH had significantly lower VO\textsubscript{2} max and VT, and had significantly higher VE/VCO\textsubscript{2}, VE, and RF (Table 4).

The ROC curve (Fig. 1) was used for different parameters to detect a cut-off value for predicting PH, and it was found that resting SaO\textsubscript{2} 92.9% or less and less had sensitivity of 84.6 and 100% and specificity of 90.9 and 81.8%, respectively, with area under the curve 0.858 for resting SaO\textsubscript{2} and 0.958 for exercise SaO\textsubscript{2}.

Discussion
PH is a common complication of IPF as a result of progressive fibrosis and honeycomb changes with destruction of pulmonary vasculature and hypoxic pulmonary vasoconstriction [10]. In our study, comparison between IPF patients with and without PH showed that oxygen tension and saturation reduced significantly in PH patients, and on constructing an ROC curve (Fig. 1) to establish a cut-off value, resting SaO\textsubscript{2} less than 92.9% had sensitivity of 84.6% and specificity of 90.9%, and exercise SaO\textsubscript{2} less than 87% had a sensitivity of 100% and a specificity of 81.8%. Many studies support our results. Hamada et al. [11] reported that hypoxia is a frequent consequence of PH; they found a significant correlation between resting PaO\textsubscript{2} and mPAP in IPF (\( r = -0.47, P < 0.001 \)). Also, intermittent nocturnal hypoxia for a long duration may play a significant role in the development of disproportionate PH [11]. Agarwal et al. [12] documented that fibrosis in IPF leads to entrapment of segments of pulmonary vasculature and thrombosis, with resulting fibrosis. These changes result in hypoxia, which leads to pulmonary vasoconstriction with permanent structural changes in pulmonary blood vessels, even those far from areas of fibrosis [12]. Shorr et al. [13] reported that PaCO\textsubscript{2} in IPF patients with mild to moderate PH was higher compared with those with normal pulmonary artery pressure; this is consistent with our results. Assessment of dyspnea
Factors predicting pulmonary hypertension in idiopathic pulmonary fibrosis (IPF) patients Sadek and Kasem

Table 1 Comparison between both groups in resting clinical and arterial blood gases parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NPH (n = 22)</th>
<th>PH (n = 13)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex [N (%)]</td>
<td></td>
<td></td>
<td>0.868</td>
</tr>
<tr>
<td>Male</td>
<td>7 (31.8)</td>
<td>3 (23.1)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>15 (68.2)</td>
<td>10 (76.9)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>51.77 ± 9.23</td>
<td>45.15 ± 13.67</td>
<td>0.096</td>
</tr>
<tr>
<td>Resting Borg scale</td>
<td>1.59 ± 1.18</td>
<td>3.08 ± 1.61</td>
<td>0.004*</td>
</tr>
<tr>
<td>Resting PaO₂</td>
<td>73.23 ± 11.05</td>
<td>61.54 ± 10.34</td>
<td>0.004*</td>
</tr>
<tr>
<td>Resting SaO₂</td>
<td>95.06 ± 1.86</td>
<td>91.36 ± 3.08</td>
<td>0.000*</td>
</tr>
<tr>
<td>Resting PaCO₂</td>
<td>34.99 ± 4.09</td>
<td>42.09 ± 9.56</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

NPH, non-pulmonary-hypertension; PH, pulmonary hypertension; value below 0.05 for P value is significant.

Table 2 Comparison between both groups in postexercise clinical and arterial blood gases parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NPH (n = 22)</th>
<th>PH (n = 13)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postexercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borg scale</td>
<td>3.73 ± 3.17</td>
<td>6.62 ± 3.53</td>
<td>0.018*</td>
</tr>
<tr>
<td>Postexercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO₂</td>
<td>59.41 ± 11.37</td>
<td>46.38 ± 4.43</td>
<td>0.000*</td>
</tr>
<tr>
<td>Postexercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SaO₂</td>
<td>89.79 ± 3.87</td>
<td>81.04 ± 3.99</td>
<td>0.000*</td>
</tr>
<tr>
<td>Postexercise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaCO₂</td>
<td>35.50 ± 5.56</td>
<td>43.35 ± 10.99</td>
<td>0.008*</td>
</tr>
</tbody>
</table>

NPH, non-pulmonary-hypertension; PH, pulmonary hypertension; value below 0.05 for P value is significant.

Table 3 Comparison between pulmonary hypertension and non-pulmonary-hypertension patients in resting pulmonary function parameters pulmonary function test

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NPH (n = 22)</th>
<th>PH (n = 13)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV/FVC (%)</td>
<td>79.18 ± 7.90</td>
<td>80.39 ± 7.82</td>
<td>0.665</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>67.00 ± 13.31</td>
<td>50.23 ± 13.05</td>
<td>0.001*</td>
</tr>
<tr>
<td>FEV₁ (%)</td>
<td>63.43 ± 16.22</td>
<td>45.95 ± 15.16</td>
<td>0.003*</td>
</tr>
<tr>
<td>DLCO (%)</td>
<td>47.77 ± 18.38</td>
<td>40.48 ± 19.12</td>
<td>0.266</td>
</tr>
<tr>
<td>TLC (%)</td>
<td>72.41 ± 11.73</td>
<td>68.92 ± 16.04</td>
<td>0.464</td>
</tr>
<tr>
<td>IC (%)</td>
<td>69.73 ± 23.06</td>
<td>43.32 ± 21.73</td>
<td>0.002*</td>
</tr>
</tbody>
</table>

FEV₁, forced expiratory volume in 1 second; TLC, total lung capacity; IC, inspiratory capacity; NPH, non-pulmonary-hypertension; PH, pulmonary hypertension; value below 0.05 for P value is significant.

Table 4 Cardiopulmonary exercise testing parameters in pulmonary hypertension and non-pulmonary-hypertension patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>NPH (n = 22)</th>
<th>PH (n = 13)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO₂ (%)</td>
<td>55.00 ± 15.59</td>
<td>43.38 ± 10.57</td>
<td>0.023*</td>
</tr>
<tr>
<td>VE/VO₂</td>
<td>35.23 ± 10.92</td>
<td>51.38 ± 15.17</td>
<td>0.001*</td>
</tr>
<tr>
<td>VT (L/min)</td>
<td>0.96 ± 0.17</td>
<td>0.78 ± 0.21</td>
<td>0.008*</td>
</tr>
<tr>
<td>VE (L/min)</td>
<td>38.07 ± 7.17</td>
<td>45.15 ± 11.95</td>
<td>0.038*</td>
</tr>
<tr>
<td>RF (Hz)</td>
<td>40.50 ± 7.96</td>
<td>46.49 ± 6.01</td>
<td>0.025*</td>
</tr>
</tbody>
</table>

VO₂, maximum oxygen consumption; VE/VO₂, ventilatory equivalent for CO₂; VT, tidal volume; P value < 0.05 is significant.

Comparison of resting PFT showed that each of FEV₁, FVC, and IC reduced significantly in PH patients, whereas there were no significant differences in DLCO% and TLC%. Although Gläser et al. [14] documented that except for diffusing capacity, PFT showed no significant differences between both groups, Shorr et al. [13] observed that FEV₁ was lower in patients with PH (50.0 ± 16.5 vs. 52.7 ± 16.5% predicted, P < 0.0001) and FEV₂ was significantly correlated with mPAP. Also, Agarwal et al. [12] found a statistically significant difference in PaO₂ levels and FVC in patients with PH compared with NPH patients, and a significant association was observed between the presence of decreasing FVC and hypoxemia and the development of PH in IPF patients. Javier and Sicilian [15] observed that FVC was significantly positively correlated with IC%; thus, we can predict that IC decreased in PH patients as observed in our study. Although many studies have documented that DLCO decreased significantly in PH patients [14], our study found that DLCO decreased in the PH group compared with the NPH group, but not significantly differently; correcting DLCO for alveolar volume will result in significant difference between both groups. CPET evaluation of IPF patients showed that VO₂% and VT reduced significantly in the PH group; meanwhile, VE/VO₂, RF, and VE reduced significantly in the NPH group. The results of Gläser et al. [14] were in agreement with ours as they observed that peak VO₂ was significantly lower in patients with PH, and the ventilatory inefficiency (VE/VO₂) slope was significantly pronounced in patients with PH. They reported that hyperventilation causes increased VE/VO₂ slope and this is the result of a reduced pulmonary capillary bed with shortened red blood cell

using the Borg scale both at rest and during exercise was higher in the PH group compared with NPH patients. Gläser et al. [14] studied the impact of PH on gas exchange and exercise capacity in patients with pulmonary fibrosis and confirmed our results as they observed a mean score of 3 for patients without PH and 6 for patients with PH (P < 0.05).
transit times and thus impaired oxygenation, and also increased functional intrapulmonary right to left shunt. Javier and Sicilian [15] studied lung function, breathing pattern, and gas exchange in interstitial lung disease and observed that lower values of FVC were associated with an increased RF and decreased VT, and in our study, PH patients had lower values for FVC in comparison with NPH patients. Javier and Sicilian [15] reported that possible mechanisms of rapid shallow breathing are the mechanical effects of increased lung elastance, perceived as increasing load by mechanoreceptors, and stimulation of intrapulmonary receptors, for example, J receptors.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References


Interstitial lung diseases and lung in systemic diseases

Introduction
Systemic lupus erythematosus (SLE) is a chronic systemic disease involving multiple organs such as the kidneys, skin, and brain [1]. Lung is another organ that can be affected. A number of pulmonary complications including pleurisy, pneumonitis, infectious pneumonia, pulmonary hemorrhage, pulmonary hypertension, and pneumothorax have been reported in patients with SLE [2]. The lung involvement in SLE patients may be a direct involvement, or the lungs may be affected as a consequence of other organ impairments. Pulmonary involvement has also been found in children affected with SLE, with an incidence ranging from 5 to 67% [3]. It is possible that a subclinical disease occurs more frequently than reported previously [3]. The use of more sensitive pulmonary function tests (PFTs) may be a valuable diagnostic tool for the diagnosis of subclinical pulmonary involvement [4]. PFT results in patients with SLE, with and without respiratory symptoms and abnormal chest radiographs, have shown several abnormalities in many studies [5–7]. Restrictive lung disease, measured by PFTs, is the most frequent alteration reported in adult SLE [3]. However, few studies have been carried out on children with juvenile-onset systemic lupus erythematosus (jSLE) to assess this. Also, there is a claim that abnormal PFTs seem to be even more common in children than in adults [8].

The aim of the present work was to explore the frequency and the features of respiratory function tests alterations in a group of Egyptian children with jSLE, with no clinical or radiological manifestations of lung involvement, and explore their clinical significance and correlations.

Patients and methods

Participants
The study randomly enrolled 20 jSLE patients (three male and 17 female, age range 8–23 years, mean 14.8 ± 3.03 years), all fulfilling at least four of the 1997 revised American Rheumatism Association SLE criteria for the diagnosis of SLE [9]. All selected patients were followed up at the Pediatric Rheumatology Clinic, Cairo University Children’s Hospital, from January 2011 to December 2011. Disease manifestations

Objective
The aim of this study was to investigate the presence and frequency of abnormalities in subclinical pulmonary function tests (PFTs) in a group of Egyptian children with juvenile-onset systemic lupus erythematosus (jSLE) asymptomatic for respiratory manifestations.

Patients and methods
The study enrolled 20 children with jSLE followed up at the Pediatric Rheumatology Clinic, Cairo University. For all patients, pulmonary function testing was performed including measurement of lung volumes and lung flows using spirometry. Lung diffusion testing was performed using the transfer factor of the lung for carbon monoxide (DLCO) utilizing the single-breath method. Findings were correlated with clinical manifestations and lupus disease activity, and assessed using Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores.

Results
Among our study group, musculoskeletal, mucocutaneous, hematologic, renal, and neurological manifestations were the most frequent lupus manifestations throughout the course of disease, occurring in 85, 80, 65, 45, and 35% of the patients, respectively. The mean SLEDAI score was 21.3 ± 9.515. Overall, 95% of our patients had at least one PFT abnormality within a mean of 4.9 ± 1.94 years after disease onset. Diffusion defect was the most frequent defect detected in 14 (70%) patients, restrictive pathology was found in seven (35%) patients, obstructive pathology was found in six (30%) patients, and mixed restrictive and obstructive pathology in one (5%) patient. In terms of the correlation between PFTs and the SLEDAI, DLCO was correlated positively (r = 0.37, P = 0.05) to a high SLEDAI, that is, a diffusion defect was significantly evident in patients with high disease activity even without symptoms.

Conclusion
Occult pulmonary disease as shown by a PFT occurs frequently in our group of Egyptian patients with childhood-onset systemic lupus erythematosus. Egypt J Broncho 2015 9:59–63

Keywords: Egyptian children, pulmonary functions, systemic lupus erythematosus

Department of Pediatrics, Faculty of Medicine, Cairo University, Cairo, Egypt
Correspondence to Eman F. Halawa, MD, Department of Pediatrics, Faculty of Medicine, Cairo University, 23 Dr. Naguib Mahfouz Street, Nasr City, Cairo, 11471, Egypt
Tel: +20 100 159 6090; fax: 02 33386832; e-mail: emanhalawa3@yahoo.com

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throughout the course of disease were obtained from the patients’ follow-up charts. Disease activity was assessed at the time of study enrollment and scored according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) [10]. The disease was considered active when the index was 10 or more. All patients were receiving a low dose of corticosteroids (0.5–1 mg/kg/day) and hydroxychloroquine (200–400 mg/day) from the time of diagnosis of disease, and treated according to the type and extent of organ involvement.

Before undergoing PFTs, all patients underwent a complete clinical evaluation. Information on pulmonary symptoms was obtained by a detailed pretested questionnaire requesting information on dry or productive cough, dyspnea, and cyanosis and chest pain. We included children free from asthma, chronic bronchitis, or emphysema according to the American Education Program criteria. The presence or absence of other organ impairment was also recorded, with a plus or minus, in all patients.

At the time of PFT, hemoglobin levels were measured. A chest radiography was performed for all patients at baseline.

The study was approved by the Cairo University Clinical Research Ethics Committee. Informed consents were obtained from the parents of all participants. All patients’ data were kept confidential.

Serological tests
The following laboratory tests were performed for all patients at study enrollment: complement components (C3 and C4); antinuclear antibodies and anti-DNA by indirect immunofluorescence using Hep-2 and *Crithidia luciliae* as substrates, respectively; anticardiolipin, both IgM and IgG by the solid phase radioimmunological technique of Harris and Pierangeli [11], as modified by Lakos et al. [12]; and lupus anticoagulant by the Russell’s viper venom time.

Pulmonary function tests
Pulmonary function measurements were performed for all patients. Measurement of lung volumes, lung flows, and airway resistance (Raw) was carried out using spirometric techniques. The best of three forced vital capacity (FVC) measurements was registered [13]. Postbronchodilator measurement of the FVC was performed if there were obstructive abnormalities. Seated patients were asked to inhale maximally from tidal respiration to total lung capacity and then rapidly exhale to the fullest extent until no further volume is exhaled at residual volume. The maneuver was performed in a forceful manner to generate a FVC. The volume of air expired during the first second is the FEV1. Peak expiratory flow rate was measured on the basis of how much the patients could blow out of their lungs in one breath. The tests were performed using the MasterScreen machine (Jaeger, Germany). The percentage–range method was used to determine abnormal values in which a range of 20% above and/or below a patient’s predicted mean normal value is considered abnormal [14].

The transfer factor of the lung for carbon monoxide (DLCO) was determined using the single-breath method [15] using the MasterScreen machine (Jeager). The patient was asked to breathe in (inhale) air containing a very small amount of a tracer gas, such as carbon monoxide, hold his/her breath for 10 s, and then rapidly blow it out (exhale). The exhaled gas was tested to determine how much of the tracer gas was absorbed during the breath. Patients were asked not to eat a heavy meal before the test. Diffusion capacity below 80% of the predicted mean value is considered abnormal [14]. Oxygen saturation was measured using a pulse oximeter.

**Statistical analysis**
The data were coded and entered using the statistical package for the social sciences (SPSS; version 15; SPSS Inc., Chicago, Illinois, USA). Data were summarized using descriptive statistics: mean and SD. The relationship between pulmonary function parameters and disease duration, disease activity, clinical features, and immunological data was assessed by Spearman’s correlation.

**Results**
The study enrolled 20 unrelated Egyptian jSLE children (three male and 17 female; mean age 14.8 ± 3.03 years); the mean disease duration was 4.9 ± 1.94 years (range 2–10 years).

All anthropometric and demographic data are presented in Table 1. The clinical manifestations of our SLE study group are shown in Table 2. Musculoskeletal, mucocutaneous, hematologic, renal, and neurological manifestations were the most frequent manifestations throughout the course of disease, respectively.

None of the patients complained of respiratory symptoms at the time of study enrollment.

Disease activity was assessed using the SLEDAI score at the time of performance of PFTs. The individual values of SLEDAI and the results of the FEV1, FVC,
Enrolled 20 Egyptian jSLE patients with no clinical or radiological evidence of chest involvement. Clinical and laboratory data of our study group are in concordance with the manifestations of jSLE commonly found in Egyptian children [16].

Our study showed that highly significant functional lung impairment was present in 95% of jSLE children asymptomatic for chest manifestations. This high incidence of abnormal PFTs in the current study is similar to the results of studies by Delgado et al. [17], De Jongste et al. [18], and Cerveri et al. [19], who reported abnormal PFTs in 62, 87, and 84% of patients with jSLE, respectively. The frequency of PFTs abnormalities in our study group was higher than the frequency in Italian and Canadian studies, which reported abnormal PFTs in 40 and 48% of asymptomatic patients, respectively [3,20].

The restrictive pattern (reduced FVC) represents the main feature of pulmonary involvement in our jSLE patients. This finding may be attributed to parenchymal impairment because of interstitial connective tissue involvement or to reduction of respiratory muscle strength, caused by the disease itself or by the medications, especially the corticosteroids.

The presence of diffusion defects, as measured by DLCO, suggests that the restrictive pattern may be mainly because of parenchymal damage rather than respiratory muscle involvement. As it is not easy to detect respiratory muscle dysfunction (except with specialized electromyography (EMG) for chest muscles) in young patients, because it is difficult to measure maximal in-expiratory mouth pressures correctly, the involvement of respiratory muscles in the restrictive ventilator pattern remains unclear. A report by Decramer et al. [21] showed that in adult patients with chronic obstructive pulmonary disease or asthma, respiratory muscle strength and steroid treatment are interrelated despite a relatively low average daily dose of corticosteroids.

Our study is not without limitations, primarily, the relatively small sample size of jSLE patients, which may be explained by the presence of only one MasterScreen machine for performance of the PFT in the Cairo University Pediatric Hospital, together with the high cost of the tests. We consider this study a preliminary one, and aim to involve a larger number of patients in future studies and to perform PFT as a routine assessment for follow-up of jSLE patients to study the actual prevalence of PFT abnormalities in Egyptian children with jSLE and to intervene as early as possible.
Table 3 Disease activity scores and pulmonary function test results of our study group of juvenile-onset systemic lupus erythematosus patients

<table>
<thead>
<tr>
<th>Patients</th>
<th>SLEDAI (%predicted value)</th>
<th>FEV₁ (%predicted value)</th>
<th>FVC (%predicted value)</th>
<th>PEF25–PEF50 (l/s)</th>
<th>DLCO (ml/min/mmHg)</th>
<th>VA (%) (ml/min/mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22</td>
<td>73</td>
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<td>81</td>
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<td>100</td>
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<td>99</td>
<td>87.5</td>
<td>83</td>
</tr>
</tbody>
</table>

Mean ± SD 21.3 ± 9.5 96.9 ± 17.7 89.175 ± 19.5 99.250 ± 23.5 87.7 ± 191 100 ± 20

DLCO, diffusion lung capacity for carbon monoxide; FEV₁, forced expiratory volume after 1 s; FVC, forced vital capacity; PEF25–50, peak forced expiratory flow at 25–50%; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; VA, alveolar volume.

In conclusion, the present study showed that occult pulmonary disease occurs frequently in childhood-onset SLE, and that PFT abnormalities were found in 95% of these children. Whether progression of these subclinical abnormalities occurs or can be prevented cannot be determined from this study. The results do suggest that serial PFT studies may be useful in assessing the presence of lung involvement in childhood-onset SLE and monitoring the course of the disease.

Acknowledgements
Special thanks are due to all Rheumatology and Pulmonology Clinics members, who helped us with our work, and to our dear patients, who participated in the study.
Dr Hala M. lofty: concept and design of the study, collection of data, statistical analysis of the results, drafting the article, and revising it critically for important intellectual content, guarantor (responsible for the integrity of the work as a whole from inception to published article). Dr Eman F. Halawa: concept and design of the study, sharing in writing the manuscript, statistical analysis of the results, supervision of the work, drafting the article and revising it critically for important intellectual content. Dr Mohamed El Baz: performance of PFTs, final approval of the manuscript.

Conflicts of interest
There are no conflicts of interest.

References
Pulmonary involvement in juvenile lupus Lotfy et al. 63


Serum surfactant protein D as a prognostic factor in idiopathic pulmonary fibrosis
El-Miligy Dawalat\textsuperscript{a}, Zakaria Mohamed W.\textsuperscript{b}, Rashed Laila\textsuperscript{a}, Abu-Hussein Ha\textsuperscript{d}

\textbf{Introduction}

Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, occurring primarily in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of UIP \cite{1}.

IPF is a progressive, life-threatening, interstitial lung disease of unknown etiology. For optimal therapeutic management of IPF, an accurate tool is required for discrimination between reversible and irreversible types of the disease. However, such noninvasive tools are few, and even with high-resolution computed tomography, which is the most trusted method for this purpose, the nature of the disease activity in IPF cannot always be predicted accurately \cite{1}.

Surfactant protein D (SP-D), produced and secreted by type II cells, can be detected in serum and are elevated in patients with certain inflammatory lung diseases, including IPF \cite{2}. Although the exact mechanism of the increase in SP-D in the circulation is not known, it is probably a combination of a loss of epithelial integrity due to injury and an increased mass of type II cells due to hyperplasia. Because the concentrations of serum SP-D probably vary with disease and lung inflammation, measurement of these two proteins might prove to be useful markers for the pathogenesis and detection of IPF \cite{3,4,5}.

This study aims to investigate the possible role of SP-D in the pathogenesis and the prognosis of IPF.

\textbf{Materials and methods}

The present work was conducted on 10 healthy volunteers and 30 patients from the Department of Chest Diseases, Faculty of Medicine, Cairo University, during the period from November 2009 to May 2010 and they were categorized into four groups as follows:

(1) \textit{Group 1}: Ten healthy volunteers (control group, six male and four female): nonsmokers aged 54.7 ± 7.13 years (mean ± SD) (range: 45–65 years).

(2) \textit{Group 2}: Ten patients with IPF receiving steroid therapy for 1 month (six male and four female), consisting of two current smokers, four ex-smokers, and four nonsmokers aged 57 ± 6.63 years (mean ± SD) (range: 45–65 years).

\textbf{Results}

There was no statistical significance in the mean age of the four included groups. With regard to smoking in patients in groups 2, 3, and 4, there was no statistical significance in the duration or the number of cigarettes smoked per day. There was a significant decrease in FEV\textsubscript{1}, FVC, and FEV\textsubscript{1}/FVC in groups 2, 3, and 4 compared with the control group (group 1). SP-D shows a significant increase in groups 2, 3, and 4 compared with the control group, and also shows a significant increase in IPF patients not receiving steroids (group 3) compared with IPF patients receiving steroids (group 2) and patients with chronic chest diseases (group 4). A negative correlation was found between SP-D and FEV\textsubscript{1}, FVC, and FEV\textsubscript{1}/FVC. No correlation was found between SP-D, age, the duration of smoking, or the number of cigarettes smoked per day.

\textbf{Conclusion}

The SP-D assay may indicate the rate of decline in the pulmonary function in cases of IPF and in the follow-up of disease progress. It may also assist in making clinical choices for the therapeutic management of patients with IPF. \textit{Egypt J Broncho} 2015 9:64–68 © 2015 Egyptian Journal of Broncho.

\textbf{Keywords:} idiopathic pulmonary fibrosis, prognostic factor, surfactant protein D

\textsuperscript{a}Departments of Biochemistry, \textsuperscript{b}Chest Diseases, Cairo University, Cairo and \textsuperscript{c}Department of Biochemistry, 6th October University, Egypt

Correspondence to Mohamed W. Zakaria, Department of Chest Diseases, Cairo University, 5, Makrize Street, Zamalek, Cairo 11211, Egypt

e-mail: mw_khalil@hotmail.com

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(3) **Group 3**: Ten patients with IPF not receiving steroid therapy (five male and five female), consisting of two current smokers, three ex-smokers, and five nonsmokers aged 54.3 ± 5.27 years (mean ± SD) (range: 45–65 years).

(4) **Group 4**: Ten patients with chronic chest disease without IPF and not receiving steroids (five male and five female), consisting of two current smokers, three ex-smokers, and five nonsmokers aged 55.1 ± 8.17 years (mean ± SD) (range: 45–65 years).

**Inclusion criteria**
All IPF patients fulfilled the major and minor criteria of ATS/ERS consensus classification of the idiopathic interstitial pneumonias.

**Exclusion criteria**
(1) All known causes of ILD: for example, connective tissue diseases, sarcoidosis, or drug induced.
(2) Malignancy and other cause of interstitial pneumonia.

Patients were subjected to the following:
(1) Full history taking.
(2) Full clinical examination.
(3) Chest radiography and high-resolution computed tomography of the chest.
(4) Pulmonary function tests.
(5) Determination of serum SP-D levels.

**Collection and analysis of blood samples**
Ten milliliters peripheral venous blood samples were collected from the patients at their initial visits and from healthy participants at the time of registration for the study. The serum samples were stored at -80°C and analyzed in a blinded manner with regard to the clinical status of the patients.

**Determination of surfactant protein D**
The SP-D assay was performed with enzyme-linked immunosorbent assay kits provided by the Teijin Institute of Bio-medicine (Tokyo, Japan). A method based on that of Shimizu et al. [6] was adapted with minor modifications [7]. The concentration of SP-D was measured using recombinant SP-D as a standard and two monoclonal antibodies against human SP-D [8]. This assay system was able to detect SP-D at concentrations of 1.56–100 ng/ml. All assays were performed in duplicate, and the results are given as the mean value. In immunoblot analyses, specific antibodies used for the SP-D assay systems showed no nonspecific cross-reactivity, such as with mannose-binding protein or with other serum proteins.

**Statistical analysis**
Data are expressed as mean ± SD. Differences between SP-D values in the three study groups, variables were assessed with the Mann–Whitney U-test. Concentrations of SP-D were further analyzed using the Student t-test for the healthy group to find the cutoff levels indicating the best sensitivity and specificity of these two measures [9]. Significance was defined as P-value less than 0.001.

**Results**
In our study, the mean age of the control group was 54.70 ± 7.13 years and the mean age of the steroidal group was 57.00 ± 6.63 years.

The mean age of the nonsteroidal group was 54.30 ± 5.27 years, whereas that of the chronic group was 55.10 ± 8.17 years. There was no significant difference between the four groups.

Among current smokers, the mean duration of smoking per month was 25.00 ± 7.07 months among chronic patients, whereas 21.50 ± 4.95 months among nonsteroidal current smokers and 15.00 ± 7.07 months among steroidal current smokers; no significant differences was detected between the three groups.

In addition, the mean number of cigarettes smoked per day by current smokers was 120.00 ± 33.94 cigarettes among chronic patients, whereas it was 75.00 ± 21.21 cigarettes among nonsteroidal current smokers and 126.00 ± 8.49 cigarettes among steroidal current smokers; there was no significant difference between the three groups.

Table 1 shows a statistically significant decrease in FEV₁, FVC, and FEV₁/FVC (%) in the three disease groups compared with the control group. No significant difference was detected between the three disease groups.

The following observations can be made from Table 2.
Table 2 Mean ± SD and P-value of the serum surfactant protein D (ng/ml) level in the different study groups

<table>
<thead>
<tr>
<th>SP-D (ng/ml)</th>
<th>Control group</th>
<th>Steroidal group</th>
<th>Nonsteroidal</th>
<th>Chronic group</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-values</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P₁ = 0.000</td>
<td>P₁ = 0.000</td>
<td>P₂ = 0.000</td>
<td>P₂ = 0.000</td>
<td></td>
</tr>
<tr>
<td>P₂ = 0.000</td>
<td>P₂ = 0.001</td>
<td>P₂ = 0.005</td>
<td>P₂ = 0.005</td>
<td></td>
</tr>
</tbody>
</table>

Values are represented as mean ± SD; SP-D, surfactant protein D; P₁ = significant difference between the control group and the steroidal group; P₂ = significant difference between the control group and the nonsteroidal group; P₃ = significant difference between the control group and the chronic group; P₄ = significant difference between the steroidal group and the nonsteroidal group; P₅ = significant difference between the steroidal group and the chronic group; P₆ = significant difference between the nonsteroidal group and the chronic group; *Values are significant when P < 0.05.

(1) There is a significant increase in SP-D in the three disease groups compared with the control group.

(2) There is a significant increase in SP-D in the nonsteroidal and the chronic groups compared with the steroidal group; there is also a significant increase in the nonsteroidal group compared with the chronic group (the nonsteroidal group showed the highest mean values).

The following observations can be made from Table 3.

A negative correlation was found between the SP-D serum level and FEV₁ (l), with P-value greater than 0.000 and r-value of -0.541.

In addition, a negative correlation was found between the SP-D serum level and FVC (l), with P-value greater than 0.000 and r-value of -0.530.

Also, a negative correlation was found between the SP-D serum level and FEV/FVC, with P-value greater than 0.000 and r-value of -0.546.

In Table 4, no correlation was found between the SP-D serum level and the duration of smoking per month, with P-value less than 0.146 and r-value of -0.669.

In addition, no correlation was found between the SP-D serum level and the number of cigarettes smoked per day, with P-value less than 0.433 and r-value of 0.399.

Table 5 shows no correlation between the SP-D serum level and the age, with P-value less than 0.678 and r-value of 0.068 (Figs 1–4).

Discussion
Regarding the relation between the age of the patients and the development of IPF, many reports proved that the incidence undoubtedly increases with age. All patients enrolled in our study were above 50 years of age. This is in agreement with the study of Thomas et al. [10], who mentioned that patients with IPF are usually between 40 and 70 years of age. Also, the authors found that two-third of the IPF cases present over the age of 60 years at the time of diagnosis.

Collard et al. [11] demonstrated a strong association between cigarette smoking and pulmonary fibrosis.

The results of SP-D in the present study showed a significant increase in the three disease groups compared with the control group. Moreover, the value was significantly higher in the nonsteroid and the chronic groups compared with the steroid-receiving group. Also, the value was significantly higher in the nonsteroidal group than in the chronic group.
that the concentration of serum SP-D varies with disease severity and lung inflammation and that differences in response to corticosteroid products and solubility could also affect concentrations of SP-D in the serum. This finding agrees with our study, where we found the level of SP-D to be lower in IPF patients receiving corticosteroid compared with those not receiving corticosteroids and the group with chronic disease. Takahashi [15] found that the concentrations of SP-A and SP-D in patients who died within 3 years were significantly higher than in patients who were still alive after 3 years. It has been proposed that assays of SP-A and SP-D in sera from IPF patients are useful tools for understanding some pathologic characteristics of the disease, that SP-D may be a good predictive indicator of the rate of decline in pulmonary function, and that a combination of the assays for SP-A and SP-D may be

Schwartz et al. [12] stated that patients exhibiting higher serum levels of SP-D may have a greater chance of developing restrictive pulmonary dysfunction, and more rapidly than patients with low serum levels of SP-D. He also concluded that it may be more effective to start treatment for IPF before the manifestations of severe pulmonary fibrosis occur. Our results raise the possibility that the assay of SP-D can help guide the therapy with corticosteroids agents.

McCormack et al. [13] evaluated the utility of assays of serum SP-D in establishing the prognosis of patients with IPF. None of the patients showing SP-D levels below the respective levels died throughout the period of the study (2 years). His findings suggest that an SP-D assay is useful to identify patients with the best prognosis in IPF.

A difference between levels of SP-D was also observed in the four studied groups. Honda et al. [14] concluded that the concentration of serum SP-D varies with disease severity and lung inflammation and that differences in response to corticosteroid products and solubility could also affect concentrations of SP-D in the serum.

This finding agrees with our study, where we found the level of SP-D to be lower in IPF patients receiving corticosteroid compared with those not receiving corticosteroids and the group with chronic disease.

Fig. 1

Mean ± SD of serum surfactant protein D level (ng/ml) in the different study groups.

Fig. 2

The serum surfactant protein D level (ng/ml) in relation to FEV₁ (l).

Fig. 3

The serum surfactant protein D level (ng/ml) in relation to FVC (l).

Fig. 4

The serum surfactant protein D level (ng/ml) in relation to pulmonary function tests.
helpful in predicting the outcome of patients with IPF.

This study is in agreement with our results where a negative correlation was found between the SP-D level and FEV₁/FVC, and FEV₁/FVC.

Part of our results is in agreement with data from Takahashi et al. [16] and Barlo et al. [17] and it showed that SP-D in the serum can predict worsening in IPF patients, and that the value of SP-D remains stable after adjustment for known predictors of worsening. The author mentioned that a serum SP-D level higher than 460 ng/ml indicates a significantly worse prognosis compared with levels lower than 460 ng/ml. This value can be useful in clinical practice. It might help in estimating the survival time, which is important for the optimal timing of referral for lung transplantation [16].

According to Kinder et al. [18], an increased serum SP-D level is a strong and independent predictor of early mortality among patients with IPF. A prediction model containing SP-A and SP-D was substantially superior to a model with clinical predictors alone.

SP-D is a noninvasive marker that can be easily determined in the serum and has been proven to be a diagnostic marker in IPF patients. This study adds clinically useful levels that could identify patients with a significantly worse prognosis using SP-D for the follow-up of the patients. This prognostic value of SP-D persists after adjustment for known predictors of mortality.

Acknowledgements
Conflicts of interest
None declared.

References
**Introduction**

Idiopathic pulmonary fibrosis (IPF) is a progressive invariably fatal condition that severely compromises pulmonary function [1]. Major advances have been made in understanding the pathogenesis of the inflammatory and fibrotic mechanisms at work in IPF. The exact triggers, which initiate this fibrotic process, remain unknown. Viruses, for example, hepatitis C virus (HCV), have long been suspected of playing a role in IPF etiology; however, data on the prevalence of HCV infection in IPF patients were limited.

**Aim of the study**

Our aims were to assess the prevalence of HCV antibodies in IPF patients and to assess the relationship between severity of pulmonary and hepatic dysfunction.

**Materials and methods**

IPF patients were prospectively enrolled from Chest Department, Assiut University Hospital. HCV antibodies were detected using the third-generation enzyme-linked immunosorbent assay. Patients’ pulmonary and hepatic functions were evaluated.

**Results**

HCV antibodies were significantly higher in IPF patients than in controls (29.4 vs. 14%, \( P = 0.04 \)). Patients with HCV had significantly more severe hypoxemia and lower diffusing capacity for carbon monoxide than those without HCV (47.7 ± 11.3 vs. 54 ± 18.7, \( P = 0.03 \) and 52.7 ± 8.4 vs. 67.3 ± 9.5, \( P = 0.01 \), respectively). There was no significant difference between HCV-positive IPF patients and HCV-negative IPF patients regarding spirometric parameters and liver function parameters.

**Conclusion**

This higher prevalence of HCV and its effect on pulmonary functions in IPF patients may contribute in IPF pathogenesis, which hopefully will allow currently available antiviral drugs or novel therapeutic approaches to treat or modify the course of this devastating disease.

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**Keywords:** hepatitis C virus, idiopathic pulmonary fibrosis, immunopathogenesis

* Departments of Tropical Medicine and Gastroenterology, *Chest, *Clinical Pathology, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to Elham Ahmed Hassan, MD, Department of Tropical Medicine and Gastroenterology, Assiut University Hospital, Assiut 71111, Egypt
Tel: 01002963415; fax: +20 882 333 327; e-mail: mam_elham75@yahoo.com

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of FVC, forced expiratory volume in the first second (FEV₁), and FEV₁/FVC ratio.

(3) Diffusion capacity of the lung for carbon monoxide (DLCO%) using single-breath method.

(4) Arterial blood gas (ABG) analysis by measuring pH, PaCO₂, PaO₂, and SaO₂.

(5) Liver function tests (aspartate aminotransferase, alanine transaminase, alkaline phosphatase, albumin, bilirubin, and prothrombin time).

(6) Serological tests for HBV and HCV infection (anti-HCV antibodies and HBsAg).

(7) Abdominal ultrasound.

The degree of pulmonary restriction of IPF patients was classified according to % predicted of FVC [9]:

Mild: predicted FVC below lower limited normal but at least 70%.

Moderate: predicted FVC below 70% and at least 50%.

Severe: predicted FVC below 50% and at least 34%.

Very severe: predicted FVC below 34%.

Methods

Venous blood sample of 3–5 ml was obtained from each participant. Samples were collected and centrifuged immediately. Serum samples were frozen at −70°C until assayed. Anti-HCV antibodies were detected using the third-generation enzyme-linked immunosorbent assay (AiD anti-HCV ELISA) (Diagnostic Automation Group, Sunnyvale, California, USA) and HBsAg was tested by ELISA (AiD HBsAg ELISA) (Beijing Wantai Biological Pharmacy Enterprise Co. Ltd, Beijing, China) in accordance with the protocol of the manufacturer.

Statistical analysis

All statistical analyses were conducted using SPSS for Windows, version 17 (SPSS Inc., Chicago, Illinois, USA). The continuous data were expressed as mean ± SD and were compared using Student’s t-test. Categorical variables were expressed as percentage and compared using the χ²-test. For all analyses, P value less than 0.05 was considered statistically significant.

Results

During the period between January 2014 and June 2014, 104 patients with IPF were admitted to Chest Department; 30 of them had HCV and only two patients had HBV. The remaining patients were seronegative for viral hepatitis. HBV patients were excluded from this study.

Hence, the study included 102 IPF patients; 22 were male patients and 80 were female patients with a mean age of 48.7 ± 5.3 years (range 20–66 years). The control group was formed of 37 women and 13 men with a mean age of 47.5 ± 7.6 years. HCV infection was significantly higher in IPF patients than in controls (29.4 vs. 14%, P = 0.04).

Table 1 shows the characteristics of the IPF patients with and without HCV infection. We noticed that HCV-positive IPF patients were younger than those IPF patients without HCV infection but with no statistical significance. In addition, there were no significant differences between the two groups with respect to sex ratio and smoking (Table 1).

Regarding ABG, patients with HCV infection had significantly more severe hypoxemia as compared with those without HCV (47.7 ± 11.3 vs. 54 ± 18.7, P = 0.03). In addition, DLCO% was significantly lower in patient with HCV than in patients without HCV (52.7 ± 8.4 vs. 67.3 ± 9.5, P = 0.01). With respect to spirometric findings, % predicted of FVC was not significantly altered but showed a tendency toward decreased values in IPF patients with HCV infection (P > 0.05) (Table 1).

Among HCV-positive IPF patients, there was decrease in the % predicted of FVC and DLCO% in cirrhotic patients than in those without liver cirrhosis; however, these differences were not statistically significant. In addition, ABG parameters showed no significant difference between both groups (Table 2).

Table 3 shows no significant differences between HCV-positive IPF patients with moderate and severe pulmonary restriction regarding liver function parameters and sonographic liver pattern changes.
Table 2 Pulmonary function and ABG parameters of HCV-positive IPF patients according to the severity of liver disease

<table>
<thead>
<tr>
<th>Variables</th>
<th>IPF, HCV patients without liver cirrhosis (n = 22)</th>
<th>IPF, HCV patients with liver cirrhosis (n = 8)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>FVC (% predicted)</td>
<td>60 ± 12.5</td>
<td>56 ± 11.8</td>
<td>0.872</td>
</tr>
<tr>
<td>DLCO (%)</td>
<td>54.2 ± 4.8</td>
<td>49.3 ± 6.2</td>
<td>0.860</td>
</tr>
<tr>
<td>Hypoxemia</td>
<td>50 ± 3.2</td>
<td>45 ± 6.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Blood gases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.5 ± 0.06</td>
<td>7.4 ± 0.05</td>
<td>0.132</td>
</tr>
<tr>
<td>PaO₂</td>
<td>56.2 ± 17.6</td>
<td>45.6 ± 7.4</td>
<td>0.064</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>39.4 ± 8.5</td>
<td>40.2 ± 13.4</td>
<td>0.798</td>
</tr>
<tr>
<td>SO₂</td>
<td>87.2 ± 8.3</td>
<td>82.2 ± 10.2</td>
<td>0.087</td>
</tr>
<tr>
<td>HCO₃</td>
<td>27 ± 6.2</td>
<td>30.7 ± 5.9</td>
<td>0.264</td>
</tr>
</tbody>
</table>

Table 3 Liver function parameters and sonographic liver pattern in HCV-positive IPF patients according to the severity of pulmonary restriction

<table>
<thead>
<tr>
<th>Variables</th>
<th>Moderate pulmonary restriction (n = 8)</th>
<th>Severe pulmonary restriction (n = 22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (mean ± SD) (IU/l)</td>
<td>66.4 ± 46.5</td>
<td>62.6 ± 95.4</td>
<td>0.858</td>
</tr>
<tr>
<td>ALT (mean ± SD) (IU/l)</td>
<td>90.2 ± 48.8</td>
<td>75.5 ± 82.8</td>
<td>0.429</td>
</tr>
<tr>
<td>Serum albumin (mean ± SD) (g/dl)</td>
<td>3.3 ± 7.9</td>
<td>32 ± 6.8</td>
<td>0.935</td>
</tr>
<tr>
<td>Serum bilirubin (mean ± SD) (μmol/l)</td>
<td>19.4 ± 16.2</td>
<td>20.1 ± 37.3</td>
<td>0.931</td>
</tr>
<tr>
<td>INR (mean ± SD)</td>
<td>1.1 ± 0.4</td>
<td>1.3 ± 0.4</td>
<td>0.623</td>
</tr>
<tr>
<td>Abdominal ultrasound [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>2 (25)</td>
<td>6 (25)</td>
<td>0.343</td>
</tr>
<tr>
<td>DHP</td>
<td>4 (50)</td>
<td>10 (41.7)</td>
<td></td>
</tr>
<tr>
<td>LC</td>
<td>2 (25)</td>
<td>8 (33.3)</td>
<td></td>
</tr>
</tbody>
</table>

Discussion

In this study, we tried to answer whether HCV infection affects the prevalence and has a role in the pathogenesis of IPF. The present study showed significant higher prevalence of chronic HCV infection in IPF patients (29.4%) compared with healthy controls (14%). This result was within the range of the previous estimates for the prevalence of HCV infection in IPF patients, where Ueda et al. [10] detected anti-HCV antibodies in 28.8% of patients with IPF. In addition, Meliconi et al. [11] reported a higher prevalence of HCV antibody in patients with IPF compared with the general population. However, Irving et al. [2] was unable to find any connection between HCV and IPF. These controversial results may be explained by the geographical differences and other factors where people from Japan and Mediterranean countries are more susceptible to HCV than those from northern Europe [12].

This high prevalence of HCV antibodies among IPF patients may suggest a possible role for HCV infection in the pathogenesis of IPF. HCV is a well-known cause of liver fibrosis, and it could potentially provoke similar abnormalities in the lung, mainly because of its lymphotropism, which can induce chronic immune activation and inflammation [13]. Viral infections including occult ones may play a pathogenetic role as cofactors in the development of fibrosis. This hypothesis is based on the assumption that this inflammatory agent (HCV) disrupts the normal healing process, thereby making the lung to be highly susceptible to injurious triggers [14]. Chronic HCV infection may contribute to the immune responses that modulate the pathogenic processes underlying pulmonary disorders— for example, accumulation to lung tissue of immunoglobulin and/or immune complex or direct involvement of HCV-RNA [15]. Idilman et al. [16] reported an increased bronchoalveolar lavage neutrophil count in individuals with chronic HCV hepatitis. This finding suggests that HCV may have the potential to induce an alveolitis leading to fibrotic changes in the lung [15].

Our findings were in agreement with previous studies, which reported that HCV infection was complicated by a number of extrahepatic manifestations including restrictive lung diseases [17,18]. In addition, some conditions, such as mixed cryoglobulinemia and sicca syndrome, are observed in HCV infection and can involve the lung [19,20].

The higher prevalence of HCV infection in IPF patients may be explained in part by acquiring the HCV through frequent hospitalization, injections, or other ancillary factors; especially, we have not been able to determine whichever happened first. However, this hypothesis can be refuted because of the lack of the number of patients infected with HBV, despite being subjected to the same factors.

The mean age of IPF patients in our study was younger than that reported in the literatures that stated IPF is common in elderly [4]. In addition, HCV-positive IPF patients were younger age compared with those without infection in our series. This may reflect the background rate (10%) of HCV infection among persons aged 15–59 years suggesting that HCV may implicate in pathogenesis of IPF [5].

The current study revealed that HCV-positive IPF patients had significant reduction in PaO₂ and DLCO% compared with IPF patients without HCV infection. Erturk et al. [21] demonstrated abnormal DLCO% results that occurred early in HCV infection.
suggesting a high rate of subclinical pulmonary destruction in patients with chronic HCV infection.

We speculated that the underlying mechanism predisposing to more severe hypoxemia and impairment of gas exchange may be chronic immune activation and inflammation-induced HCV infection causing accelerated decline of pulmonary function [18,22]. Moreover, polymyositis, a complication of chronic HCV infection, can also impair respiration through weakened respiratory muscles [23]. Saleh et al. [6] demonstrated that HCV-related cryoglobulinemia may have an impact on both gas exchange and airway parameters. In addition, pulmonary vascular dilatation and ventilation perfusion mismatch that occurs in cirrhotic patients may be another explanation of decreased oxygen level [23].

In agreement with the study by Saleh et al. [6], our study found that the severity of pulmonary involvement was not parallel to the liver impairment; thus, patient management and prediction of disease outcome can be subject to marked variability.

Conclusion
This higher prevalence of HCV and its effects on pulmonary functions in IPF patients may contribute in IPF pathogenesis, which hopefully will allow currently available antiviral drugs or novel therapeutic approaches to treat or modify the course of this devastating disease. However, further studies should be performed to determine whether there is a causal relationship between HCV infection and IPF. In addition, screening for early parenchymatous lung changes in patients with HCV is recommended.

Acknowledgements
Conflicts of interest
There are no conflicts of interest.

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The diagnostic utility of pleural fluid viscosity in lymphocytic pleural effusion
Sayed Labiba, Ibraheem Dwidarc, Eman Riada, Basma B. Hasanb

Context The first step in the diagnostic work up of pleural effusion is the distinction between transudative and exudative pleural effusions (TPEs and EPEs). This discrimination is based on some biochemical tests that are relatively costly and time consuming. Lymphocyte-predominant EPE is the result of many diseases with malignancy, tuberculosis being the most common among them.

Aims The aim of this study was to assess the role of pleural fluid viscosity in the differentiation between exudates and transudates and to identify the cause of pleural effusion.

Patients and methods The study comprised 10 patients with TPE and 48 patients with EPE: 18 of them had tuberculous (TB) effusion, 25 patients had malignant pleural effusion (MPE) (patients with MPE included 10 with lung cancer and 15 with other known or unknown cancers) and five patients had connective tissue disease (CTD)-associated effusion. Pleural fluid protein, albumin, lactic dehydrogenase, and viscosity were measured in all patients.

Results Pleural fluid viscosity was higher in patients with EPE with a highly significant difference ($P < 0.01$), and a cutoff value of 1.01 cP could distinguish between TPE and EPE with a sensitivity of 97.7%, a specificity of 93.9%, a positive predictive value of 97.5%, and a negative predictive value of 92.5%. It also showed significant positive correlation with protein, albumin, and lactic dehydrogenase.

Conclusion Pleural fluid viscosity can reliably differentiate between TPE and EPE. It can also help in the discrimination between TB effusion and MPE with moderate sensitivity and high specificity. Egypt J Broncho 2015 9:73–78 © 2015 Egyptian Journal of Bronchology.

Introduction Pleural effusion denotes abnormal accumulation of fluid within the pleural cavity. It may be caused by increased production, decreased drainage, or more commonly both. It is the most common manifestation of pleural disease, with etiologies ranging from cardiopulmonary disorders to systemic inflammatory or malignant diseases requiring urgent evaluation and treatment [1].

These effusions may be transudates needing only treatment of the cause or exudates requiring a definite diagnosis with specific treatment modalities. This classification was based on the criteria of Light et al. [2] and more recently, other tests such as protein and cholesterol levels in effusion and serum-effusion albumin gradient (SEAG) have been shown to have a statistically similar diagnostic accuracy [3,4].

Distinction between transudates and exudates to determine the origin of pleural effusions is an essential first step in the diagnostic work up. Other tests include radiologic and sonographic assessment, pleural fluid cytology, bacteriology, biochemistry, and blind pleural biopsy. However, after exhaustion of these tests, 20% of exudative pleural effusion (EPE) is still undiagnosed [5], and more advanced tests, such as image-guided pleural biopsy, pleuroscopy or video-assisted thoracoscopy, bronchoscopy, and open pleural biopsy are needed in individual patients [6].

Lymphocytic pleural effusion (lymphocytes constitute >50% of the white cell population) indicates that the patient probably has a malignant pleural effusion (MPE) or a tuberculous (TB) pleural effusion [7,8].

Viscosity means the resistance of fluid to flow; in other words, the viscosity of any type of fluid is the expression of the ratio of shear stress to the shear rate of the particles in that fluid. Plasma viscosity is related to the concentration of plasma proteins (especially fibrinogen) and lipoproteins. Other factors affecting plasma viscosity include their molecular weights, rigidity, and the shape of individual molecules [9].
The same could apply to pleural fluid in patients with pleural effusion as shown by Yektin et al. [10], who found that pleural exudates have a higher fluid viscosity. The cellular content of pleural fluid as well as the size and the rigidity of cells also cause increased fluid viscosity [11]; hence, diseases with a relatively high cellular content in the pleural space, such as TB pleural effusions and MPEs, could have a higher viscosity.

Aim of the work
The study aimed to assess the role of pleural fluid viscosity measurement in the differentiation between exudates and transudates and the identification of the cause of exudative lymphocytic pleural effusion.

Patients and methods
This cross-sectional comparative study was conducted in the Chest Unit, Suez Canal University Hospital, Ismailia, Egypt, and the Chest Department, Ain Shams University Hospitals, Cairo, Egypt. The study population included 58 patients with pleural effusion: 10 of them had transudative pleural effusion (TPE) and 48 patients had EPE with lymphocytic predominance (i.e. lymphocytes constituted more than 50% of cells in the pleural fluid). Transudates were defined by a negative test for all items of the Light criteria as well as by a SEAG greater than 1.2, and the reverse is true regarding EPE.

Patients with eosinophilic and neutrophilic pleural effusions as well as patients with lymphocyte-predominant effusion with unknown cause were excluded. All patients gave an informed written consent to be involved in the study.

All patients were subjected to the following: complete medical history and careful clinical examination, radiological assessment, diagnostic thoracentesis, routine blood investigations, measurement of pleural fluid viscosity, serum and pleural fluid proteins, albumin, lactic dehydrogenase (LDH), and glucose. Other investigations were performed in patients with EPE, which included pleural fluid cytology, differential cell count, pleural biopsies with histopathological examination, adenosine deaminase when TB pleural effusion was suspected, and antinuclear antibody and rheumatoid factor when connective tissue disease (CTD) was suspected. Further investigations were dictated by the clinical presentation of each patient. MPE was suggested in patients with a known malignancy and diagnosed by positive cytology and/or pleural biopsy specimens for malignancy. TB pleural effusion was diagnosed by positive tuberculin skin testing, lymphocytic predominance, and the presence of caseating granuloma in biopsy specimens; otherwise, the diagnosis was confirmed by the presence of adenosine deaminase level higher than 43 IU/l [12], in patients younger than 40 years of age, with a highly suggestive clinical picture and with good response to anti-TB medications.

Patients with CTD were diagnosed by the rheumatologist on the basis of specific criteria [13,14]. Rheumatoid pleural effusion was suggested by a glucose level in pleural fluid less than 30 mg/dl and rheumatoid factor of at least 1 : 320 with values higher than the serum titer [15], and lupus pleuritis was diagnosed if the antinuclear antibody in the pleural fluid was higher than in the serum in the proper clinical setting with good response to corticosteroids [16].

Measurement of pleural fluid viscosity
Ten milliliters of pleural fluid mixed with EDTA were used for the measurement of viscosity using a portable viscometer (Viscolite 100; Hydramotion, Malton/York, UK) before and after centrifugation with digital expression of the viscosity \((h)\) readings in centipoises (cP) units.

Statistical analysis
Data were analyzed using Statistical Program for Social Science (SPSS version 20, 2009, Echosoft Corporation, USA). Quantitative data were expressed as mean ± SD. Qualitative data were expressed as frequency and percentage.

The following tests were performed:

1. Independent-sample \(t\)-test of significance was used when comparing between two means.
2. A one-way analysis of variance was used when comparing between more than two means.
3. The \(\chi^2\)-test of significance was used to compare proportions between two qualitative parameters.
4. Pearson's correlation coefficient \((r)\) test was used for correlating data.
5. Probability \((P\)-value) \n   (a) \(P\)-value less than 0.05 was considered significant.
   (b) \(P\)-value less than 0.01 was considered as highly significant.
   (c) \(P\)-value greater than 0.05 was considered insignificant.

Results
The study comprised 58 patients with pleural effusion: 10 of them had TPE, three men and seven women with a mean age of 59.2 ± 10.2 years (Table
1) (two with hepatic hydrothorax, two with nephrotic syndrome, and six with congestive heart failure), and 48 patients had EPE with lymphocyte predominance, 32 men and 16 women with a mean age of 55.15 ± 12.72 years; 25 patients with exudative pleural effusion (EPE) received a diagnosis of MPE (10 with bronchogenic carcinoma, five with cancer breast, three with lymphoma, two with cancer cervix, and five with unknown primary cancer) (Figs. 1–4). Eighteen patients with EPE were diagnosed as TB pleural effusion and five were diagnosed as pleural effusion associated with CTD (three with rheumatoid arthritis and two with systemic lupus erythematosus) (Tables 2–6).

**Discussion**

Although there are more than 50 recognized causes of pleural effusion, malignancy, infections including tuberculosis, congestive heart failure and venous thromboembolism are the most common underlying etiologies [17,18]. Pleural fluid exudate is identified by any of the following criteria [19,20]:

1. The ratio of pleural fluid protein to serum protein is greater than 0.5.
2. The pleural fluid LDH to serum LDH is greater than 0.6 or two-third of the upper limit of the normal of serum LDH.

However, in some patients with TPE receiving diuretics, serum effusion protein or albumin gradients can be used [21,22]. EPEs with lymphocytes greater than 50% of the total cell population are caused by many diseases with malignancy, tuberculosis being the most common among them [23].

In the present study, pleural fluid viscosity was measured in 10 patients with TPEs and 48 patients with lymphocytic EPEs. It revealed significantly higher values in EPEs than in TPEs, and a significant positive correlation with pleural fluid protein, albumin, LDH, and the SEAG. Using the receiver operating characteristics curve, it was found that a cutoff value of 1.01 cP could discriminate between both types of effusions, with a sensitivity of 97.7%, a specificity of 93.9%, a positive predictive value (PPV) of 97.5%, and a negative predictive value (NPV) of 92.8% with a diagnostic accuracy of 98%.

These results are consistent with those of Hurth et al. [24] who demonstrated that an EPE had a viscosity around 1.39 ± 0.08 cP, whereas a TPE measured at 0.89±0.09 cP, and those of Yetkin et al. [10] who found that using a cutoff value of 1 Cp for pleural fluid viscosity could differentiate between both types of effusions with a sensitivity of 94%, a specificity of 93%, and PPV and NPV of 97%.

Plasma viscosity is almost twice as high as that of water, which is due to dissolved macromolecules, mainly fibrinogen, immunoglobulins, albumin, and lipoproteins [25]. Pleural fluid transudate results from diseases that do not directly involve the pleural, but instead produce an imbalance of Starling’s forces, resulting in the movement of fluid into the pleural space [26]. It is expected for a transudate, which is a...
The number and the percent distribution of primary cancers in patients with malignant pleural effusion.

Table 1 A comparison between transudative and exudative pleural effusions with regard to age and sex

<table>
<thead>
<tr>
<th>Sex</th>
<th>Transudative pleural effusion</th>
<th>Exudative pleural effusion</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 10)</td>
<td>(n = 48)</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>59.20 ± 10.20</td>
<td>55.15 ± 12.72</td>
<td>2.110 0.394</td>
</tr>
<tr>
<td>Sex [n (%)]</td>
<td>3 (30.00)</td>
<td>32 (66.67)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7 (70.00)</td>
<td>16 (33.33)</td>
<td>4.650 0.106*</td>
</tr>
<tr>
<td>Female</td>
<td>10 (100.00)</td>
<td>48 (100.00)</td>
<td></td>
</tr>
</tbody>
</table>

There is a nonsignificant statistical difference between both types of effusions with regard to age and sex; *χ², χ²-test; †-test, independent-sample †-test; P-value > 0.05, nonsignificant.

Table 2 A comparison between transudative and exudative pleural effusions with regard to protein, albumin, LDH, and SEAG

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>Transudative pleural effusion (n = 10)</th>
<th>Exudative pleural effusion (n = 48)</th>
<th>t  P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (g/dl)</td>
<td>1.74 ± 0.80</td>
<td>4.94 ± 0.80</td>
<td>11.585 &lt;0.01</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>1.29 ± 0.47</td>
<td>3.84 ± 0.49</td>
<td>14.959 &lt;0.01</td>
</tr>
<tr>
<td>LDH (IU/l)</td>
<td>149.44 ± 44.16</td>
<td>387.56 ± 108.29</td>
<td>6.458 &lt;0.01</td>
</tr>
<tr>
<td>SEAG (g/dl)</td>
<td>1.48 ± 0.18</td>
<td>0.49 ± 0.33</td>
<td>9.087 &lt;0.01</td>
</tr>
</tbody>
</table>

There is a highly significant statistical difference between both types of effusions with regard to all chemistry parameters; LDH, lactate dehydrogenase; SEAG, serum-effusion albumin gradient; †-test, independent-sample †-test; P-value < 0.01, highly significant.

Table 3 A comparison between transudative and exudative pleural effusions with regard to the pleural fluid viscosity

<table>
<thead>
<tr>
<th>Pleural fluid viscosity (cP)</th>
<th>Transudative pleural effusion (n = 10)</th>
<th>Exudative pleural effusion (n = 48)</th>
<th>t  P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precentrifugation</td>
<td>0.75 ± 0.11</td>
<td>1.70 ± 0.18</td>
<td>15.663 &lt;0.01</td>
</tr>
<tr>
<td>Postcentrifugation</td>
<td>0.63 ± 0.08</td>
<td>1.37 ± 0.16</td>
<td>13.838 &lt;0.01</td>
</tr>
</tbody>
</table>

There is a highly significant statistical difference between both types of effusions with regard to the pleural fluid viscosity; †-test, independent-sample †-test; P-value < 0.01, highly significant.

In contrast, EPEs result from local or systemic diseases that directly involve the pleural surface [26], leading to increased permeability and influx of cells and macromolecules into the pleural space, with subsequent increased viscosity. Our study revealed that the precentrifugation pleural viscosity showed nonsignificant differences among malignant, TB, and CTD-associated effusions. However, postcentrifugation pleural fluid viscosity was higher in both TB and CTD-associated effusions compared with MPEs, with a highly significant statistical difference (0.01). We also found nonsignificant differences in the viscosity in MPE with regard to cases secondary to bronchogenic carcinoma versus other cases with known and unknown primary cancer. TB pleural effusions had significantly higher viscosity than CTD-associated effusions (P < 0.5). Using receiver operating characteristic curve for the differentiation between MPEs and TB pleural effusions, it was shown that at a cutoff value of pleural fluid viscosity of 1.5 cP, values of at least 1.5 cP were in favor of TB pleural effusion with a sensitivity of 67%, a specificity of 84%, a PPV of 75%, and an NPV of 77%, with a diagnostic accuracy of 75.7%. Our results are in agreement with those of Yetkin et al. [27] who found that pleural viscosity of at least 1.57 mPa s indicates TB effusion with a sensitivity of 100% and a specificity of 95% and pleural fluid viscosity of less than 1.39 mPa s indicates malignancy with a sensitivity of 100% and a specificity of 94%. In contrast, Chang et al. [28] claimed that MPE, with positive fluid cytology for malignant cells, had a significantly higher pleural fluid viscosity than infectious causes. These results could be explained by the higher protein content frequently encountered in TB pleural effusion, and values above 5 g/dl suggest a TB effusion [29]. Moreover, the variability of protein composition between malignant and benign effusions might potentially explain the difference [30]. Even a more recent study by Ji et al. [31] disclosed different profiles of acute-phase proteins (C-reactive protein) and prealbumin between infections (TB and parapneumonic) and MPE, and this might be reflected in the pleural fluid viscosity. Actually, as suggested by Yetkin et al. [32] plasma viscosity could be considered as an acute-phase reactant surrogate in patients with pneumonia. Fibrinogen, because of its molecular size and shape, is a major determinant of plasma viscosity, and during an acute-phase reaction, the expression of this protein is increased in hepatocytes and may be also in lung epithelial cells [33]. However, it is not known as to how much fibrinogen in the pleural fluid can affect the pleural fluid viscosity. The higher precentrifugation pleural fluid viscosity in MPE, as suggested by Chang
Table 4 A comparison among different causes of exudative lymphocytic pleural effusion with regard to laboratory parameters in the pleural fluid

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>Malignant pleural effusion (n = 25)</th>
<th>Tuberculous pleural effusion (n = 18)</th>
<th>CTD-associated effusion (n = 5)</th>
<th>ANOVA F</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein (g/dl)</td>
<td>4.19 ± 0.88</td>
<td>4.88 ± 0.53</td>
<td>4.12 ± 0.11</td>
<td>2.112</td>
<td>0.071</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.72 ± 0.61</td>
<td>4.02 ± 0.30</td>
<td>3.82 ± 0.11</td>
<td>1.913</td>
<td>0.159</td>
</tr>
<tr>
<td>LDH (IU/I)</td>
<td>391.44 ± 129.86</td>
<td>409.78 ± 71.71</td>
<td>288.20 ± 9.31</td>
<td>2.678</td>
<td>0.126</td>
</tr>
<tr>
<td>Viscosity (cP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Precentrifugation</td>
<td>1.71 ± 0.22</td>
<td>1.71 ± 0.16</td>
<td>1.64 ± 0.05</td>
<td>0.287</td>
<td>0.752</td>
</tr>
<tr>
<td>Postcentrifugation</td>
<td>1.26 ± 0.12</td>
<td>1.61 ± 0.11</td>
<td>1.42 ± 0.16</td>
<td>25.680</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>SEAG (g/dl)</td>
<td>0.58 ± 0.37</td>
<td>0.37 ± 0.21</td>
<td>0.48 ± 0.44</td>
<td>2.154</td>
<td>0.128</td>
</tr>
</tbody>
</table>

ANOVA, analysis of variance; CTD, connective tissue diseases; LDH, lactic dehydrogenase; SEAG, serum-effusion albumin gradient; *The postcentrifugation viscosity shows a highly significant difference between malignant and (tuberculous and CTD-associated) pleural effusions; **A significant difference between tuberculous and CTD-associated pleural effusions. Other parameters show nonsignificant differences; F, ANOVA test.

Fig. 4
(a) A positive correlation between the postcentrifugation pleural fluid viscosity and pleural fluid protein in exudative lymphocytic pleural effusion. (b) A positive correlation between the postcentrifugation pleural fluid viscosity and pleural fluid albumin in exudative lymphocytic pleural effusion. (c) A positive correlation between the postcentrifugation pleural fluid viscosity and pleural fluid lactic dehydrogenase (LDH) in exudative lymphocytic pleural effusion. (d) A negative correlation between the postcentrifugation pleural fluid viscosity and the pleural fluid serum-effusion albumin gradient (SEAG) in exudative lymphocytic pleural effusion.

et al. [28] could be explained by the contribution of cell rigidity and the size of malignant cells to pleural fluid viscosity in cases with a positive fluid cytology; however, in contrast to our results, they also found nonsignificantly lower values of pleural fluid viscosity in infectious pleural effusions than in MPE.
Table 5 A comparison between pleural effusion secondary to lung cancer versus other cancers or unknown primary cancer with regard to precentrifugation and postcentrifugation pleural fluid viscosities

<table>
<thead>
<tr>
<th>Viscosity (cP)</th>
<th>Pleural effusion (primary lung cancer) (n = 10)</th>
<th>Pleural effusion (other cancers or unknown primary) (n = 15)</th>
<th>t</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precentrifugation</td>
<td>1.76 ± 0.19</td>
<td>1.68 ± 0.23</td>
<td>-0.923</td>
<td>0.367</td>
</tr>
<tr>
<td>Postcentrifugation</td>
<td>1.3 ± 0.15</td>
<td>1.24 ± 0.09</td>
<td>1.243</td>
<td>0.227</td>
</tr>
</tbody>
</table>

There is a nonsignificant difference between pleural effusion secondary to lung cancer versus other cancers or unknown primary cancer with regard to precentrifugation and postcentrifugation pleural fluid viscosities, with P-value > 0.05.

Table 6 The correlation between postcentrifugation viscosity and protein, albumin, LDH, and SEAG in exudative lymphocytic pleural effusions

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>Postcentrifugation pleural fluid viscosity (cP)</th>
<th>r</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural fluid protein (g/dl)</td>
<td>0.202</td>
<td>0.023</td>
<td></td>
</tr>
<tr>
<td>Pleural fluid albumin (g/dl)</td>
<td>0.374</td>
<td>0.023</td>
<td></td>
</tr>
<tr>
<td>Pleural fluid LDH (IU/l)</td>
<td>0.499</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>SEAG (g/dl)</td>
<td>-0.350</td>
<td>0.017</td>
<td></td>
</tr>
</tbody>
</table>

There is a significant positive correlation between the postcentrifugation viscosity and other chemistry parameters in exudative lymphocytic pleural effusions, but a negative correlation with the serum-effusion albumin gradient; LDH, lactic dehydrogenase; r, Pearson’s correlation coefficient; SEAG, serum-effusion albumin gradient; P < 0.05, significant; P < 0.01, highly significant.

Conclusion
The measurement of pleural viscosity is a simple, cheap, and accurate test, and it can be used as a bedside test to reliably distinguish pleural fluid exudates from transudates. It can also help in differentiating TB pleural effusion from MPEs with moderate sensitivity and high specificity in lymphocytic EPE.

Acknowledgements
Conflicts of interest
None declared.

References
Introduction
Ultrasonography (US) has become an invaluable tool in the management of critically ill patients.

Objectives
This study aimed to evaluate the role of US in the diagnosis and treatment of pleural diseases in patients in the respiratory intensive care unit.

Patients and methods
This study recruited 55 patients who presented with suspected clinical and/or radiological evidence of pleural disease in whom US and chest radiography were performed. In addition, US-guided interventions were carried out whenever needed and computed tomography scans of the chest where obtained whenever possible.

Results
Pleural effusion was the most common pleural disease encountered (54.5%). US correctly predicted the nature of most pleural effusions, whether transudative or exudative (84%). US was significantly more sensitive than chest radiography in the diagnosis of pleural effusion and pleural thickening \((P = 0.00\) and \(0.004\), respectively) and had significantly better sensitivity for unilateral effusions and for septations compared with computed tomography \((P = 0.004\). There was almost perfect agreement between US results and the final diagnosis in all pleural diseases, with \(\kappa\) values ranging from 0.9 to 0.98. A total of 67 US-guided interventions were carried out, with a success rate of 94%, and only one (1.5%) complication was encountered in the form of partial pneumothorax. US affected the diagnosis and altered the treatment policy, with recorded favorable outcomes. Short-term training programs enable pulmonologists to acquire US examination skills after 30 examinations.

Conclusion
US is an efficient and suitable method for evaluating pleural disease in the respiratory intensive care unit, especially pleural effusion. US-guided pleural interventions have been successful and have shown favorable outcomes and minimal complications. Short-term training could enable mastering of US use.

Keywords: intensive care unit, interventions, pleura, ultrasound

Departments of *Chest Diseases* and Radiodiagnosis, Ain Shams University, Cairo, ‘Abbassia Chest Hospital, Cairo, Egypt

Correspondence to Nehad M. Osman, MD, PhD, 7, Kadry ST, Hamamat El Kobba, 2111 Cairo, Egypt

Tel: +20 122 354 9008; e-mail: osman_nehad@yahoo.com

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Introduction
The benefits of ultrasonography (US) include its portability, low cost, lack of radiation exposure, and ability to provide dynamic and real-time procedural guidance at the bedside [1]. Lung consolidation, atelectasis, and pleural effusions are common in intensive care unit (ICU) patients and are often present at the same time. Portable, supine, and anteroposterior chest radiographs taken in these patients offer limited sensitivity for the diagnosis of pleural effusion [2].

The use of portable US machines has greatly enhanced the evaluation and management of patients with pleural disease [1]. US examination of the pleural space has proven to be of high value for the diagnosis of effusion, distinguishing transudative from exudative pleural fluid, accurately estimating the volume of pleural fluid, and aiding the drainage of pleural effusions with a catheter or by simple thoracocentesis [3–6]. US-guided pleural interventions have been associated with increased success in thoracocentesis even after a failed clinically directed thoracocentesis and lower frequencies of post–thoracocentesis pneumothorax [7,8]. This seems crucial in critically ill patients, especially those with low lung reserve, who are under oxygen therapy or under positive pressure mechanical ventilation.

In comparison with CT scanning, US is easier to perform and may better distinguish pleural thickening from pleural effusion [3]. In addition, it detects thoracic empyema in its early stages [9]. The US diagnosis of pneumothorax is well established and has been reported to be of value in the acute assessment of patients when an upright chest radiograph is not possible to achieve, most notably in trauma patients and those in the ICU [10].

US is a valuable and accessible tool for intensivists and pulmonary physicians. With proper training, intensivists and pulmonary physicians can achieve a high level of competence in all aspects of US relevant to their specialty. A machine with good-quality two-dimensional imaging capability must be continuously available in the ICU [11].
This study aimed to evaluate the role of US in the diagnosis and treatment of pleural diseases in respiratory intensive care unit (RICU) patients.

Patients and methods
This prospective study included consecutive patients who presented with suspected clinical and/or radiological evidence of pleural disease to the RICU of Abbassia Chest Hospital during the period between January 2011 and January 2013. Patients with parenchymal lung diseases with no pleural involvement were excluded.

All patients were subjected to full history taking, thorough clinical examination, chest radiography performed anteroposteriorly for the bedridden and posteroanteriorly for ambulant patients (MUX-10 Mobile Art eco; Shimadzu, Kyoto, Japan), and diagnostic chest US. A CT scan of the chest was performed whenever possible (Asterion 4 Multi Slice; Toshiba, Tokyo, Japan). Chest US-guided interventions were performed whenever needed.

In each patient, laboratory or radiological investigations were selected according to the suspected disease etiology to reach a final diagnosis, as described by Tu et al. [12].

Chest ultrasonographic examination
All patients underwent chest sonographic examinations with an US machine (Sonoline G6OS, Ultrasound Imaging System; Siemens, Mountain View, California, USA) as described by Mathis et al. [13] under completely aseptic conditions. For every patient, the two hemithoraces (right and left) were examined.

Examination steps
(1) Patients were instructed to sit erect whenever possible. In comatose patients, the back of the bed was elevated to 45° and the patients were turned to the oblique position. US transmission gel was used on clean, dry skin.

(2) The examination was performed initially using a convex C 3.2 MHz transducer, scanning both sides of the chest, starting from the costophrenic angle upward, dorsal to ventral. The transducer was placed intercostally with a perpendicular orientation. The patients’ arms were raised and crossed behind their heads to extend the intercostal spaces and facilitate access. Thereafter, a linear L 7.5 MHz transducer was used to obtain additional information in the same manner.

(3) Two-dimensional format US imaging was used; Doppler was used whenever needed. Split images were used to compare both sides. US images were collected for each patient and real-time videos were recorded for selected patients.

At the end of each chest US examination we achieved the following:

(1) We clarified the nature of unknown pleural densities.

(2) We detected pleural effusion, estimated its volume, and classified the different sonographic patterns.

(3) We differentiated subpulmonary effusion from subphrenic fluid accumulation and diaphragmatic paralysis in radiographically elevated hemidiaphragms.

(4) We localized pleural tumors or pleural thickening and measured their size. Pleural thickening appeared in US images with different densities, ranging from hypoechoic to echoic. ‘Color Doppler sign’ was used to differentiate between thickenings and effusions.

(5) We assessed the invasion of tumors into the pleura and chest wall and guided transthoracic needle biopsy of the pleura.

(6) We recognized pneumothorax: pneumothorax was diagnosed with a combination of the two key sonographic signs (lung sliding and B lines), and whenever possible ‘lung point’ sign was used as described by Mathis et al. [13].

(7) We recorded complications resulting from US-aided interventions.

(8) We compared US findings with radiographic and CT findings when available.

Classification of sonographic patterns in pleural effusions

(1) Pleural effusions were classified as follows:
   (a) anechoic pattern: no echogenic density within the effusion;
   (b) complex nonseptated pattern: with some visible bright spots as echogenic density within the effusion;
   (c) complex septated pattern: with prominent fibrinous septation within the effusion; and
   (d) homogenously echogenic pattern: with echogenic spot densities evenly distributed within the effusion [13].

(2) The volume of pleural effusion was classified as follows: minimal if the echo-free space was seen within the costophrenic angle; small if the space was greater than the costophrenic angle but still within a one-probe range; moderate if the space was greater than a one-probe range but within a two-probe range; and large or massive if the space was bigger than a two-probe range [13].
Chest ultrasonography-guided interventions

Diagnostic thoracocentesis

US scanning was performed to confirm the presence of fluid and to select and mark the best puncture site. The puncture was then made during real-time scanning while visualizing the needle during penetration. A 22 G needle attached to a syringe was generally used for diagnostic aspiration. Occasionally, larger needles (20 or 18 G) were used in highly viscous pleural fluid. The procedure was carried out under local anesthesia induced with 2% lidocaine administered through a 4 cm injection.

Catheter drainage of pleural collection

The best puncture site was marked as stated previously. A Flexima (10 Fr) pigtail catheter was used to drain the pleural fluid, especially loculated pleural fluid. The catheter was then attached to a closed urinal bag or an underwater seal in cases of hydropneumothorax. The procedure was carried out under local anesthesia induced with 2% lidocaine administered through a 10 cm injection. Daily output was recorded to follow-up patient progress. Occasionally, transcatheter infusion of fibrinolytics was performed to facilitate drainage of septated and loculated pleural fluid collections. A volume of 250 000 IU of streptokinase diluted in 50 ml saline was injected twice daily. The catheter was then clamped for 45 min before reopening it.

Pleural biopsy of pleural thickening or tumor

US scanning was performed to confirm the presence of pleural thickening or a pleural mass and to select the best puncture site. The puncture was then made during real-time scanning while visualizing the needle during penetration. Either fine-needle aspiration using a 16–20 G needle attached to a syringe was performed or a biopsy sample was obtained using an Abrams needle or an Egemen semiautomatic biopsy needle (16 G). The procedure was carried out under local anesthesia induced with by injection (10 cm) of 2% lidocaine.

Ultrasonography-guided intercostal tube readjustment

US was also used to readjust already placed nonfunctioning intercostal tubes.

The training program

One of the objectives of this study was to design, implement, and evaluate a training program for one of the researchers (I.A.) on the use of US for the diagnosis and treatment of pleural disease. The following order of training was implemented:

(i) a brief academic background concentrating on US management of pleural disease given by the radiology consultant;
(ii) attendance of at least 15 cases of US examinations and/or interventions in pleural disease patients performed by the radiology consultant;
(iii) performance of examination and/or intervention in at least 15 cases of pleural diseases under the supervision of the radiology consultant;
(iv) performance of examination and/or intervention of at least 15 cases of pleural disease single-handedly, which were re-examined by a radiology consultant later on.

Evaluation of the training program

Efficacy and efficiency of the training program was evaluated using the evaluation checklist presented in Table 1. A score percentage was given by the radiology consultant on each item. The learning curve of the research candidate was assessed as regards the number of supervised examinations needed to obtain competency in the US examination.

All patients underwent chest radiography and US evaluation. US assessment included examination of both chest sides (hemithoraces). Thus, 110 sides were evaluated by US. In contrast, only 43 patients underwent both US examination and CT scanning and thus 86 sides were evaluated by US. Sensitivities and specificities were calculated for 110 sides and 86 sides while comparing US with radiography and US with CT scanning, respectively. It is to be noted that some patients may have more than one pleural pathology – for example, pleural mass with pleural effusion.

Table 1 Checklist evaluation of the training program

<table>
<thead>
<tr>
<th>Checklist</th>
<th>Trainee finding</th>
<th>Consultant score percentage and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient position</td>
<td></td>
<td></td>
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<tr>
<td>Probe selection</td>
<td></td>
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<tr>
<td>Probe manipulation</td>
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<tr>
<td>Technical limitations</td>
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<tr>
<td>Image quality</td>
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<tr>
<td>Anatomic landmarks</td>
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<tr>
<td>Pleural effusion echogenicity</td>
<td></td>
<td></td>
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<tr>
<td>Pleural effusion volume</td>
<td></td>
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<tr>
<td>Miscellaneous findings</td>
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<tr>
<td>Lung overview</td>
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<td>Dynamic findings</td>
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<tr>
<td>Machine control</td>
<td></td>
<td></td>
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<tr>
<td>Identifying safe puncture sites</td>
<td></td>
<td></td>
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<tr>
<td>Placement of drainage catheter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleural biopsy</td>
<td></td>
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</tr>
<tr>
<td>Anesthesia</td>
<td></td>
<td></td>
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<tr>
<td>Final diagnosis</td>
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<td>Complications</td>
<td></td>
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<tr>
<td>Total score</td>
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</tbody>
</table>
Statistics
Data were analyzed using the SPSS statistical package, version 15.0 for windows (SPSS Inc., Chicago, Illinois, USA). Statistical measures were expressed as means and SDs for quantitative variables and as percentages for qualitative variables. Cross-table statistics with Pearson’s correlation coefficients was used to assess the correlation between two qualitative variables. Differences in sensitivity and specificity between the different imaging modalities tested were evaluated using McNemar’s test statistic. The χ²-test for unpaired data was used to test differences for statistical significance. The κ statistic with linear weighting was used. The linear weighted κ-value measures the relative concordance between US result and the final diagnosis. κ-values less than 0 represent less than chance agreement, 0.01–0.20 slight agreement, 0.21–0.40 fair agreement, 0.41–0.60 moderate agreement, 0.61–0.80 substantial agreement, and 0.80–0.99 almost perfect agreement. For all comparisons, P-values less than 0.05 were taken to indicate statistically significant differences. The final diagnosis was considered the reference standard to compare the results of all imaging modalities.

Results
Study population characteristics
Fifty-five patients were recruited during the study period. Thirty-nine were male (71%) and 16 were female (29%). Their ages ranged from 19 to 81 years, with a mean of 49.5 ± 18.3 years.

At the time of examination, 25 patients were mechanically ventilated (45%), 24 were on oxygen therapy [20 on nasal prong (36%), two on venturi mask (4%), and two on a face mask (4%)], and six were on room air (11%).

As regards the patients’ temperatures at the time of examination, the highest recorded temperature was 40°C and the lowest recorded temperature was 35°C. The mean temperature was 37.2 ± 0.93°C. Twenty-six patients were normothermic (47%), 17 patients were feverish (31%), and 12 patients were hypothermic (22%).

Final diagnosis and ultrasonographic findings
The characteristics of the different pleural pathologies as detected by US are illustrated in Table 2. Pleural effusions were the most common pleural pathology encountered.

There was almost perfect agreement between US results and the final diagnosis, with κ values 0.98 for pleural effusion, 0.95 for pleural thickening, 0.92 for pneumothorax, and 0.9 for pleuroparenchymal masses.

Pleural effusion
Sixty pleural effusions were recorded on final diagnosis. US detected 59 effusions (98.3%). Table 3 describes the characteristics of pleural effusions with regard to site, loculation, volume, and echogenicity as seen on chest US.

Forty-two effusions were exudative (70%), 14 effusions were transudative (23.3%), and four effusions were undetermined (6.7%). The chest US prediction of the nature of the pleural effusion (transudative or exudative) was in agreement with the true nature of the effusion in 84% of the pleural effusions that were chemically analyzed.

Comparison between chest ultrasonography and chest radiography findings
The results of the comparison between chest US and chest radiography findings as regards the different pleural pathologies are shown in Table 4. US was more statistically significantly sensitive and specific in the detection of pleural effusion

<table>
<thead>
<tr>
<th>Pleural pathology</th>
<th>Final diagnosis (100%)</th>
<th>US finding (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural effusions</td>
<td>60</td>
<td>59 (98.3)</td>
</tr>
<tr>
<td>Pleural thickening</td>
<td>24</td>
<td>22 (92)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>14</td>
<td>13 (92)</td>
</tr>
<tr>
<td>Pleuroparenchymal masses</td>
<td>6</td>
<td>5 (83.5)</td>
</tr>
</tbody>
</table>

Table 2 Characteristics of different pleural pathologies as detected by ultrasonography

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Final diagnosis [n (%)]</th>
<th>Detected by US [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>60 (100)</td>
<td>59 (98.3)</td>
</tr>
<tr>
<td>Site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral</td>
<td>36 (60)</td>
<td>36 (60)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>24 (40) (12 patients)</td>
<td>23 (36.6) (12 patients)</td>
</tr>
<tr>
<td>Loculation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free</td>
<td>46 (76.7)</td>
<td>45 (75)</td>
</tr>
<tr>
<td>Encysted</td>
<td>14 (23.3)</td>
<td>14 (23.3)</td>
</tr>
<tr>
<td>Volume</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minimal</td>
<td>10 (16.7)</td>
<td>10 (16.7)</td>
</tr>
<tr>
<td>Small</td>
<td>18 (30)</td>
<td>17 (28.3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>23 (38.3)</td>
<td>23 (38.3)</td>
</tr>
<tr>
<td>Massive</td>
<td>9 (15)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>Echogenicity pattern</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anechoic</td>
<td>33 (55)</td>
<td>32 (53.3)</td>
</tr>
<tr>
<td>Complex</td>
<td>16 (26.7)</td>
<td>16 (26.7)</td>
</tr>
<tr>
<td>nonseptated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex</td>
<td>9 (15)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>septated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homogenously echogenic</td>
<td></td>
<td>2 (3.3)</td>
</tr>
</tbody>
</table>

Table 3 Characteristics of pleural effusion as detected by ultrasonography

*Number of hemithoraces (sides); US, ultrasonography.
Role of ultrasound in the management of pleural diseases in respiratory intensive care patients Helala et al. 83

Compared with chest radiography. A sensitivity of 0.92 for US examination against 0.54 for chest radiography in the detection of pleural thickening \((P < 0.05)\) was noted. US had a more statistically significant negative predictive value and accuracy in the detection of pleural effusions and thickening compared with chest radiography. No statistically significant difference was seen between the sensitivity and specificity of chest US and chest radiography in the detection of pneumothorax and pleuropulmonary masses.

Comparison between chest ultrasonography and chest computed tomography findings

The results of the comparison between chest US and chest CT findings with regard to different pleural pathologies are shown in Table 5. There were no statistically significant differences between the sensitivity and specificity of chest US and chest CT in the detection of different pleural pathologies. Further, the results of the comparison between chest US and chest CT as regards pleural effusion characteristics (site, loculation, and volume) are shown in Table 6. Chest US is statistically significantly better than chest CT in the detection of unilateral effusions and septated effusions.

Empyema

Eighteen empyemic sides were detected among 16 patients. Two of the patients had bilateral empyema. Eight patients had their empyema drained with US-guided interventions (50%). Four patients underwent therapeutic drainage (25%) and six drainage catheters were inserted in the remaining four (25%) patients. Drainage in the other eight (50%) patients was carried out using non-US-guided methods. This study showed that empyema drainage using US-guided interventions in ICU patients was significantly correlated with favorable outcome (cure or transfer from the ICU; Table 7).

Correlation between patient temperature and ultrasonography finding

The relation between US findings and the body temperature of the patients was studied. There was a significant relation between being feverish and obtaining an US image suggestive of empyema (complex and echoic effusions; Table 8).

Role of ultrasonography in the management of pleural diseases

The role of US in the diagnosis, treatment, and guided interventions of pleural diseases is illustrated in Figs 1–3.
US reached a definite diagnosis, added new findings, confirmed a provisional diagnosis, and excluded differential diagnosis in 27.2, 30.9, 32.7, and 14.5% of cases, respectively. In some patients, US changed the diagnosis in more than one aspect (Fig. 1).

US findings impacted medical treatment and led to US-guided therapeutic interventions, determination of treatment choice, modification of treatment choice, and follow-up of treatment progress in 10.9, 30.9, 16.3, 1.8, and 1.8% of cases, respectively. US had no effect on treatment in 47.2% of cases (Fig. 2).

A total of 67 US-guided interventions were carried out. Diagnostic thoracentesis, catheter drainage, therapeutic drainage, fine-needle aspiration, and pleural biopsy were performed in 58, 13.5, 15, 6, and 3% of cases, respectively. Other interventions such as mechanical septolysis, medical fibrinolysis, and thoracostomy tube position adjustment were also performed in one case each (1.5%; Fig. 3).

The success rate of all interventions was 94%. Failed diagnostic thoracentesis due to extremely thick gelatinous effusions and a very thick chest wall occurred in two and one case, respectively. Failure of catheter drainage due to technical reasons occurred in one case.

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US-guided interventions in patients, with or without oxygen therapy and encountered complications are listed in Table 9. Only one complication was encountered during the 67 interventions (1.5%). A partial pneumothorax occurred after therapeutic drainage of a pleural effusion of a mechanically ventilated patient, which was managed accordingly without compromising the patient’s condition.

### Table 5 Comparison between chest US and chest CT findings as regards different pleural pathologies

|------------------|-------------------------|------------------------|----------------|----------------|---------------------|------------------------|------------------------|----------------|----------------|---------------------|---
| PE              | 0.98 (98)               | 0.9 (90)               | 0.97 (97)      | 0.99 (99)      | 0.94 (94)           | 0.219                  | 0.219                  | 0.219           | 0.219           | 0.219               |   
| PT              | 0.9 (90)                | 0.95 (95)              | 1              | 1              | 0.97 (97)           | 0.98 (98)              | 0.98 (98)              | 1              | 1              | 1                   |   
| PNX             | 0.92 (92)               | 0.92 (92)              | 0.93 (93)      | 0.99 (99)      | 0.99 (99)           | 1                      | 1                      | 1              | 1              | 1                   |   
| PPM             | 0.8 (80)                | 1 (100)                | 1              | 1 (100)        | 1                   | 0.99 (99)              | 1                      | 1              | 1              | 1                   |   

CT, computed tomography; NPV, negative predictive value; PE, pleural effusion; PNX, pneumothorax; PPM, pleuroparenchymal masses; PPV, positive predictive value; PT, pleural thickening; US, ultrasonography; *Test parameters were based on 86 sides.

### Table 6 Comparison between pleural effusion characteristics in US and CT

<table>
<thead>
<tr>
<th>Findings</th>
<th>No. (side)</th>
<th>Detection</th>
<th>Ultrasound</th>
<th>CT scan</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>30</td>
<td>Unilateral</td>
<td>Detected</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not detected</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>Bilateral</td>
<td>Detected</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Not detected</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Loculation</td>
<td>14</td>
<td>Detected</td>
<td>14</td>
<td>13</td>
<td>0.309</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not detected</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Septation</td>
<td>9</td>
<td>Detected</td>
<td>8</td>
<td>2</td>
<td>0.004*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not detected</td>
<td>1</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Volume</td>
<td>8</td>
<td>Minimal</td>
<td>Detected</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not detected</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>Small</td>
<td>Detected</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not detected</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>Moderate</td>
<td>Detected</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not detected</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Large</td>
<td>Detected</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not detected</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

CT, computed tomography; US, ultrasonography; *The differences were based on samples of 86 sides.

### Table 7 Outcome of empyema patients

<table>
<thead>
<tr>
<th>Method</th>
<th>Outcome</th>
<th>Death</th>
<th>Cure</th>
<th>Transfer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-US-guided methods</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>US-guided methods</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Pearson’s correlation coefficient: 0.59; US, ultrasonography; P-value: 0.05.

### Table 8 US images in feverish patients

<table>
<thead>
<tr>
<th>Fever</th>
<th>US finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complex effusion</td>
<td>12</td>
</tr>
<tr>
<td>Other finding</td>
<td>5</td>
</tr>
<tr>
<td>Feverish</td>
<td></td>
</tr>
<tr>
<td>Normo/hypothermic</td>
<td></td>
</tr>
</tbody>
</table>

Pearson’s correlation coefficient: (0.33); US, ultrasonography; P-value: 0.01.

US reached a definite diagnosis, added new findings, confirmed a provisional diagnosis, and excluded differential diagnosis in 27.2, 30.9, 32.7, and 14.5% of cases, respectively. In some patients, US changed the diagnosis in more than one aspect (Fig. 1).

US findings impacted medical treatment and led to US-guided therapeutic interventions, determination of treatment choice, modification of treatment choice, and follow-up of treatment progress in 10.9, 30.9, 16.3,
Seventeen patients underwent different therapeutic interventions. Some degree of favorable outcomes followed these interventions ($n = 12, 70.6\%$). In seven patients (41.1\%) the fever subsided. Five patients (29.4\%) showed improved oxygenation; three of them (17.6\%) were successfully weaned from mechanical ventilation. Random blood sugar levels were controlled in two diabetic patients (11.7\%). One patient (5.8\%) showed improved drainage from the thoracostomy tube. Sometimes, more than one effect was elicited in the same patient. In only five patients (29.4\%) was no effect noticed (Fig. 4).

**Evaluation of the training program**
One of the researchers (I.A.) was evaluated as a model of the training process. The trainee performed a total of 34 examinations and 25 interventions. The trainee observed 21 cases before performing supervised examinations of 19 subsequent cases. The trainee then performed 15 cases single handedly with later confirmation by a radiology consultant. The trainees’ scores were plotted chronologically against examinations, and a learning curve was obtained (Fig. 5). The learning curve initially showed steep fluctuations in scores, which then progressed to a more stable higher level. The mean score was 89.2 ± 8.84\%. The minimum score recorded was 66\% and the highest was 100\%. Proficiency was acquired after 30 examinations – that is, the trainee was able to score 100\% in the evaluation sheet after performing 30 examinations.

**Selected cases**

**Case 1**
Case 1 was a 25-year-old man with no special habits of medical importance. He complained of progressive dyspnea, fever, cough, and expectoration of a large amount of sputum and was admitted to the RICU with diabetic ketoacidosis and fever. He was on room air.

Plain radiography showed multiple air–fluid levels on the right side (Fig. 6).

CT scanning showed encysted right hydropneumothorax and pleural thickening (Fig. 7).

US showed large encysted hydropneumothorax (complex nonseptate pleural effusion with air locules) and thickened pleura (6 mm; Fig. 8). US-guided thoracocentesis, followed by US-guided catheter insertion for drainage of the pus was performed. The radiograph obtained immediately after insertion of the pigtail catheter into the pyopneumothorax showed evacuation of the pus and obliteration of the right costophrenic angle (Fig. 9).

A volume of 700 ml of pus was drained in the first 24 h.

The CT scan showed the pigtail catheter situated in the basal pleura, with evacuation of empyema (Fig. 10).

Follow-up US showed only pleural thickening (6 mm), which was detected using a linear transducer (L7.5 MHz) and in the Doppler mode to differentiate it from minimal effusion (Fig. 11). Blood sugar was controlled and the fever subsided, and the patient was transferred to the ward to continue treatment.
Case 2
Case 2 was a 21-year-old woman with no special habits of medical importance. She complained of right-sided heaviness for 2 months. The patient was admitted to the RICU with respiratory distress and respiratory failure type I. She was on nasal prong at 5 l/min.

The radiograph obtained showed homogenous opacity occupying all of the right hemithorax, obliterating the right costophrenic angle and shifting the mediastinum to the opposite side (Fig. 12). The CT scan showed a right large pleural mass occupying...
all of the right hemithorax only (Fig. 13). US showed an echoic pleural mass and minimal anechoic pleural effusion not seen on the CT scan (Fig. 14). US-guided core pleural biopsy was performed (Fig. 15). Histopathological analysis proved the case to be solitary pleural fibroma.

**Case 3**

Case 3 was a 57-year-old man who was a smoker with a 60 pack-year history. He complained of progressive dyspnea and stabbing chest pain on the right side and was admitted to the RICU after a cardiac arrest, in a comatose state, and was mechanically ventilated. He had inaudible arterial blood pressure and bradycardia. Radiography showed homogenous opacity occupying all of the right hemithorax (Fig. 16). CT scanning showed a large free pleural effusion with multiple focal pleural thickening (Fig. 17). US showed a large complex septated effusion with multiple focal pleural thickening ranging from 2.5 to 10 mm (Fig. 18).

US-guided thoracocentesis was performed (Fig. 19). Cytological analysis of the pleural effusion confirmed malignant mesothelioma of the sarcomatous type.

**Discussion**

The role of US in diagnosing and treating pleural diseases in a non-ICU setting has been studied previously [14–22]. However, nowadays bedside chest US is being increasingly used among patients managed in the ICU and has been a focus of research [23–25].

The main finding of this study is that, in RICU patients, chest US is more significantly sensitive than chest radiography in the diagnosis of pleural effusions and pleural thickening. In contrast, US had a comparable diagnostic performance to chest radiography in the diagnosis of pneumothorax and pleuroparenchymal masses. There was almost perfect agreement between US results and the final diagnosis. US examination and/or interventions affected the diagnosis and altered the treatment policy, with recorded favorable outcomes. US-guided interventions had a success rate of 94%, with only one recorded iatrogenic pneumothorax, which did not compromise the patient’s condition. Short-term, goal-directed training programs could enable intensivists to master chest US after 30 examinations.
In this study, the final diagnosis was considered the reference standard to compare the results of all available imaging modalities. This methodology was similar to that of several previous studies dealing with US and pleural disease [26–28]. Other studies used CT scans as the reference standard for comparison [16,21,29], whereas this methodology requires CT scans to be performed in all studied patients, which is impossible in critically ill patients.

The mean age of the patients (49.5 ± 18.3 years) and the age range (19–81 years) in the current study were comparable to those in previous US studies of pleural disease in non-ICU settings in Egypt [14,17]. A different mean age (58.8 ± 14.64 years) was reported by Yousef [25] in a population of 25 mechanically ventilated patients while studying the possibility of
replacement of routine chest radiography by chest US in mechanically ventilated patients admitted to the RICU of Ain Shams University Hospitals. In contrast, a higher mean age (66 ± 19 years) and an extended age range (22–92 years) were reported in a Taiwanese study dealing with the role of chest US in pleural effusions in febrile medical ICU patients [12].

In the present study, US was more significantly sensitive and specific than radiography as regards the detection of pleural effusion. A similar significance was reported by Zanobetti and colleagues while studying the possibility of replacing standard chest radiography with chest US in the evaluation of critically ill patients in an emergency department in Italy. In their study, ultrasonography exhibited significantly greater sensitivity than radiography in patients with free pleural effusion ($P < 0.001$) [29]. A similar significance was reported by Yousef. In his study, ultrasonography exhibited significantly greater sensitivity than chest radiography in patients with free pleural effusion ($P < 0.001$) [25]. In another Greek study, conducted on 42 mechanically ventilated patients in a medical–surgical ICU, US demonstrated significantly greater sensitivity, specificity, positive predictive value (PPV), negative predictive value, and accuracy than radiography in the detection of pleural effusion, in agreement with the results of the current study [23]. In addition, Motogna et al. [21] reported similar superiority of US over radiography in pleural effusion detection, with sensitivities of 100 and 70%, respectively.

In the present study, US was superior to CT scanning in detecting pleural effusions. However, the differences did not reach significance. A similar experience was described by Chira et al. [22]. They retrospectively reviewed files of 131 hospital patients while comparing US and CT scanning. The study reported that US diagnosed a higher number of cases of pleural effusion compared with CT. However, their results did not report a statistically significant difference.

In this study, US was significantly more sensitive than chest radiography for detecting pleural thickening. These results were in concordance with those of many other studies in the literature [16,21].

In the present study, the sensitivity of US for pneumothorax was 93% and the PPV was 93% because of one false-positive result. Comparing US parameters with either radiography or CT rendered no statistically significant differences. Galbois et al. [30] compared US with radiography in detecting pneumothorax in intermediate ICU patients. They reported comparable PPVs (90%), with one false-positive result on US. However, they still reported the sensitivity of US to be higher than that of radiography. They added that when lung point was observed the PPV reached 100%. In addition, Zanobetti et al. [29] reported no significant statistical differences between the sensitivities of US and radiography for detecting pneumothorax in their evaluation of patients presenting with acute dyspnea to the emergency department. In the current study, CT scanning and US had equal sensitivities for detecting pneumothorax. The same result was elicited by Rowan et al. [31] who studied 27 critically ill patients in the emergency department.

In the present study, radiography showed 100% sensitivity for detecting pleuroparenchymal masses. However, there was no statistically significant difference on comparing it with US sensitivity. This result coincided with that of Uibu et al. [32], who conducted a case–control study to investigate asbestos-related pleural diseases in a non–ICU setting. They reported that all pleural masses were visible on chest radiography (i.e. 100% sensitivity for radiography).

The results in the present study were identical to those of Kamel et al. [17]. In both studies US was able to diagnose five pleuroparenchymal masses out of six diagnosed by the CT scanning. As in the present study, the difference was not statistically significant. Both studies were conducted in Cairo, Egypt, and enrolled a small number of patients (52 patients in the study by Kamel and colleagues vs. 55 in the present study).

In the present study, $\kappa$-values were calculated for each of the different pleural pathologies as a measure of concordance between the US imaging results and the final diagnosis. There was almost perfect agreement between US results and the final diagnosis for all pleural diseases. This is in accordance with the results obtained by Lichtenstein and Mezière, who performed US on patients admitted to the ICU with acute respiratory failure, comparing lung ultrasonography on initial presentation with the final clinical diagnosis by the ICU team. Ultrasonography provided an overall almost–perfect agreement (90.5%) in their cases [26].

In the present study, there was a significant relation between being feverish and obtaining US images suggestive of empyema (complex and echoic effusions). While studying pleural effusions in febrile medical ICU patients, Tu and colleagues found that most febrile patients had a common pleural effusion pattern (40% anechoic pattern), which disagreed with the current results. This was mostly because the study by Tu and colleagues took place in the general medical ICU and the causes of fever were general, and empyema constituted only 16% of effusions. However, when all patients with thoracic empyema where analyzed,
they had distinct sonographic patterns, consisting of complex and homogenously echogenic patterns [12].

In the present study, US impacted the patient’s diagnosis either by specifying a definite diagnosis, adding new findings, confirming a provisional diagnosis, or excluding differential diagnosis in an appreciable number of patients. Medford and Entwisle reported comparable findings. In their observational study on the indications for thoracic US in chest medicine that included 80 patients they reported that US significantly changed patient management in 65% of cases, including 18% of cases in which US detected an effusion not visible on chest radiography, and led to exclusion of deferential diagnosis in 25% of cases [19].

In the current study US-guided empyema drainage in ICU patients was significantly correlated with favorable outcome in patients in comparison with non-US-guided drainage. Akhan and colleagues reported an improvement rate of 92.5% on image-guided catheter drainage of infected effusions at the radiology department only. The difference in the improvement may be attributed to enrollment of no critically ill patients in the radiology department and confinement of therapeutic interventions to drainage of infected pleural effusions only. Further, Akhan and colleagues considered patient improvement after 3 months. In addition, in the study by Akhans and colleagues, study image guidance was either by ultrasonography, fluoroscopic guidance, or CT [19].

The success rate for different US-guided interventions (94%) was close to the success rate reported by Wafy et al. [16], who reported 95.6% successful thoracocentesis. However, the success rate of the present study was attributed to all US-guided interventions and not merely thoracocentesis. Segura [33] retrospectively studied various US-guided interventions in a thoracic surgery department in Argentina. They reported 100% success rate for different interventions including intrapleural catheter placement, pleural biopsies, thoracocentesis, and fine-needle aspiration.

In the study on critically ill patients receiving mechanical ventilation by Mayo et al. [3], the rate of iatrogenic pneumothorax after US-guided thoracocentesis was 1.3%, in comparison with 1.4% in the present study. In contrast, Heidecker et al. [34] reported a higher percentage of iatrogenic pneumothorax (5.7%), in addition to other complications such as hemotorax and hypotension, while performing thoracocentesis in a critical care setting. The higher level of complications in their study might be attributed to the larger size of the study population (401 interventions) in comparison with the present study (67 interventions).

The study researcher in this study achieved a steep US learning curve. Comparably, Bandi and colleagues described the same curve pattern for chest US. In their study, house officers were trained to detect chest wall invasion from a thoracic mass in 90 non-ICU patients. They reported increased proficiency after ~4 h of training, followed by 20 supervised examinations. Both learning curves demonstrated the rapid nature of acquiring US examination skills [35].

In the present study, the trainee score ranged from 66 to 100%, which is close to the range reported by Galbois [30] (80–100%). The trainees in both studies reached full concordance with the radiologist at the end of the training program, after 30 examinations in this study in comparison with 40 examinations in theirs. However, Galbois et al. [30] were studying only pneumothoraxes in the ICU.

The present study has some limitations, mainly the small number of patients. This was because of the limited number of patients in the ICU. However, evaluation of the performance of chest US separately on each hemithorax, thus increasing the number (from 55 to 110), partly helped overcome this limitation. The small number led to defects in representing some pathologies such as pleuropulmonary masses. In addition, some interventions were not studied thoroughly because of the small number of patients. Not all patients underwent CT scanning, and among those who did the time interval between thoracic US and CT scanning could not be controlled. This might contribute to an unknown extent to the observed discrepancy between the methods. As the study was conducted in the ICU, US accessibility was difficult for some patients because of tissue edema, a pre-existing chest tube, subcutaneous emphysema, and obesity. The training program was applied only to one researcher, and thus the results cannot be generalized.

Finally, it can be concluded that US is an efficient and suitable method for the evaluation of different pleural diseases in critically ill patients in the RICU. US is mostly sensitive and specific in diagnosing pleural effusions. US-guided diagnostic and therapeutic pleural interventions are successful in achieving their goal with favorable outcomes and minimal complications. Short-term, goal-directed training programs could enable pulmonologists to properly use US.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.
Role of ultrasound in the management of pleural diseases in respiratory intensive care patients Helala et al. 91

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25. Yousef Y. Could chest ultrasonography replace routine chest X-rays in mechanically ventilated patients? MSc Thesis Ain Shams University, Faculty of Medicine Cairo, Egypt 2013.
Ultrasound-assisted medical thoracoscopy
Amr Shoukri

Introduction Medical thoracoscopy is an important tool for the diagnosis and management of several pleural diseases. The presence of fibrous pleural adhesions may prevent medical thoracoscopy to access the pleural space properly, which may lower the diagnostic yield of the procedure and may also increase the risk for associated complications. The role of on-table chest ultrasound (US) before medical thoracoscopy is investigated in this study.

Aim of the study The aim of this study was to evaluate the utility of on-table chest US before medical thoracoscopy and its ability to locate a safe point of entry, its impact on the facility of the procedure, and the risk for complications.

Patients and methods Forty patients who underwent medical thoracoscopy for investigation of undiagnosed pleural effusion were included in this study. They were randomized into two groups. In group I, chest US was performed on table immediately before medical thoracoscopy and in group II, no chest US was performed.

Results Computed tomography chest detected pleural adhesions in one patient (5%) in group I and in two patients (10%) in group II, whereas medical thoracoscopy detected five patients (25%) in group II and six patients (30%) in group I. Chest US was able to detect all cases with pleural adhesions in group I. Four patients (20%) in group II needed extra procedures to access the pleural cavity due to unsuccessful primary point of entry, and two (10%) had complications in the form of bleeding. All patients in group I had successful access to the pleural cavity with no needed extra procedures and no complications. The mean duration of the procedure in group I was 42 ± 5.4 versus 50 ± 10.4 min in group II.

Conclusion Chest US performed before medical thoracoscopy can facilitate the procedure; it reduces the unsuccessful attempts to access the pleural cavity, minimizes the risk for complications, and reduces the duration of the procedure. Egypt J Broncho 2015 9:92–95 © 2015 Egyptian Journal of Bronchology.

Keywords: chest ultrasound, medical thoracoscopy, pleural adhesions

Department of Chest, Faculty of Medicine, Ain Shams University, Cairo, Egypt
Correspondence to Amr Shoukri, MD, Department of Chest, Faculty of Medicine, Ain Shams University, Cairo, 11566, Egypt
Tel: 20 100 660 1870; E-mail: amr_shoukri@hotmail.com
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Ultrasound-assisted medical thoracoscopy

Shoukri

93

Medical thoracoscopy

In all patients, fasting for at least 6 h is required, with no other special preoperative preparation. The patients are monitored before and during the whole procedure (blood pressure, pulse, ECG, and pulse oximetry); the procedure was performed in lateral decubitus position with the affected side upward under general analgesia using a combination of inhalation anesthetic (isoflurane) and intravenous anesthetic (propofol). Skin sterilization was performed followed by incision and blunt dissection in the appropriate intercostal space to enter the pleural space. A 7-mm trocar was then inserted, and a 0° telescope was inserted through it and connected to a video camera; the pleural space was carefully inspected through the thoracoscope (Richard Wolf rigid thoracoscopy; Knittlingen, Germany). Abnormal (suspicious) areas were biopsied. The appearance of the parietal and visceral pleural surfaces and the extent of their involvement were assessed visually through the thoracoscope. Following the procedure, a chest tube was inserted and after recovery a control chest radiograph was performed.

Statistical analysis

Quantitative data were represented as mean ± SD, and qualitative data were represented as number and percentage. Data entry and statistical analysis were performed using SPSS for Windows, version 20.0 (SPSS Inc., Chicago, Illinois, USA).

Results

This study enrolled 40 patients with undiagnosed pleural effusion with a mean age of 57.77 ± 9.73 years; 28 patients were men (70%) and 12 were women (30%), and 40% of all patients were nonsmokers and 60% were smokers. History of occupational or residential exposure to asbestos was positive in 25% and negative in 75% of the patients. Demographic data of the included patients are displayed in Table 1.

The patients were randomized into two groups, 20 patients in each group. All patients underwent CT chest before the procedure. In group I, patients underwent chest US on table before medical thoracoscopy to identify the most appropriate point of entry, whereas in group II, no chest US was performed before medical thoracoscopy.

In group II, during medical thoracoscopy, six of 20 patients (30%) were found to have pleural adhesions, and CT chest was able to detect only two (10%) of them (Table 2). Of those patients, four (20%) needed extra procedures to access the pleural cavity due to unsuccessful primary point of entry, and two (10%) had complications in the form of bleeding.

In group I, during medical thoracoscopy, six patients (30%) were found to have pleural adhesions; CT chest was able to detect only one of those patients (5%) (Table 2), whereas chest US was able to recognize all patients (30%) with pleural adhesions (Table 3). A statistically significant difference was found between chest US and CT chest in detection of pleural adhesions ($P = 0.0374$) ($P < 0.05$) (Table 4). All patients in group I had successful access to the pleural cavity with no needed extra procedures and no complications.

The comparison between both groups shows no difference in the prevalence of pleural adhesions. However, it shows

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
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</tr>
<tr>
<td>Range</td>
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<tr>
<td>Sex</td>
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<td>Male</td>
<td>28 (70)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (30)</td>
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<td>Positive</td>
<td>10 (25)</td>
</tr>
<tr>
<td>Negative</td>
<td>30 (75)</td>
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<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>24 (60)</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>16 (40)</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Pleural adhesions</th>
<th>Pleural adhesions [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT chest</td>
<td>Medical thoracoscopy</td>
</tr>
<tr>
<td>Group I (20 patients)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Group II (20 patients)</td>
<td>2 (10)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pleural adhesions</th>
<th>Pleural adhesions [n (%)]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest ultrasound</td>
<td>Medical thoracoscopy</td>
</tr>
<tr>
<td>Group I (20 patients)</td>
<td>6 (30)</td>
</tr>
</tbody>
</table>
statistically significant difference with respect to the successful access to the pleural space and the need for extra procedures \((P = 0.0350)\) \((P < 0.05)\) (Table 5). The mean duration of the procedure for group I was 42 ± 5.4 min, whereas it was 50 ± 10.4 min in group II. There was a statistically significant difference between the two groups with respect to the length of the procedure \((P = 0.004)\) \((P < 0.05)\) (Table 6). There was no statistically significant difference between the two groups with respect to the occurrence of complications (Table 7).

Discussion

Undiagnosed pleural exudates are commonly seen in the practice of pulmonary medicine. Medical thoracoscopy is an easy and usually safe technique; it is considered the gold standard in the diagnosis of unexplained pleural effusion [1]. Pleural adhesions represent a problem confronting operators at medical thoracoscopy; these adhesions are not always detected by CT chest, and it is better visualized by thoracic US [10].

This study evaluates the utility of portable chest US immediately before medical thoracoscopy and its ability to facilitate the procedure and to minimize the risk for complications.

The results of our study showed a significant reduction in unsuccessful pleural access and the need for extra procedures from 20% in group II (the non-US group) to 0% in group I (the US group) \((P < 0.05)\), knowing that there was no difference in the prevalence of pleural adhesions between the two groups. These results are in accordance with the study by Andrew and colleagues, who found that there was a strong trend in reduction of pleural access failure rates from 16.7 to 0% \((P = 0.0522)\). The prevalence of fibrous septations reported in their study was 26.7%, which is quite similar to that in our study (27.5%) [11]. Another prospective study on 20 patients in a tertiary center used transhthoracic US before medical thoracoscopy in the presence of fibrous adhesions; the pleural access was successful in 100% of cases, which is consistent with our findings [4]. The prevalence of thick fibrous adhesions reported in the study (15%) was slightly less than that in our study (27.5%). The study of Macha et al. [12], another uncontrolled study that used chest US premedical thoracoscopy, showed a 100% pleural access rate and the prevalence of thick fibrous adhesions in their study was 22% compared with 27.5% in our study.

The rate of failed pleural access in group II in our study was 20%, which is comparable with the study by Andrew et al. (16.7%) [11] but is definitely higher than that in other published studies in which it ranged from 4 to 12% [13–15].

We also found that there was a significant difference in the length of the procedure; the mean duration for group I was 42 ± 5.4 versus 50 ± 10.4 min for group II \((P < 0.05)\).

The results demonstrated that two patients in group II had complications in the form of bleeding during the procedure, which was basically due cutting some of the vascular adhesions that could not be avoided due to inappropriate trocar position. Group I showed no complications in any patient.

On the basis of the results of this study, whenever chest US is available, we recommend its use before medical thoracoscopy, as a complementary tool with CT chest, to better assess the pleural space, making the procedure easier and safer.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References


Extrapulmonary tuberculosis situation in El-Behira Governorate, Egypt
Nabil A. Abdelghaffar Hibah

Aim There have been little published data about extrapulmonary tuberculosis (EPTB) situation in Egypt. The aim was to throw some light over EPTB patterns in Egypt regarding demographics, sites of affection, and treatment outcome.

Methods This work was approved by the Research Ethics committee in the Faculty of Medicine, Benha University. This work was a retrospective, descriptive analysis of EPTB cases, carried out at El-Behira Chest Hospital and 14 related dispensaries. All available data about registered EPTB cases from January 1996 to December 2010 (15 years duration) were collected including demographic data, site of EPTB, previous treatment history, treatment category, and treatment outcome. A descriptive analysis of the data was performed using the SPSS statistical program. Data were described in absolute numbers and percentages. Statistical significance was set at P value less than 0.05.

Results EPTB [n = 2119 (21%) of all diagnosed tuberculosis] occurred more in age groups between 15 and 29 and 30 and 44 years [n = 965 (45.5%) and n = 572 (27%), respectively] and in male patients [n = 1233 (58%)] than in female patients [n = 886 (42%)]. Pleural [n = 1341 (63.3%)], bone [n = 157 (7.5%)], and renal [n = 34 (1.6%)] tuberculosis were more common in male patients [n = 856 (64%), n = 99 (63%), n = 22 (64.5%), respectively], whereas lymph node [n = 427 (20%)] and genital [n = 70 (3.3%)] tuberculosis were more common in female patients [n = 240 (56.5%), n = 42 (60%), respectively]. Regarding treatment outcomes, successful treatment was obtained in 1725 cases (81.5%), treatment failure in 13 cases (0.5%), defaulting in 179 cases (8.5%), death in 77 cases (3.5%), and transfer-out in 125 cases (6%). Number of cases diagnosed declined through the years of study and was the highest in winter months, peaking in March.

Conclusion EPTB is a burden of reproductive age groups (15–44 years), with pleura being the commonest site of the disease that occurred more in male patients and age groups 15–44 years, followed by lymph nodes that occurred more in female patients and age group below 15 years. Successful treatment outcome was obtained in 81.5% of EPTB cases. Egypt J Broncho 2015 9:96–100 © 2015 Egyptian Journal of Bronchology.

Keywords: Egypt, extrapulmonary, lymph nodes, pleura, tuberculosis

Department of Chest, Faculty of Medicine, Benha University, Benha, Egypt
Correspondence to Nabil Ali Abdelghaffar Hibah, MD, Department of Chest, Benha University Hospitals, Benha City 13512, Egypt
Tel: 013-3227518; fax: 013-3227518; e-mail: nabil.hibah@yahoo.com
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Introduction and aim of the work
There have been little published data about extrapulmonary tuberculosis (EPTB) situation in Egypt. The aim of this work was to throw some light over EPTB patterns in Egypt regarding demographics, sites of affection, and treatment outcome.

Most studies are directed to the pulmonary form because it is the most common and the most infectious, neglecting the EPTB. EPTB should drag more attention after increasing numbers of immunocompromised individuals (including HIV-positive) with higher risk of developing EPTB than the rest of the population [1].

For proper application and assessment of any guideline for treatment of tuberculosis (TB), data about the target population and disease patterns must be available first.

The site of EPTB may differ from one geographic location to another and from a population group to another with wide variety of host factors [2,3].

Methods
This work was approved by the Research Ethics committee in the Faculty of Medicine, Benha University. This work was a retrospective descriptive analysis of EPTB cases carried out at El-Behira Chest Hospital and 14 related dispensaries and included all registered EPTB cases from January 1996 to December 2010 (15 years duration). Extrapulmonary TB was defined as TB of any organ other than the lung (e.g. pleural TB, bone TB, intestinal TB, and lymph nodes TB).

Data collection
Demographic data, TB registration code, site of EPTB, previous treatment history, treatment category, and treatment outcome were recorded.

Statistical analysis
A descriptive analysis of the data was performed using the SPSS statistical program (version 14, SPSS Inc., Chicago IL, USA). Data were described in absolute numbers and percentages. Statistical significance was set at P value less than 0.05. For comparison of data, t-test was used. The Student’s t-test was used for paired
data, if they followed a normal distribution. Otherwise, χ²-test was used to compare more than two percentages.

Results

Demographic data

Extrapulmonary cases (n = 2119) collected in this study represented 21% of all diagnosed TB cases (n = 10 035); 147 cases (7%) were below 15 years of age, 965 cases (45.5%) were between 15 and 29 years of age, 572 cases (27%) were between 30 and 44 years of age, 316 cases (15%) were between 45 and 59 years of age, and 119 cases (5.5%) were 60 years of age or above (Tables 1–3).

Male patients constituted 1233 cases (58%) and female patients constituted 886 cases (42%) with no significant differences between age groups distribution of male patients and female patients (Tables 2 and 3).

Site of extrapulmonary disease

Plural TB constituted 63.3% (n = 1341) of all EPTB cases [male n = 856 (64%) and female n = 485 (36%)] (Tables 4 and 5). Lymph node TB constituted 20% (n = 427) of EPTB cases [male n = 187 (43.5%) and female n = 240 (56.5%)]. Bone TB constituted 7.5% (n = 157) cases [male n = 99 (63%) and female n = 58 (37%)]. Genital TB constituted 3.3% (n = 70) of all EPTB cases [male n = 28 (40%) and female n = 42 (60%)]. Renal TB constituted 1.6% (n = 34) of all EPTB cases [male n = 22 (64.5%) and female n = 12 (35.5%)]. Intestinal TB constituted 1.3% (n = 27) of all EPTB cases [male n = 14 (51.5%) and female n = 13 (48.5%)]. Other sites of TB (central nervous system, eye, and others) constituted 3% (n = 63) of all EPTB cases [male n = 41 (65%) and female n = 22 (35%)].

Plural TB (n = 1341) was the most common site in all age groups except in those below 15 years (n = 64) (lymph node TB takes its place). Lymph node TB (n = 427) was the second most common site except in those below 15 years (n = 66) as mentioned earlier, and in age group 60 years or above (n = 7) it became third common (bone TB takes its place). Bone TB (n = 157) comes third in all groups except in age group 60 years or above (n = 16) as mentioned earlier. Genital TB (n = 70) was more common in age groups 15–29 years (n = 36) and 30–44 years (n = 26) and was rare in age group below 15 years (n = 1). Renal TB occurred more in the three age groups of 30 years or above.

History of previous treatment

Newly diagnosed cases accounted for 94.4% (n = 1998) of all EPTB cases [male n = 1151 (57.5%) and female n = 847 (42.5%)] (Table 6). Defaulters constituted 2.2% (n = 47) of all EPTB cases [male n = 37 (78.5%) and female n = 10 (21.5%)]. Cases with history of previous treatment failure constituted 1.8% (n = 40) of all EPTB cases [male n = 23 (57.5%) and female n = 17 (42.5%)]. Cases with history of relapse constituted 1.6% (n = 34) of all EPTB cases [male n = 22 (64.5%) and female n = 12 (35.5%)].

Treatment and outcome

Majority of cases in this study were under category I treatment [n = 1141 (54%)]. Category II contained 372 cases (17.5%), category III contained 346 cases (16.5%), and 260 cases (12%) were with unknown category (not found in their records) (Tables 7 and 8).

Of the 2119 EPTB cases, 1725 (81.5%) cases [male n = 988 (57%) and female n = 737 (43%)] successfully completed their treatment. Treatment failure was met in 13 (0.5%) cases [male n = 8 (61.5%) and female n = 5 (38.5%)]. Defaulters accounted for 179 (8.5%) cases [male n = 106 (59%) and female n = 73 (41%)]. Death was the outcome (no available details about cause of death) in 77 (3.5%) cases [male n = 45 (58.5%) and female n = 32 (41.5%)]. Transfer-out was carried out in 125 (6%) cases [male n = 86 (69%) and female n = 39 (31%)]. There was a significant difference in treatment outcome between male patients and female patients.
Annual and seasonal changes

EPTB diagnosis and notification rate seems to have a gradual decline in the number of cases (Graphs 1 and 2). The rate of EPTB diagnosis seems to peak in March then decline in warm summer months.

Discussion

After reviewing the published literature for data about the situation of EPTB in Egypt, very little published data were available. This study was conducted to put light on EPTB regarding the demographic patterns, clinical patterns, and treatment outcome in Egypt.

EPTB was more likely to occur in male patients \( n = 1233 \) (58.2\%) than in female patients \( n = 886 \) (41.8\%).

Table 5 shows different EPTB site in age groups

<table>
<thead>
<tr>
<th>Site</th>
<th>Age group</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural</td>
<td>(&lt;15)</td>
<td>147</td>
</tr>
<tr>
<td></td>
<td>15–29</td>
<td>965</td>
</tr>
<tr>
<td></td>
<td>30–44</td>
<td>316</td>
</tr>
<tr>
<td></td>
<td>44–59</td>
<td>316</td>
</tr>
<tr>
<td></td>
<td>(\geq60)</td>
<td>2119</td>
</tr>
<tr>
<td>Lymph node</td>
<td>(&lt;15)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>15–29</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>30–44</td>
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</tr>
<tr>
<td></td>
<td>44–59</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>(\geq60)</td>
<td>6</td>
</tr>
<tr>
<td>Bone</td>
<td>(&lt;15)</td>
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<td>4</td>
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<tr>
<td></td>
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<td>2</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td>(\geq60)</td>
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<tr>
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<td>316</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2119</td>
</tr>
</tbody>
</table>

Table 5 Shows different EPTB site in age groups

EPTB, extrapulmonary tuberculosis; *Other EPTB Sites (e.g. central nervous system, eye).

Table 6 shows history of previous treatment in absolute \( n \) (%) in both sexes

<table>
<thead>
<tr>
<th>History of previous treatment</th>
<th>New cases</th>
<th>Treatment after default</th>
<th>Treatment after failure</th>
<th>Relapsed</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1151</td>
<td>73 (78.5)</td>
<td>23 (57.5)</td>
<td>22 (64.5)</td>
<td>147</td>
</tr>
<tr>
<td>Female</td>
<td>847</td>
<td>10 (21.5)</td>
<td>17 (42.5)</td>
<td>12 (35.5)</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>1998</td>
<td>83 (41.8)</td>
<td>40 (100)</td>
<td>34 (100)</td>
<td>2119</td>
</tr>
</tbody>
</table>

Table 6 Shows history of previous treatment in absolute \( n \) (%) in both sexes

Table 7 shows distribution of EPTB cases according to their treatment category

<table>
<thead>
<tr>
<th>Category of treatment</th>
<th>( N ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category I*</td>
<td>1141 (54)</td>
</tr>
<tr>
<td>Category II*</td>
<td>372 (17.5)</td>
</tr>
<tr>
<td>Category III*</td>
<td>346 (16.5)</td>
</tr>
<tr>
<td>Unknown category</td>
<td>260 (12)</td>
</tr>
<tr>
<td>Total</td>
<td>2119 (100)</td>
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</tbody>
</table>

Table 7 Shows distribution of EPTB cases according to their treatment category

Table 8 shows treatment outcome in both sexes in absolute \( n \) (%)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Completed</th>
<th>Treatment failure</th>
<th>Default</th>
<th>Death (\geq58.5)</th>
<th>Death (\geq41.5)</th>
<th>Death (\geq31)</th>
<th>Transfer-out</th>
<th>Total</th>
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<tr>
<td>Male</td>
<td>988</td>
<td>8 (61.5)</td>
<td>106</td>
<td>45</td>
<td>32</td>
<td>39</td>
<td>86</td>
<td>1233</td>
</tr>
<tr>
<td>Female</td>
<td>737</td>
<td>5 (38.5)</td>
<td>73</td>
<td>32</td>
<td>39</td>
<td>39</td>
<td>886</td>
<td>1471</td>
</tr>
<tr>
<td>Total</td>
<td>1725</td>
<td>13 (0.5)</td>
<td>179</td>
<td>77</td>
<td>125</td>
<td>125</td>
<td>2119 (100)</td>
<td></td>
</tr>
</tbody>
</table>
Extrapulmonary tuberculosis situation

Hibah. 99

whereas lymph node affection is more with primary TB infection. Prevalence of pleural TB in Egypt suggests more relation to secondary or reactivation TB.

Genital TB rate \([n = 70 (70\%)]\) was more in female patients \([n = 42 (5\%)\) of EPTB in females\] than in male patients \([n = 28 (2.25\%)\) of EPTB in males\], whereas renal and bone TB were more common in male patients \((n = 22, n = 99)\) than in female patients \((n = 12, n = 58)\). Another study by Forssbohm et al. \([4]\) found nearly equal rates of genitourinary and bone TB in male patients \((n = 489, n = 235)\) and in female patients \((n = 469, n = 222)\).

Pleural TB \((n = 1341)\) is the most common site in all age groups except in those below 15 \((n = 64)\) years (lymph node TB takes its place). Lymph node TB \((n = 427)\) is the second most common site except in those below 15 \((n = 66)\) years as mentioned earlier, and in age group 60 years or above \((n = 7)\) it became third common (bone TB takes its place). Bone TB \((n = 157)\) comes third in all groups except age group 60 years or above \((n = 16)\) as mentioned earlier. Genital TB \((n = 70)\) was more common in age groups 15–29 \((n = 36)\) and 40–59 \((n = 26)\) and was rare in age group below 15 \((n = 1)\). Renal TB occurred more in age group 30 years and above. Sites of EPTB may show predilection of some age over another as reported by some authors \([10,11]\), and as evidenced in this study genital and urinary TB were rare in children (age group<15 years) \([12]\).

Newly diagnosed EPTB cases constituted the majority of cases in this study \([n = 1998 (94.4\%)]\); other cases with history of default \([n = 47 (2.2\%)]\), cases with history of treatment failure \([n = 40 (1.8\%)]\), and cases with history of relapse \([n = 34 (1.6\%)]\) are minority in this study \([n = 121 (5.6\%)]\).

There is a gradual decline in the occurrence of EPTB during the duration of this study that can be attributed to DOTS (direct observed therapy short course strategy) since 1999.

The rate of EPTB diagnosis seems to peak in March, which shows the highest number of diagnosed EPTB cases, then decline in warm summer months. Similar finding of seasonal variation in TB was reported by others \([13,14]\).

**Conclusion**

EPTB burden is much more during the reproductive age, between 15 and 44 years, in both male patients and female patients. Male patients have higher rates of pleural effusion than female patients and female patients have higher rates of lymph node and genital TB. Some sites of EPTB have predilection to some age groups over other age groups, such as lymph nodes in children, pleural in young and middle aged, and bone in old age. Regarding treatment outcomes, successful treatment was obtained in 1725 cases \((81.5\%)\), treatment failure in 13 cases \((0.5\%)\), defaulting in 179 cases \((8.5\%)\), death in 77 cases \((3.5\%)\), and transfer-out in 125 cases \((6\%)\). There is a gradual decline in the occurrence of EPTB with seasonal variation of case diagnosis and gradual rise through winter months during the duration of this study.

**Acknowledgements**

**Conflicts of interest**

None declared.

**References**

Incidence of tuberculosis before and after DOTS (direct observed therapy short course strategy) implementation in El-Behira Governorate, Egypt

Ali K. Alwani\textsuperscript{a}, Abdelsadek H. Al-Aarag\textsuperscript{b}, Magdy M. Omar\textsuperscript{b}, Nabil A. Abdelghaffar Hibah\textsuperscript{b}

Introduction

The WHO’s stop tuberculosis (TB) strategy, which is recommended for implementation by all countries and partners, aims to markedly reduce TB through public and private actions at national and local levels, such as \cite{1}:

(1) Pursue high-quality DOTS (direct observed therapy short course strategy) expansion and enhancement. DOTS is a five-point package to:

(a) Secure political commitment, with adequate and sustained financing.

(b) Ensure early case detection and diagnosis through quality-assured bacteriology.

(c) Provide standardized treatment with supervision and patient support.

(d) Ensure effective drug supply and management.

(e) Monitor and evaluate performance and impact.

(2) Address TB–HIV, multi-drug resistant (MDR)-TB, and the needs of poor and vulnerable populations.

(3) Contribute to health system strengthening based on primary healthcare.

(4) Engage all care providers.

(5) Empower people with TB, and communities through partnership.

(6) Enable and promote research.

Aim

The aim of this work was to study the incidence of tuberculosis (TB) in El-Behira Governorate before and after application of DOTS to evaluate the National Tuberculosis Control Program in El-Behira Governorate as a representative part of Egypt.

Patients and methods

This work was a retrospective, descriptive, analytical study of the TB situation before and after DOTS, carried out at Chest Hospital, El-Behira Governorate, Egypt, and related dispensaries. All available data on registered TB cases from January 1996 until December 2010 (15-year duration) were collected, including demographic data, diagnosis of disease, sputum smear results, previous treatment history, and treatment outcome. A descriptive analysis of the data was performed using the SPSS statistical program. Data were described in absolute numbers and percentages. Statistical significance was set at $P$ values less than 0.05.

Results

The incidence of TB ($n = 10,035$) was higher in age groups 15–29 and 30–45 years [$n = 3829$ (38.2%) and $n = 2827$ (28.1%), respectively], and in male patients [$n = 6511$ (64.8%)] compared with female patients [$n = 3524$ (35.2%)]. Pulmonary cases (78.8%) were more than extrapulmonary cases (21.2%). There was improvement in cure rate, treatment completion rate, treatment success rate, number of retreatment cases, and default rate after DOTS application (46–61.1, 16.1–18.6, 62.1–79.7, 29.1–12.4, and 20.4–6.8%, respectively).

Conclusion

TB is a burden of the productive age group of 15–45 years, with a higher incidence in men than in women, and DOTS is an effective tool for controlling TB in El-Behira Governorate. The implementation of this tool has led to significant increase in treatment success and decrease in default and failure rates. \textit{Egypt J Broncho} 2015 9:101–108 © 2015 Egyptian Journal of Bronchology.

Keywords: DOTS, Egypt, El-Behira, tuberculosis

\textsuperscript{a}Department of Chest Diseases, \textsuperscript{b}Department of Chest Diseases, Faculty of Medicine, Benha University Hospitals, Benha University, Benha, Egypt

Correspondence to Nabil Ali Abdelghaffar Hibah, MD, Department of Chest, Benha University Hospitals, Benha University, Benha 13512, Egypt Tel: 013-3227518; Fax: 013-3227518

e-mail: nabil.hibah@yahoo.com

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Measurement of indicators
These indicators were designed by the WHO to determine National Tuberculosis Program quality and effectiveness and are the following [2]:

1. Incidence rate (case notification rate): for new cases, new and relapsed cases, all cases and new smear-positive pulmonary cases.
2. New pulmonary cases with no smear result.
3. New adult smear-positive cases.
4. Retreatment TB cases.
5. New extrapulmonary TB cases.
6. New TB cases with no smear conversion result.
7. Sputum conversion rate at the end of the initial phase of treatment.
8. Cure rate.
9. Treatment completion rate.
10. Death rate.
11. Treatment failure rate.
12. Default rate.
13. Transfer-out rate.

Comparison of indicators
Comparison of indicators was made before and after DOTS.

Statistical analysis
A descriptive analysis of data was carried out. The unpaired Student t-test was used for comparison of independent data that followed a normal distribution. The Student t-test for repeated measurements was used for paired data if they followed a normal distribution. Otherwise, the Wilcoxon rank-sum test was applied, and the \( \chi^2 \)-test was used to compare between more than two percentages; all analyses were carried out using the SPSS (version 14, SPSS Inc., Chicago, Illinois, USA) statistical program. Statistical significance was set at \( P \) values less than 0.05. The analysis was performed using SAS software (version 9.1; SAS Institute, Cary, North Carolina, USA) for Windows. The test of proportion (Z-test) was used to compare between two percentages \( (P_1 \) and \( P_2 \) (Knapp et al., 1992) [3].

Level of significance
\( P \) value more than 0.05 was considered nonsignificant; \( P \) value less than 0.05 was considered significant; and \( P \) value less than 0.001 was considered highly significant.

Results and discussion
This study was a retrospective, descriptive, and analytic study carried out at El-Behira Chest Hospital and dispensaries and included all registered cases of TB from January 1996 until December 2010. The DOTS implementation started in 1999.

Difficulties met during the study included lack of a computerized system for patient records and follow-up and the wide area of the governorate to be covered. The records were lacking important data — for example, some of the smear-positive patients had no follow-up sputum, associated comorbidities were not recorded, socioeconomic status was not recorded, and in case of patient death the cause of death was not recorded.

The total number of recorded TB cases from January 1996 until December 2010 was 10035 (3404 before DOTS and 6631 after DOTS). Graph 1 shows the number of recorded cases with a noticeable decline in the number of recorded cases after DOTS.

Demographic data

Age groups
The highest incidence occurred in the age group of 15 to less than 30 years (38.2%), followed by the age group 30 to less than 45 years (28.1%), then 45 to less than 60 years (19.6%), and then over 60 years. The lowest incidence occurred in the lowest and highest extremes of age: below 15 years the incidence was 4.4% and over 60 years it was 9.7% (Table 1).

Others studies showed similar results: in the study by Hindi [4], 35.3% were in the age group of 15 to less than 30 years; in the study by Abdel-Rahman [5], 56% of patients out of 625 were in the age group of 20–40 years; in the study by Abdelghany [6], 34.72% were in the age group of 15 to less than 30 years; in the study by George [7], 30.92% of patients were in the age group of 15 to less than 30 years; in the study by El-Zeheiry [8], 32.3% were in the age group of 15 to less than 30 years; in the study by Al-Aarag [9],

Graph 1

Number of tuberculosis cases notified during the period of study (1996–2010).
### Situacion de tuberculosis

**Situation of tuberculosis**

**Alwani et al.** 103

31.25% were in the age group of 20–29 years; and in the study by Chengsorn et al. [10], 51.8% of patients were in the age group of 15–44 years. In Nigeria, Bello and Itiola [11] found that about 82% of TB patients were between 16 and 45 years.

In developing countries the majority of cases infected with TB are younger than 50 years, and about half of them may be younger than 15 years. In developed countries of Western Europe (having an aging population) the majority of cases are older than 50 years [12].

These findings could also be explained by the increased incidence of smoking in this active age group. Poverty, malnutrition, and physical, mental, and occupational stress are well known to be associated with this age group.

**Sex**

Male patients (64.9%) were more than female patients (35.1%). Many female patients do not seek medical advice because of factors such as illiteracy and the socioeconomic traditions prevailing in the society, which may prohibit them from going out and seeking medical advice. Higher TB notification rates in men may partly indicate differences in exposure due to more frequent social contacts, risk of infection, and progression from infection to disease caused by sex differences in association with other risk factors for TB such as cigarette and shisha smoking (Table 1).

Similar results were obtained by El-Zeheiry [8] (65.6% male and 34.4% female patients) and Chengsorn et al. [10] (66.5% male and 33.5% female), and lower results were obtained by George [7] (53.34% male and 46.65% female) and Shargie and Lindtjørn [13] (55.8% male and 44.2% female).

Higher results were obtained by Hossam [14] (76% male and 24% female patients), Fouad [15] (72.5% male and 27.5% female), and Floyd et al. [16] (80.2% male and 19.8% female).

In contrast, a study in South India found that 57% of patient notifications were from female patients. This finding was attributed to the fact that women were unemployed and thus were more likely than men to access health services and be notified under DOTS and to adhere to treatment, whereas men cannot leave their work and attend health services [17].

**Residence**

Rural cases (72.5%) were significantly higher than urban cases (27.5%) (Table 1). Other studies [4,6–8] conducted in different Egyptian Governorates found similar results. The result of this study was higher than that of Wondimu et al. [18] in Ethiopia, who found in a cross-sectional study that 106 (53.8%) of 198 patients resided in rural areas.

Increased TB cases in rural areas could be explained by poverty, close interaction within the community, as well as a low level of water supply and sanitation; it may also be caused by drinking or handling contaminated milk; agricultural workers may acquire the disease by inhaling cough spray from infected cattle and by close physical contact with potentially infected animals [19]. This finding can also be because most of the patients in this study and in studies with similar findings lived in rural areas.

**Type of patient according to history of previous treatment**

Comparison of the type of patient according to history of previous treatment before and after DOTS revealed the following: the proportion of new cases before DOTS was 89.6% and that after DOTS was 91.2% (statistically significant increase); failure cases before DOTS was 2.1% and that after DOTS was 1.9% (statistically significant decrease); the proportion of relapse cases before DOTS was 4.2% and that after DOTS was 4.1%; transfer-in cases before DOTS was 1.7% and that after DOTS was 1.5%; and default cases before DOTS was 1.5% and that after DOTS was 1.1%. The proportion of other cases before DOTS was 0.9% and after DOTS was 0.2% (Table 2).

Other studies gave similar results [4–8] regarding the high and increasing percentage of new cases.
Sputum smear results in pulmonary tuberculosis cases on diagnosis

The percentage of smear-positive cases (60.6%) was significantly higher than the percentage of smear-negative cases (39.4%). There was an obvious decline in the percentage of diagnosed smear-negative pulmonary TB cases after DOTS. Similar results were obtained by other studies [4,6,8]. Anuwatnonthakate et al. [20] in Thailand found that 63% of pulmonary cases were sputum smear positive and 37% were sputum smear negative (Table 3).

Laboratory diagnosis of tuberculosis by culture

Laboratory diagnosis of TB on the basis of culture was very limited in chest units of El-Behira Governorate. Culture examination was done for only 0.7% (67 cases) of cases. However, from the 67 cases, 22 (32.8%) cases were positive, whereas 45 (67.2%) cases were negative. Similar results were obtained by other studies [6,8].

The limited use of culture and sensitivity tests in all chest units in El-Behira Governorate is still attributed to the lack of sufficient laboratory resources in most chest units.

Extrapulmonary tuberculosis and its sites

In the present study, the total number of extrapulmonary TB cases was 2132 (21.2% of all TB cases) (Table 4). This result was similar to that of Abdelghany [6] in Menoufia who found that 70% of cases were pulmonary TB and 30% (1209) were extrapulmonary TB. Our results were also in accordance with those of El-Zeheiry [8] in Dakahlia who found that 66.9% were pulmonary TB and 33.1% were extrapulmonary TB cases.

This result was higher compared with the result of George [7] in El-Minia who found 66.4% of pulmonary cases and 33.58% of extrapulmonary cases. The high proportion of pulmonary cases compared with extrapulmonary ones could be explained by the fact that TB occurs almost exclusively from inhalation of droplet nuclei containing Mycobacterium tuberculosis.

In contrast, a study of Somalian TB patients in Minnesota showed a higher incidence of extrapulmonary TB than pulmonary TB, which may be due to impaired immunity caused by factors such as vitamin D deficiency, dietary changes, and restricted social conditions, which may cause reaction in extrapulmonary sites [21].

The most common extrapulmonary TB in this study was pleural TB (62.8%), followed by tuberculous lymphadenitis (20%).

The high incidence of pleural TB in El-Behira Governorate could be due to the efficient diagnosis of pleural effusion by physicians, as pleural effusion due to other causes of TB such as hepatic, cardiac, and renal was common in this governorate. The facility for pleural aspiration and other laboratory services used for pleural effusion diagnosis are available in El-Behira Governorate.

The current study matched the results of Abdelghany [6] in Menoufia who found that the

<table>
<thead>
<tr>
<th>Table 3 Pulmonary smear result on diagnosis and extrapulmonary cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relation to DOTS</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Before DOTS</td>
</tr>
<tr>
<td>After DOTS</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

DOTS, direct observed therapy short course strategy.

<table>
<thead>
<tr>
<th>Table 4 Extrapulmonary tuberculosis case distribution by site of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relation to DOTS</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Before DOTS</td>
</tr>
<tr>
<td>After DOTS</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

DOTS, direct observed therapy short course strategy; *Cases with tuberculosis in other sites such as the central nervous system, eye, and larynx.*
most common type of extrapulmonary TB was pleural TB. Our results also matched those of El-Zeheiry [8] in Dakahlia who found that pleural cases (50.9%) represented the highest number of extrapulmonary cases.

Other studies found that lymph node TB is the most common type of extrapulmonary TB [7,22,23].

**Conversion in smear-positive pulmonary tuberculosis**

The conversion rate increased from 59, 59.8, 77.2, and 79% (at 2, 3, 5 months, and at the end of treatment, respectively) before DOTS to 72.2, 73.4, 85.3, and 91.5% (at 2, 3, 5 months, and at the end of treatment, respectively) after DOTS (Tables 5–7).

The high conversion rate can be attributed to the competency of healthcare workers with regular supervision, mobilization of healthcare services, stable supply of antituberculous drugs, and better patient adherence to treatment.

In Menoufia Governorate the conversion rate increased from 39.95% before DOTS at the end of the second month to 66.44% after DOTS [6].

Higher results were reported by Mohan et al. [24] in a study in Baghdad: cases that converted to sputum negative were 85, 90, and 92.9% at 2, 5 months, and at the end of treatment, respectively. Abassi and Mansourian [25] found in a study in Gorgan, Iran, that 98.3% of smear-positive cases became sputum negative at the end of 5 months of treatment.

### Indicators

**Incidence rate for new cases and new smear-positive pulmonary tuberculosis cases**

In El-Behira Governorate before DOTS (1996–1998), the incidence rate of new cases was 24.7 in 100 000 and the incidence rate for new smear-positive pulmonary TB cases was 10.0 in 100 000. After DOTS (1999–2010), the incidence rate of new cases was 10.9 in 100 000 and the incidence rate for new smear-positive pulmonary TB cases was 6.4 in 100 000 (Table 8).

There was high statistically significant difference in the incidence rate for new cases, which was significantly higher before DOTS than after DOTS; thus, the incidence rate decreased, which indicates a decrease in the burden of TB because the annual risk of infection and the incidence rate decreased.

**Pulmonary tuberculosis cases with no smear result**

In this study, before DOTS the incidence rate of new pulmonary TB cases with no smear result was 54.8% and that after DOTS was 29.2%.

**New adult smear-positive cases**

In this study, before DOTS the incidence rate of new adult smear-positive cases was 82.6% and that after DOTS was 83% (the change was not statistically significant). The change was minimal before and after DOTS and the role and efficacy of radiological and laboratory diagnosis was the same in this study.

In El-Minia Governorate, the incidence rate of new adult smear-positive cases was 75.08 and 85.58% (before DOTS and after DOTS, respectively) [7].

### Table 5 Results of sputum examination for acid fast bacilli at the end of the second month for positive pulmonary cases

<table>
<thead>
<tr>
<th>Years</th>
<th>Number of positive sputum cases at diagnosis</th>
<th>Number of negative sputum cases at the end of 2nd month</th>
<th>Number of positive sputum cases at the end of 2nd month</th>
<th>Number of cases not examined at the end of 2nd month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before DOTS (1996–1998)</td>
<td>1234 (100)</td>
<td>729 (59.0)</td>
<td>299 (24.2)</td>
<td>206 (16.7)</td>
</tr>
<tr>
<td>After DOTS (1999–2010)</td>
<td>3557 (100)</td>
<td>2569 (72.2)</td>
<td>467 (13.1)</td>
<td>521 (14.6)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.000001</td>
<td>&lt;0.000001</td>
</tr>
<tr>
<td>Statistical significance</td>
<td>Highly significant</td>
<td>Highly significant</td>
<td>Highly significant</td>
<td>Highly significant</td>
</tr>
</tbody>
</table>

N = 4791; DOTS, direct observed therapy short course strategy.

### Table 6 Results of sputum examination for acid fast bacilli at the end of the third month for positive pulmonary tuberculosis cases

<table>
<thead>
<tr>
<th>Years</th>
<th>Positive sputum cases at diagnosis</th>
<th>Negative sputum cases at the end of the 3rd month</th>
<th>Positive sputum cases at the end of the 3rd month</th>
<th>Cases not examined at the end of the 3rd month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before DOTS (1996–1998)</td>
<td>1234 (100)</td>
<td>738 (59.8)</td>
<td>196 (15.9)</td>
<td>300 (24.3)</td>
</tr>
<tr>
<td>After DOTS (1999–2010)</td>
<td>3557 (100)</td>
<td>2610 (73.4)</td>
<td>270 (7.6)</td>
<td>677 (19)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.000001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Statistical significance</td>
<td>Highly significant</td>
<td>Highly significant</td>
<td>Highly significant</td>
<td>Highly significant</td>
</tr>
</tbody>
</table>

N = 4791; DOTS, direct observed therapy short course strategy.
Retreatment tuberculosis cases
In this study, before DOTS the incidence rate of retreatment TB cases was 29.1% and that after DOTS was 12.4% (highly significant decrease). The decrease after DOTS indicates the effectiveness of the National Tuberculosis Program in the treatment and follow-up of new cases under direct observed therapy with efficient drug supply and highly efficient treatment regimen.

In Menoufia Governorate, before DOTS the incidence rate of retreatment TB cases was 13.29%. After DOTS, the incidence rate of retreatment TB cases was 6.72% [6].

New extrapulmonary tuberculosis cases
In the present study, before DOTS the incidence rate of new extrapulmonary TB cases was 18.6% and that after DOTS was 22.9% (statistically significant increase). This increase may be due to improved methods of extrapulmonary TB diagnosis and/or increases in risk factors that may increase the risk of reactivation of extrapulmonary focus (e.g. diabetes), which is not known because of lack of these data in the records of the studied cases (comorbidity and other data).

Al-Aarag [9] found that the average incidence of extrapulmonary TB was 6.13%, which means that the incidence was lower compared with our study; this may be due to less efficient diagnostic methods 30 years ago, which have improved now with a better reporting system.

Higher increase was found in El-Minia Governorate (before DOTS the incidence rate of new extrapulmonary TB cases was 27.75% and that after DOTS was 37.9%) [7].

New tuberculosis cases with no smear conversion result
In this study, before DOTS the rate of new TB cases with no smear conversion result was 11.0% and that after DOTS was 8.3% (statistically significant reduction).

In Menoufia Governorate, before DOTS the rate of new TB cases with no smear conversion result was 24.41% and that after DOTS was 18.89% [6].

Sputum conversion rate at the end of the initial phase of treatment
In this study, before DOTS the sputum conversion rate at the end of the initial phase of treatment was 60.9% and that after DOTS was 75.4% (highly significant increase).

This finding indicates effective initial therapy and improvement in the follow-up of cases after DOTS.

Table 7 Sputum conversion rate before and after DOTS

<table>
<thead>
<tr>
<th>Relation to DOTS</th>
<th>At the end of 2nd month</th>
<th>At the end of 5th month</th>
<th>At the end of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before DOTS (N = 1234)*</td>
<td>729 (59)</td>
<td>953 (77.2)</td>
<td>976 (79)</td>
</tr>
<tr>
<td>After DOTS (N = 3557)*</td>
<td>2569 (72.2)</td>
<td>3134 (88.1)</td>
<td>3253 (91.5)</td>
</tr>
<tr>
<td>Total (N = 4791)</td>
<td>3298 (68.8)</td>
<td>4087 (85.3)</td>
<td>4229 (88.3)</td>
</tr>
</tbody>
</table>

Table 8 Comparison between indicators before and after DOTS (and statistical analysis)

<table>
<thead>
<tr>
<th>Serial N</th>
<th>Indicator</th>
<th>Mean before DOTS (%)</th>
<th>Mean after DOTS (%)</th>
<th>P value</th>
<th>Statistical significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Incidence rate: new cases (per 100 000 population)</td>
<td>24.7</td>
<td>10.9</td>
<td>0.0001</td>
<td>Highly significant</td>
</tr>
<tr>
<td>2</td>
<td>Incidence rate: new and relapsed cases (per 100 000 population)</td>
<td>25.8</td>
<td>11.5</td>
<td>0.0001</td>
<td>Highly significant</td>
</tr>
<tr>
<td>3</td>
<td>Incidence rate: all cases (per 100 000 population)</td>
<td>27.6</td>
<td>12.0</td>
<td>0.0001</td>
<td>Highly significant</td>
</tr>
<tr>
<td>4</td>
<td>Incidence rate: new smear-positive pulmonary TB cases (per 100 000 population)</td>
<td>10.0</td>
<td>6.4</td>
<td>0.001</td>
<td>Significant</td>
</tr>
<tr>
<td>5</td>
<td>New pulmonary TB cases with no smear result</td>
<td>54.8</td>
<td>29.2</td>
<td>0.0001</td>
<td>Highly significant</td>
</tr>
<tr>
<td>6</td>
<td>New adult smear-positive cases</td>
<td>82.6</td>
<td>83</td>
<td>0.554</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>7</td>
<td>Retreatment TB cases</td>
<td>29.1</td>
<td>12.4</td>
<td>0.0001</td>
<td>Highly significant</td>
</tr>
<tr>
<td>8</td>
<td>New extrapulmonary TB cases</td>
<td>18.6</td>
<td>22.9</td>
<td>0.037</td>
<td>Significant</td>
</tr>
<tr>
<td>9</td>
<td>New TB cases with no smear conversion result</td>
<td>11.0</td>
<td>8.3</td>
<td>0.018</td>
<td>Significant</td>
</tr>
<tr>
<td>10</td>
<td>Sputum conversion rate at the end of the initial phase of treatment</td>
<td>59.8</td>
<td>73.4</td>
<td>0.0001</td>
<td>Highly significant</td>
</tr>
<tr>
<td>11</td>
<td>Cure rate</td>
<td>46</td>
<td>61.1</td>
<td>0.0001</td>
<td>Highly significant</td>
</tr>
<tr>
<td>12</td>
<td>Treatment completion rate</td>
<td>16.1</td>
<td>18.6</td>
<td>0.057</td>
<td>Significant</td>
</tr>
<tr>
<td>13</td>
<td>Treatment success rate</td>
<td>62.1</td>
<td>79.7</td>
<td>0.0001</td>
<td>Highly significant</td>
</tr>
<tr>
<td>14</td>
<td>Death rate</td>
<td>2.8</td>
<td>3.8</td>
<td>0.158</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>15</td>
<td>Treatment failure rate</td>
<td>4.6</td>
<td>2.7</td>
<td>0.04</td>
<td>Significant</td>
</tr>
<tr>
<td>16</td>
<td>Default rate</td>
<td>20.4</td>
<td>6.8</td>
<td>0.0001</td>
<td>Highly significant</td>
</tr>
<tr>
<td>17</td>
<td>Transfer-out rate</td>
<td>6.0</td>
<td>3.7</td>
<td>0.096</td>
<td>Nonsignificant</td>
</tr>
<tr>
<td>18</td>
<td>Retreatment failure rate (chronic TB rate)</td>
<td>4.0</td>
<td>2.9</td>
<td>0.303</td>
<td>Nonsignificant</td>
</tr>
</tbody>
</table>

DOTS, direct observed therapy short course strategy; TB, tuberculosis.
A similar increase was found in the sputum conversion rate at the end of the initial phase of treatment in Menoufia Governorate (before DOTS the rate was 69.72% and after DOTS it was 76.64%) [6].

Treatment outcome

In this study, before DOTS the cure rate was 46.0% and after DOTS it was 61.1% (there was a highly significant increase).

Higher results were obtained in El-Minia Governorate (before DOTS the cure rate was 27.62%, and after DOTS it was 75.86%) [7].

In this study, before DOTS the treatment completion rate was 16.1% and after DOTS was 18.6% (there was a statistically significant increase).

In Menoufia Governorate, before DOTS the treatment completion rate was 19.41% and that after DOTS was 19.81% [6].

In this study, before DOTS the treatment success rate was 62.1% and that after DOTS was 79.7% (the increase was statistically significant).

There was improvement in cure rate, treatment completion rate, and treatment success rate after DOTS. This improvement was most probably due to improvement in follow-up of cases by direct observation, and new treatment regimen (short course chemotherapy), which improved the outcome of patients.

In Menoufia Governorate, before DOTS the treatment success rate was 77.01% and after DOTS it was 81.66% [6].

In this study, before DOTS the treatment failure rate was 4.6% and after DOTS it was 2.7% (the decrease was statistically significant).

In Menoufia Governorate, before DOTS the treatment failure rate was 2.23% and after DOTS the treatment failure rate was 3.54% [6].

In the present study, before DOTS the default rate was 20.4% and after DOTS it was 6.8% (the decrease was highly significant).

In Minia Governorate, before DOTS the default rate was 10.57% and after DOTS it was 4.88% [7].

In this study, before DOTS the death rate was 2.8% and after DOTS it was 3.8% (the difference was not statistically significant).

The increase in death rate in El-Behira Governorate after DOTS may be due to better reporting system compared with before implementing DOTS.

In Minia Governorate, before DOTS the death rate was 5.53% and after DOTS it was 4.84% [7].

In this study, before DOTS the transfer-out rate was 6.0% and after DOTS it was 3.7% (the difference was not statistically significant). However, the decrease in the transfer-out rate after DOTS may be due to better follow-up with short treatment duration and improved accessibility to public healthcare facilities.

Retreatment failure rate (chronic tuberculosis rate)

In this study, before DOTS the retreatment failure rate (chronic TB rate) was 4.0% and after DOTS it was 2.9% (the difference was not statistically significant). However, this decreased retreatment failure rate after DOTS may be due to better follow-up with short treatment duration after DOTS, which satisfied the patients and improved accessibility to public healthcare facilities.

In El-Minia Governorate, before DOTS the retreatment failure rate was 15% and after DOTS it was 13.77% [7].

Conclusion

TB is a burden of the productive age group 15–45 years, with a higher incidence in the male population than in the female population.

The introduction of DOTS in El-Behira Governorate has led to significant increase in treatment success and decrease in default and failure rates.

DOTS is an effective tool for controlling TB.

There are problems in case notification, laboratory services, and recording of cases in chest care centers in El-Behira Governorate.

Recommendations

Improvements are needed in case notification, laboratory services, and recording of cases (including computerization of medical records) in chest care centers in El-Behira Governorate.

A more strict application of the DOTS is needed to eliminate the problem of nonadherence to therapy.

Acknowledgements

Conflicts of interest

None declared.
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Behçet’s disease: case reports
Gamal M. Agmy

Behçet diseases is not only orogenital ulcerations but also it can have many systemic manifestations. In this article we presented 3 cases of Behçet disease associated with pulmonary artery aneurysms affecting the large branches. Pulmonary artery aneurysms are common and serious vascular complication of Behçet disease. These are usually large and accompanied with intramural thrombi and multiple pulmonary infarctions with a common presentation of haemoptysis. A detailed discussion of pulmonary manifestations of Behçet disease was demonstrated.

Case 1
A male patient 45 years of age presented with haemoptysis. He received complete regular course of antituberculous treatment on radiological basis with remission and recurrence of haemoptysis. A chest radiography was requested.

The patient was referred to Chest Department, Assiut University Hospital. History taking revealed recurrence of orogenital ulceration. Ophthalmological examination demonstrated iritis. A provisional diagnosis of Behçet’s disease was established. A computed tomography (CT) chest with pulmonary angiography was performed.

It illustrated large pulmonary artery aneurysm in the proximal part of lower lobe branch of the right pulmonary artery with intramural filling defect reflecting intramural thrombus.

Pulmonary angiography confirmed a fusiform aneurysm in proximal part of the right lower lobe branch of pulmonary artery. Hence, the recurrent haemoptysis can be explained by recurrent pulmonary infarction caused by detachment of emboli from intramural thrombus, and other cuts of CT pulmonary angiography confirmed this.

Case 2
A blind male patient presented with recurrent haemoptysis and recurrent orogenital ulcerations. He sought dermatological advice, and diagnosis of Behçet’s disease was recognized. He was referred to Chest Department, Assiut University Hospital. A Chest radiograph and CT chest with pulmonary angiography were accomplished.

CT angiography showed bilateral pulmonary artery aneurysms with large intramural filling defect in the right one reflecting bulky intramural thrombus with multiple infarcts in the right lung.

Pulmonary angiography of the right pulmonary artery confirmed a large aneurysm in the three branches of pulmonary artery.

Case 3
A patient presented with his chest radiograph.

He consulted a cardiothoracic specialist and a diagnosis of multiple hydatid cysts was made. During thoracotomy, pulsating lesions were noticed, and hence operation was ended, and the patient was referred to Chest Department, Assiut University Hospital. History taking was compatible with Behçet’s disease.

CT angiography verified bilateral pulmonary artery aneurysms with large intramural filling defect in the left one reflecting huge intramural thrombus.

Discussion

History
Behçet’s disease is a chronic inflammatory disorder of unknown aetiology characterized by recurrent attacks. Although the triple symptom complex of oral and genital ulcerations with uveitis was reported by Hippocrates and other authors who attributed the symptom triad to major infections, Hulusi Behçet, a Turkish dermatologist, discarded the association with other illnesses and was the first to delineate the disease that now bears his name. Clinical manifestations additional to this triad were described later including involvement of the skin.
joints, large vessels, lung, brain, gastrointestinal and genitourinary tracts. It is now recognized as a multisystem disease with vasculitis as the main pathological finding.

Pulmonary manifestations of Behçet’s disease
Tables 1 and 2.

Epidemiology
Although Behçet’s disease has a worldwide distribution, most cases cluster along the ancient Silk Road, which extends from far eastern Asia to the Mediterranean basin. The highest prevalence rate was reported from Turkey as 80–370 per 100 000. The prevalence ranges from two to 30 cases per 100 000 in other Asian countries, with lower figures in Europe and the USA. The age of disease onset is usually the second or third decade of life, and the male-to-female ratio is reported to be almost equal. However, the disease runs a more severe course in men and in those with an onset before 25 years of age.

Table 1 Frequency of clinical manifestations in Behçet’s disease

<table>
<thead>
<tr>
<th>Lesions</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral ulcers</td>
<td>96–100</td>
</tr>
<tr>
<td>Skin lesions</td>
<td></td>
</tr>
<tr>
<td>Folliculitis</td>
<td>40–50</td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>25–80</td>
</tr>
<tr>
<td>Positive pathergy test</td>
<td>10–50</td>
</tr>
<tr>
<td>Genital ulcers</td>
<td>65–90</td>
</tr>
<tr>
<td>Eye lesions</td>
<td>35–70</td>
</tr>
<tr>
<td>Arthritis</td>
<td>30–80</td>
</tr>
<tr>
<td>Neurological involvement</td>
<td>10–50</td>
</tr>
<tr>
<td>Gastrointestinal involvement</td>
<td>5–60</td>
</tr>
<tr>
<td>Vascular involvement</td>
<td>5–30</td>
</tr>
<tr>
<td>Pulmonary involvement</td>
<td>1–8</td>
</tr>
</tbody>
</table>

Pulmonary involvement
More than 200 cases of Behçet’s disease with pulmonary involvement have been reported in the literature. The pulmonary arteries are the second most common site of arterial involvement, preceded by the aorta. Aneurysms are more common than thrombosis.

Pulmonary artery aneurysms
Pulmonary artery aneurysms affect mainly young men. Haemoptysis of varying degrees (up to 500 ml) is the most common and predominant symptom. Rupture of an aneurysm with erosion into a bronchus and the development of in-situ thrombosis from active vasculitis have been suggested as explanations for haemoptysis. Sudden hilar enlargement or the appearance of polylobular and round opacities on the chest radiograph can represent pulmonary artery aneurysms. When associated with an acute episode of haemoptysis, they appear poorly margined; otherwise, they have a distinct outline. Helical CT is currently the method of choice for the diagnosis because it provides excellent vascular images with only a small quantity of contrast material. Aneurysms are seen as saccular or fusiform dilatations that show homogeneous contrast filling simultaneously with the pulmonary artery. Pulmonary artery aneurysms are located most frequently in the right lower lobar arteries, followed
by the right and left main pulmonary arteries. In this study, the diameter of the aneurysms ranged from 1 to 7 cm, and between two and seven aneurysms have been detected in the same patient. MRI is also helpful in the diagnosis of pulmonary artery aneurysms. Although no comparative studies are available, it is considered to be less sensitive than helical CT in demonstrating small aneurysms. Digital subtraction angiography has also been used in the diagnosis but it may be inadequate if aneurysms or vessels are completely thrombosed. Imaging techniques such as aortography, venography and pulmonary angiography are no longer used, as they carry a higher risk for complications. The frequency of such complications with digital subtraction angiography is unknown. In one case report, radionuclide angiography showed alterations in the pulmonary artery blood flow as clearly as did subsequent contrast pulmonary angiography. Normal or aneurysmally dilated pulmonary arteries frequently become obliterated by large thrombi. On chest radiography, this may result in hyperlucent areas of the lung supplied by these vessels. CT scanning can show a mosaic pattern of variable attenuation reflecting nonhomogeneous perfusion. Ventilation–perfusion lung scans show bilateral, well-defined, mismatched areas. Although deep venous thrombosis of the lower extremities frequently accompanies pulmonary artery aneurysms, pulmonary thromboembolism is very rare in Behçet’s disease because the thrombi in inflamed veins are strongly adherent.

**Pulmonary parenchymal findings**

Atelectasis, volume loss, wedge-shaped or linear shadows and ill-defined, nodular or reticular opacities have been described in Behçet’s disease, with or without pulmonary artery aneurysms. These findings are generally accepted as foci of pulmonary hemorrhage and/or infarcts. However, the pathological correlation of the parenchymal opacities has only been documented in a few cases. A recent case report reported prominent clinical, radiological and pathological findings of organizing pneumonia associated with pulmonary artery aneurysms. Organizing pneumonia may accompany various collagen vascular diseases including systemic lupus erythematosus and systemic vasculitides such as Wegener’s granulomatosis. Patients with secondary organizing pneumonia have a worse prognosis than cryptogenic or primary cases. In another patient with Behçet’s disease and peripheral nonsegmental pulmonary infiltrates, eosinophilic pneumonia was found on transbronchial biopsy.

**Other thoracic manifestations of Behçet’s disease**

Involvement of major veins including occlusion of the superior vena cava is a more prevalent finding than arteritis. Thrombosis of the innominate and subclavian veins may accompany superior vena caval occlusion. MRI is the suggested diagnostic method. Pseudoaneurysms of the aortic arch as well as the subclavian and coronary arteries have been described in Behçet’s disease. Mediastinal mass, mediastinitis, chylothorax and pleurisy are other associated conditions. Pleural effusion may result from vasculitis of the pleura or thrombosis of the superior vena cava.

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**Table 2 The International Study Group criteria for the diagnosis of Behçet’s disease**

In the absence of other clinical explanations, patients must have:

(1) Recurrent oral ulceration (aphthous or herpetiform) observed by the physician or patient recurring at least three times in one 12-month period

+ two of the following:

(2) Recurrent genital ulceration

(3) Eye lesions:

- Anterior uveitis
- Posterior uveitis (cells in the vitreous observed by slit-lamp examination) or Retinal vasculitis observed by an ophthalmologist

(4) Skin lesions:

- Erythema nodosum
- Pseudofolliculitis

Papulopustular lesions or acneiform nodules in postadolescent patients not on corticosteroids

(5) Positive skin pathergy test read by a physician at 48 h – that is, a 2 mm erythematous papule or pustule at the prick site 48 h after the application of a sterile hypodermic 20–22-G needle, which obliquely penetrated avascular antecubital skin to a depth of 5 mm
Natural history and prognosis
The natural history of Behçet’s disease is one of exacerbations and remissions. Male sex and young age of onset are markers of a more severe prognosis. Pulmonary artery aneurysm formation has a very poor prognosis and is one of the leading causes of death in Behçet’s disease; 30% of patients with this condition die within 2 years. Mean survival after the onset of haemoptysis was reported to be about 10 months in one study of patients with Behçet’s disease and pulmonary artery aneurysms. A more recent follow-up study of CT findings in 13 patients receiving immunosuppressant treatment showed complete disappearance or regression of pulmonary artery aneurysms during 3–42 (mean 21) months of treatment. Disappearance and regression of the aneurysm were preceded by thrombus formation. After treatment, the thrombi regressed and pulmonary artery aneurysms disappeared. Massive bleeding has been reported in patients receiving immunosuppressant treatment, although a partial remission was achieved.

Management

Immunosuppressant treatment
Empirical anti-inflammatory and/or immunosuppressive drugs tailored to the severity of the disease remain the mainstay of treatment. A combination of cyclophosphamide and methylprednisolone is used most frequently for patients with pulmonary artery aneurysms, although no controlled trial has assessed the efficacy of this combination. For patients with pulmonary artery aneurysms, we give cyclophosphamide 1000 mg monthly as intravenous pulses or 2 mg/kg/day orally with oral methylprednisolone 1 mg/kg. For patients with severe haemoptysis, we start with intravenous pulses of methylprednisolone 500–1000 mg for 3 days together with pulsed cyclophosphamide. The prednisolone dose is then tapered depending on the clinical response, whereas the cyclophosphamide regimen is continued for at least 1 year after complete remission when it is frequently switched to azathioprine. Cyclosporine combined with coumarin was reported to be successful in a patient with a single pulmonary artery aneurysm, and FK506 was used with good results in a patient with pulmonary infiltrates. Double-blind controlled trials are needed to assess the efficacy and long-term effects of currently used and new immunosuppressant drugs for eye lesions and/or life-threatening complications in Behçet’s disease.

Anticoagulation carries significant risks for patients with pulmonary artery aneurysms and must be used cautiously and only after systemic immunosuppressant treatment has been given. If thrombi are not extensive, antiplatelet treatment with, for example, low-dose aspirin is probably sufficient. Thrombolytic treatment with urokinase was tried in one patient with a thrombosed pulmonary artery aneurysm and streptokinase was given to a patient with superior vena cava syndrome. There was no evidence of new thrombotic episodes over the subsequent 2-year follow-up period. Both patients were also receiving immunosuppressive treatment; hence, the risks and efficacy of thrombolytic treatment are difficult to assess. There are no controlled studies on anticoagulants or antiplatelet aggregation therapy, and there is a lack of consensus on their use.

Clinical trials are needed to address the place of these drugs in the management of thrombotic disease in these patients.

Embolization
Embolization of a pulmonary artery aneurysm was attempted in one patient with massive bleeding. The size and number of aneurysms, the presence of superior or inferior vena caval occlusion and the potential complication of severe bleeding are the main limitations to the use of embolization in Behçet’s disease.

Surgery
In cases of massive haemoptysis, urgent surgical resection may be necessary. The main problem faced by the vascular surgeon is the 25% incidence of recurrent anastomotic aneurysms after both inlay graft repair and patching. False aneurysms and arteriovenous fistulae are also common at sites of previous iatrogenic trauma. Perioperative steroid cover has been suggested to reduce the risk for complications.

Conclusion
Therefore, the mainstay of treatment in Behçet’s disease is immunosuppressant therapy as in other severe vasculitides. Other treatment modalities should be used only in combination with this therapy and as palliative measures for specific complications [1].

Acknowledgements

Conflicts of interest
None declared.

Reference