İstanbul Med J 2021; 22(1): 13-8
DOI: 10.4274/imj.galenos.2020.57767

Is Sarcopenia Related to Mortality in Patients with Chronic Obstructive Pulmonary Disease in the Intensive Care Unit?

Yoğun Bakım Ünitesinde Tedavi Edilen Kronik Obstrüktif Akciğer Hastalarında Sarkopeni Mortalite ile İlişkili midir?

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ABSTRACT

Introduction: On admission to the intensive care unit (ICU), functional and general health stata are important baseline characteristics of critically ill patients with chronic obstructive pulmonary disease (COPD). The measurement of total psoas muscle area (PMA) is under investigation to determine physical frailty and sarcopenia, especially encountered in the elderly, to predict adverse outcomes and mortality in patients requiring in-hospital and ICU management. We aimed to assess the clinical value of total PMA for the prediction of mortality in COPD patients requiring ICU management of acute exacerbations.

Methods: The clinical data of 62 patients whose abdominal computed tomography (CT) scans were available in the hospital Picture Archiving Communication System were collected. The mean duration of stay in the ICU was 7.7±8.8 and 9.4±12.3 days in survivors and non-survivors. The main causes of mortality in non-survivors were respiratory failure and cardiac arrest. For measurements from CT scans, images of the caudal end of the third lumbar vertebra were used. Right and left PMAs were measured to obtain the total PMA and density.

Results: Of 62 patients, 20 (32.2%) were non-survivors (male: 13, female: 7), and 42 were survivors (male: 32, female: 10). There was no significant difference between non-survivors and survivors regarding total PMA and density values ($p>0.05$). In non-survivors and survivors, females had lower total PMA ($p<0.05$). There was no significant association between clinical and PMA data ($p>0.05$).

ÖZ

Amaç: Yoğun bakım ünitesine (YBÜ) kabul aşamasında, ileri derecede kronik obstrüktif akciğer hastalığı (KOAH) olan hastaların fonksiyonel ve genel sağlık durumları önem arz eder. Toplam psoas kas alanının (PKA) ölçümü, hastane ve YBÜ tedavisi gerektiren, özellikle yaşlı hastalarda, olumsuz sonuçları ve mortaliteyi tahmin etmek için, fiziksel kırılganlık ve sarkopeninin araştırılmasında kullanılan bir yöntemdir. Bu çalışmada, KOAH akut alevlenme nedeniyle YBÜ tedavisi gereken hastalarda, mortalitenin tahmini için total PKA'nın klinik değerini araştırmayı amaçladık.

Yöntemler: Bu kesitsel çalışmaya akut KOAH atağı ile YBÜ'de tedavi edilen hastalar alındı. Abdominal bilgisayarlı tomografisi (BT) olan 62 hastanın verileri toplandı. Yoğun bakımda kalış süresi yaşayan hastalar ve ölenlerde ortalama 7,7±8,8 ve 9,4±12,3 gün idi. Mortalite gelişen hastlarda en sık sebepler solunum yetmezliği ve kardiyak arrestti. BT ölçümlerinde 3. lumbal vertebranın kadual ucunun görüntüsü kullanıldı. Total PKA'nın hesaplanması için, sağ ve sol PKA dansite değerleri ile birlikte ölçüldü.

Bulgular: Çalışmaya dahil edilen 62 hastanın 20'si ölmüşken (erkek: 13, kadın: 7), 42'si sağ kalmıştır (erkek: 32, kadın: 10). Ölenler ile yaşayanlar arasında total PKA ve dansite değerleri açısından anlamlı bir fark bulunmadı ($p>0,05$). Kadın hastaların total PKA değeri ölenlerde yaşayanlara göre anlamlı derecede düşük bulunmuştur ($p<0,05$). Hastaların klinik verileri ile PKA değeri arasında anlamlı bir ilişki bulunmadı ($p>0,05$).

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Cite this article as/Atıf: Toptaş M, Yurt S, Haliloğlu M, Tuna L, Karapınar K, Akkoç İ, Kırkıl G, Çınarka H. Is Sarcopenia Related to Mortality in Patients with Chronic Obstructive Pulmonary Disease in the Intensive Care Unit?. İstanbul Med J 2021; 22(1): 13-8.

Received/Geliş Tarihi: 18.09.2019
Accepted/Kabul Tarihi: 19.11.2020

ABSTRACT

Conclusion: The total PMA lacks sufficient power to predict mortality in patients managed with acute exacerbations of COPD in intensive care settings. There is a need for further studies with different sets of findings to assess the contribution of physical frailty and sarcopenia to adverse outcomes in the ICU management of COPD patients.

Keywords: Chronic obstructive pulmonary disease, COPD, frailty, sarcopenia, psoas muscle area, computed tomography

ÖZ

Sonuç: Total PKA, KOAH alevlenme ile YBÜ'de tedavi edilen hastalarda mortaliteyi tahmin etmede yeterli değildir. YBÜ'de yatırılarak tedavi edilen KOAH hastalarında karşılaşılan olumsuz sonuçlara, fiziksel kırılganlık ve sarkopeninin katkısını değerlendirmek için, farklı bulgu grupları ile daha ileri araştırmalara ihtiyaç vardır.

Anahtar Kelimeler: Kronik obstrüktif akciğer hastalığı, KOAH, kırılganlık, sarkopeni, psoas kas alanı, bilgisayarlı tomografi

Introduction

Chronic obstructive pulmonary disease (COPD) is a growing healthcare concern that is gaining worldwide importance because of its relatively high prevalence and remarkable morbidity and mortality with the contribution of aging in the population (1,2). COPD can be accompanied by variable comorbidities. COPD exacerbations are associated with a considerable decline of lung function and can significantly worsen survival outcomes, especially in patients who require mechanical ventilation (3). Moreover, the presence of COPD contributes as a prominent risk factor, increasing mortality and morbidity in critically ill patients hospitalized for management of other systemic disorders (4).

During management of in-hospital patients with several systemic disorders, including acute exacerbations of COPD, some of the challenges are related to physical frailty. The presence and severity of frailty can increase the duration and usage of diagnostic and therapeutic procedures during management of main and comorbid disorders; in addition, frailty may impair the overall outcome of patients managed in the intensive care unit (ICU) (2,5).

The all-cause mortality rate in the ICU is higher than in other hospital services. Advanced age, gender, primary disease and its severity, comorbid disorders, and biomarkers such as C-reactive protein, albumin, and ferritin are among the factors considered to increase the risk of fatality (6). Unfortunately, these conditions and biomarkers lack sufficient power to be used directly for the prediction of mortality during management of COPD patients in the ICU. Within this perspective, nowadays, there are also several tools to assess frailty, mainly in the elderly population, to understand patients' basic health conditions; however, their use is not tested adequately in in-hospital patients with various clinical conditions, including the presence of comorbid disorders during intensive care requirements.

With the aging population, the contribution of frailty and pre-frailty as a comorbidity increases considerably in COPD patients (2). Frailty is accepted as a potent predictor of adverse outcomes in various clinical settings (7). Sarcopenia, defined as low muscle mass, is the preferred approach to frailty assessment (8). Sarcopenia is measured commonly by the skeletal muscle mass index (9), and the psoas muscle is the most used muscle for measuring the skeletal muscle mass. Patients managed in the ICU may need to undergo a computed tomography (CT) scan of their body among the diagnostic procedures, and these CT scans may be beneficial for evaluating sarcopenia with total psoas muscle area (PMA). Sarcopenia has the potential to be used as a predictor of the clinical and surgical course and patient morbidity (10,11). Moreover, Yokoyama et al. (12) reported that sarcopenia is a poor prognostic parameter during the management of patients with disordered peripheral arteries.

However, there is not sufficient data to determine the impact of sarcopenia on morbidity and mortality of COPD patients in the ICU. The overall objective of the present trial was to evaluate the association between in-hospital mortality and sarcopenia measured by CT scan with PMA in COPD patients requiring management in the ICU. We hypothesized that sarcopenia is an independent predictor of mortality in COPD patients in the ICU.

Methods

This cross-sectional study included COPD patients managed with acute exacerbations in the ICU of our tertiary care center between May 2012 and May 2017. This study approval was obtained from the University of Health Sciences Turkey, İstanbul Training and Research Hospital Human Research Ethics Committee (approval number:1593, date: 21.12.2018). After informed consent was obtained from the patients or their relatives, selected clinical variables at admission and during follow-up were recorded from the patients' electronic hospital records. COPD patients managed with acute exacerbations in the ICU were accepted as eligible for the study. Patients who had any comorbidities that could influence their outcomes were excluded from the study. Sixty-two COPD patients who had abdominal CT scans for any reason during their hospital stays were included in the study for further evaluation. The diagnosis of COPD was made according to radiographic findings, physical examination, and management plans, including prescriptions that were recorded in the hospital information system of our institution. Medical therapy given to these patients included systemic steroids, inhaled steroids, inhaled anticholinergics, and β2 agonists.

Measurement of PMA

With the available CT scan images, we determined the quantity of skeletal muscle. CT images obtained from 128-slice spiral CT with a 2 mm section thickness (Philips, Holland). For the measurements to obtain information about the skeletal muscle cross-sectional area (cm^2), images of the caudal end of the third lumbar vertebra were used. With these images, right and left PMAs were measured to obtain the total PMA. A radiologist performed these measurements while blinded to the severity and clinical outcomes in the study population. Intraobserver

agreement was found to be adequate with a calculated Kappa value of 0.83. A CT image of the measurement is presented in Figure 1.

Psoas muscle radiation attenuation was also calculated, and mean Hounsfield unit values as density were taken for statistics.

In the study population, selected clinical data were recorded including age, sex, smoking status, length of stay in the ICU, some laboratory measurements, and in-hospital mortality status. The relationship of these clinical parameters with the PMA values was assessed with correlation analyses.

Statistical Analysis

Statistical analyses were performed with SPSS statistical software (IBM SPSS, Version 22.0, IBM Corporation, Armonk, NY, USA). Normality tests for continuous variables were conducted with the Shapiro-Wilk test. Numeric parameters were given as means with standard deviation and analyzed with t- or Mann-Whitney U tests when they were parametric or non-parametric, respectively. Categorical data were presented as numbers with percentages and, where appropriate, they were analyzed with a chi-square test. The relationships between continuous variables were examined with the Spearman's test. A p-value of less than 0.05 was set as the threshold for statistical significance.

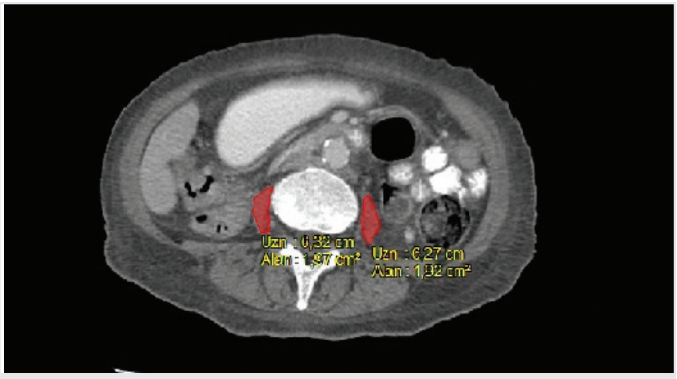

Figure 1. CT image of the measurement of bilateral psoas muscle area
CT: Computed tomography

Results

One hundred six COPD patients were followed in the ICU during the study period. Forty-four of these patients had lung cancer, so they were excluded from the study. Previous CT scans of 62 patients were found by a search in the hospital PACS system and included in the study. The mean duration of stay in the ICU was 7.7±8.8 and 9.4±12.3 days in survivors and non-survivors, respectively. Causes of mortality in non-survivor were mainly respiratory failure and cardiac arrest.

The demographic and some laboratory data of all patients (survivors and non-survivors) are presented in Table 1, and right, left, and total PMA and density values are presented in Table 2. Twenty (32.2%) of 62 patients died during ICU stay. The mean age of the study group was 59.2±15.2 years; 17 of them (27.4%) were female. Although PaO_2 values were higher, and $PaCO_2$ values were lower in survivors, this difference did not reach statistically significance, nor did other parameters (p>0.05). The mean right, left, and total PMA of 62 patients were 6.5±2.7 mm^2, 6.3±2.6 mm^2, and 12.8±5.3 mm^2, respectively. Considering the non-survivors and survivors, the PMA values were found to be comparable (p>0.05) (Table 2).

Table 1. Selected demographic and laboratory data of survivors and non-survivors

	Survivors (n=42)	Non-survivors (n=20)	p
Age (y)	60.3±14.5	56.9±16.6	>0.05
Sex (F/M)	10/32	7/13	>0.05
Albumin (g/dL)	2.9±0.6	2.8±0.8	>0.05
Total protein (g/dL)	6.0±0.7	6.0±0.9	>0.05
CRP (mg/L)	101.0±103.7	141.0±115.6	>0.05
WBC ($x10^3/mm^3$)	13.0±5.0	13.6±14.4	>0.05
Hematocrit (%)	34.3±7.0	34.6±6.8	>0.05
Platelet ($x10^3/\mu L$)	259.4±125.8	208.0±111.1	>0.05
PaO^2 (mmHg)	88.5±62.1	77.3±44.2	>0.05
$PaCO^2$ (mmHg)	49.5±17.7	59.4±25.7	>0.05

Data are presented as means with standard deviation.
F: Female, M: male, CRP: C-reaktif protein, WBC: white blood cell

Table 2. Total PMA and density values of survivors and non-survivors

	Survivors (n=42)	Non-survivors (n=20)	p
Right psoas area (mm^2)	6.4±2.4	6.8±3.3	>0.05
Left psoas area (mm^2)	6.2±2.6	6.4±2.8	>0.05
Total psoas area (mm^2)	12.6±5.0	13.15±6.0	>0.05
Density (HU)	51.5±23.1	46.7±20.1	>0.05

Data are presented as means with standard deviation.
PMA: Psoas muscle area, HU: Hounsfield unit

When we categorized the participants according to gender (Table 3), males in both survivors and non-survivors had higher total PMA values than their female counterparts ($p<0.05$). However, the density values did not differ between survivor and non-survivor males and females ($p>0.05$). There was no significant correlation between participants' demographic, laboratory, and psoas data ($p>0.05$).

Discussion

In the present study, data analyses did not support the value of total PMA and density measured with an approved method using CT images to predict in-hospital mortality in COPD patients admitted to the ICU. Although male patients had higher PMA and density than female patients, overall, the results indicated no significant difference between the 32.25% of patients who did not survive and the 67.75% of patients who survived. We could not determine any correlation among the demographic, laboratory, and PMA data. Another finding of this study was that these patients were somewhat younger than other patients admitted to the ICU. In general, elderly persons need in-hospital management because of acute exacerbations of their chronic disorders that affect several organ systems. It has been reported that 46% of patients admitted to the ICU are seniors (13). In our study, the mean age of patients hospitalized in the ICU was 59.2±15.2 years. In a study by Unal et al. (14), the mean age of patients in the ICU was 73.9 years, and 77.5% of them were in the geriatric age range (>65 years).

Some studies have examined the value of total PMA in the assessment of sarcopenia status to predict outcomes in patients with different disorders. The findings have been contradictory as discussed below. Some authors concluded that total PMA can have prognostic value in patients who undergo emergency surgery, cancer resection, or liver transplantation (15-17). In a study by Waduud et al. (18), total PMA was assessed in patients who had elective abdominal aortic aneurysm repair. Their study did not support the value of total PMA for the prediction of mortality at 30 days, 1 year, or 4 years, and for the requirement of ICU admission, prolonged hospital stay, or readmission within 30 days. On the other hand, Thurston et al. (19) and Newton et al. (20) both reported a longer duration of hospital stay in sarcopenic patients who underwent endovascular aneurysm repair. Contrary to those findings, Kays et al. (21) reported that the presence of sarcopenia was not a determining factor for the development of early or late complications. In accordance with the results of the current study, Heard et al. (22) found that sarcopenia did not influence the decision about the management strategies required after postintervention discharge. Boutin et al. (23) assessed the paravertebral muscle area at the level of T12 and the psoas muscle at the level of L4 in a group of elderly patients requiring hip fracture management. Although they found no meaningful association of decreased cross-sectional area of the psoas muscle with mortality, they noted that patients with decreased PMA also had a lower survival rate. Couch et al. (24) concluded that there was no relationship between the lower mass of psoas area and prognosis after analysis of clinical data in 225 elderly trauma patients. Their findings supported that lean psoas area cannot be used as a predictor for the mortality or complications of trauma. Patients who underwent surgery of major internal organs (25-27) showed an association between PMA and all-cause mortality: low PMA was related to increased mortality rates. Overall, to draw conclusions by comparison of findings from similar studies poses a challenge because of inconsistency among definitions related to the measurement criteria for evaluation of sarcopenia. Garg et al. (28) suggested that no meaningful association existed between PMA and mortality one year later after their management. In contrast, Saji et al. (29) demonstrated an association of PMA with mortality 6 months after their management. Patients with lower levels of PMA had higher mortality rates (30,31).

In this study, measurement of total PMA was preferred as a tool for the measurement of total abdominal muscle area, because after a short training period, the observer was able to determine the suitable area for psoas muscle measurements after performing a short scan. The measurement of total PMA was reported to be a reproducible tool in previous studies, because no intraobserver and interobserver differences considered meaningful was observed. The method is feasible using most standard PACS viewers, so there is no need for any additional resources, and is representative of likely clinical application. However, the Hounsfield-based method of image analysis has a potential benefit, because it is demonstrated that sarcopenic myosteatosis can be associated with increased mortality, suggesting that measuring the PMA may not be enough to accurately assess the actual muscle bulk (21). Therefore, we also calculated the density of the muscle for determining sarcopenia in our cohort.

The patient's gender may be a prominent contributor to the development and course of sarcopenia to predict their mortality. In a study by van Mourik et al. (32), although the PMA of females was found to be correlated with all-cause and cardiac mortality within 2 years, the PMA of males did not present a relationship with mortality. Higher baseline values of PMA were obtained with males than with females, which might serve as a larger reserve before having the negative outcome of a low PMA. Mamane et al. (33) investigated males and females separately

Table 3. Total PMA and density values according to the gender of participants in both survivor and non-survivors

	Non-survivor		
	Male (n=13)	**Female (n=7)**	**p**
PMA (mm^2)	15.1±5.9	9.5±4.7	0.045
Density (HU)	58.7±23.2	38.1±17.2	0.055
	Survivor		
	Male (n=32)	**Female (n=10)**	**p**
PMA (mm^2)	14.3±4.3	7.3±2.7	0.001
Density (HU)	46.4±18.8	46.4±18.8	0.897

PMA: Psoas muscle area, HU: Hounsfield unit

in participants who underwent transcatheter aortic valve implantation. They found higher one-year mortality in males. We also demonstrated higher values of total PMA in males, but sex-based differences were not predictive of mortality. Considering the results of the above studies, there are important differences among the characteristics of those cohorts in terms of their main and comorbid disorders. Our COPD patients were typically older and current or previous smokers with a high rate of cardiovascular and pulmonary comorbid disorders. Therefore, it is important to appreciate that it may be challenging and inadequate to capture the complex nature of the interplay between frailty and the comorbid states of subjects with a single tool such as the assessment of total PMA.

Study Limitation

This study has several limitations, including its retrospective observational nature and the single-center collection of COPD patients, which did not consider the severity of COPD and may therefore not be representative of all cohorts of COPD patients with different severity requiring ICU management. The patients included in this study were somewhat younger than those in most COPD populations. Therefore, the conclusions cannot be extrapolated to the comprehensive and long-term prognostic value of PMA as a screening tool, thereby necessitating a more prolonged follow-up period to determine time-dependent changes in the PMA and to establish its prognostic value in the future.

Conclusion

There is a need to assess physical frailty and sarcopenia in the management of acute exacerbations of COPD requiring ICU services. Overall, according to the results of the current study, the total PMA alone is not a successful tool for the prediction of in-hospital mortality in the acute exacerbations of COPD managed in the ICU. Considering the wide range of variability in its values from patient to patient, the total PMA may be a good alternative to determine the degree and change of sarcopenia during follow-up of COPD patients to improve the success of their management plan, especially in patients over than 65 years of age.

Ethics

Ethics Committee Approval: This is study approval was obtained from the University of Health Sciences Turkey, İstanbul Training and Research Hospital Human Research Ethics Committee (approval number:1593, date: 21.12.2018).

Informed Consent: Informed consent was obtained from the patients. patients.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Surgical and Medical Practices - M.T., M.H., L.T.; Concept - M.T.; Design - M.T., K.K.; Data Collection or Processing - M.T., S.Y., M.H., L.T., İ.A.; Analysis or Interpretation - M.H., L.T., İ.A., G.K., H.Ç.; Literature Search - M.T., S.Y., K.K., G.K.; Writing - M.T., S.Y., K.K., İ.A., G.K., H.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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