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Controlling Nutritional Status Score Predicts In-Hospital Mortality in Acute Pulmonary Embolism

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Highlights of the Study

- Malnutrition is not uncommon in hospitalized adult patients, and it is associated with adverse outcomes and increased costs.
- This is the first study examining the value of the Controlling Nutritional Status (CONUT) score in assessing malnutrition among acute pulmonary embolism (APE) patients.
- We showed that the presence of malnutrition defined by the CONUT score predicts in-hospital mortality following APE.

Keywords
Acute pulmonary embolism · Nutritional status · Mortality

Abstract
Objective: The association between the nutritional status and outcomes in pulmonary embolism is unclear. This study was aimed at examining the value of the Controlling Nutritional Status (CONUT) score in assessing malnutrition among acute pulmonary embolism patients. ***Subject and Methods:*** We retrospectively reviewed the records of adult patients with acute pulmonary embolism hospitalized through our ED. Demographic, clinical, and laboratory data on admission were recorded. Nutritional status was assessed with the CONUT score, which is calculated by the albumin, total cholesterol, and lymphocyte counts. The primary endpoint of the study was in-hospital mortality. ***Results:*** A total of 308 consecutive patients (mean age 68.2 ± 12.9 years, 53.9% female) were included, and 35 of the patients (11.4%) died during their in-hospital course. Multivariate analysis showed that a pulmonary embolism severity index >148 (OR 3.12, 95% CI: 1.65–8.81, $p < 0.001$), the presence of heart failure (1.25, 95% CI: 1.08–1.78, $p = 0.03$), and a CONUT score >4 (OR 1.39, 95% CI: 1.146–3.424, $p = 0.015$) were independent predictors of in-hospital mortality. ***Conclusion:*** The present study indicates that the presence of malnutrition defined by the CONUT score predicts in-hospital mortality following acute pulmonary embolism.

Introduction

A large proportion of hemodynamically stable acute pulmonary embolism (APE) patients may derive no benefit from hospitalization and may be able to be discharged

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Table 1. Definition of the CONUT score

Variables				
Serum albumin, g/mL	≥3.5	3.0–3.49	2.5–2.99	<2.5
Score	0	2	4	6
Total cholesterol, mg/dL	≥180	140–179	100–139	<100
Score	0	1	2	3
Lymphocytes, count/mL	≥1,600	1,200–1,599	800–1,199	<800
Score	0	1	2	3

from the emergency department after initiation of anticoagulation [1, 2]. Previous studies have shown mortality rates are low in patients with APE treated as outpatients but are higher among patients hospitalized for APE [3]. Therefore, several clinical, demographic, echocardiographic, and laboratory variables and scoring systems have been investigated for the prediction of adverse events in patients hospitalized due to APE [4–6]. These studies revealed that advanced age, higher natriuretic peptide levels at presentation, the presence of chronic cor pulmonale, malignancy, sinus tachycardia, hypotension, or tachypnea were associated with worse prognosis after hospitalization for APE [4–6]. Pulmonary embolism severity index (PESI) and its simplified form, simplified PESI, are the most widely known and the most commonly used scores both of which estimate the risk of 30-day mortality in APE by using 11 and 6 clinical criteria, respectively [7]. However, these scores have several limitations, such as difficulties to use in real-life daily practice, not incorporating biomarkers, and validation for only 30-day mortality. Hence, simple and effective predictors of in-hospital prognosis, which could help in risk stratification in an emergency setup by using routinely available modalities, should be investigated in patients with APE.

The prognostic value of the patient's nutritional condition, which reflects patients' health status, has been demonstrated in patients with various diseases such as acute coronary syndrome [8], stable coronary artery disease [9], heart failure [10], and acute ischemic stroke [11]. Despite many valuable prognostic factors, APE still requires an inexpensive and reliable index of the patient's nutritional status. The Controlling Nutritional Status (CONUT) score is an easily calculated index of malnutrition by using serum albumin, total cholesterol, and total lymphocyte count in the same formula [12]. This score reflects not only nutritional status but also illustrates the patient's immunologic status and calorie depletion [12]. Although the utility of the CONUT score in predicting prognosis has been generally reported in cancer patients undergoing surgery [13, 14], recent studies showed that it also predicts prognosis in patients with hypertension [15], ischemic stroke [16], or heart failure [17]. Blood biomarkers are sufficient to determine this simple and inexpensive risk index. Among the nutritional indices, CONUT is the most widely accepted index. Few studies [18, 19] have shown correlations between nutritional indicators such as albumin, lymphocyte count, and poor outcomes in patients with pulmonary embolism. The value of the CONUT score in predicting outcomes in patients with APE has not been studied. Therefore, this study aimed to investigate the prevalence and importance of malnutrition assessed by the CONUT score in APE patients.

Subjects and Methods

Subjects

This is a retrospective and single-center study. Patients with APE admitted to the Emergency Department of the university hospital, a tertiary health center, were enrolled. All consecutive adult (aged 18 years or older) APE patients requiring hospitalization between April 2016 and August 2017 were included. All patients were diagnosed and managed according to the current guidelines for the management of pulmonary embolism [20]. Patients younger than 18 years or patients who were not hospitalized were excluded from the study. Patients with incomplete laboratory data and patients who have factors that could potentially affect CONUT scores such as active tuberculosis, pregnancy, and malignancy were also excluded.

The sample size was estimated at 180 patients, with a power of 82% and a two-tailed alpha error of 0.05. This study was approved by the Muğla University Ethics Committee, and all patients or their relatives gave informed written consent.

Measurements and Study Endpoint

Patient demographic and clinical characteristics, laboratory data, and radiological findings ED were recorded. Complete blood count and routine biochemical analyses results, measured within the first 24 h of admission, were also recorded. The severity of APE was assessed by PESI [6]. The CONUT score was calculated by serum albumin level, total cholesterol level, and lymphocyte counts (Table 1) [12]. Patients were classified according to the CONUT score as normal nutritional status (CONUT score 0–1 point), mild malnutrition (CONUT score 2–4 points), and moderate to severe

Table 2. Comparison of survivor and nonsurvivor patients

	Alive (n = 273)	Death (n = 35)	p value
Gender (female)	148 (54.2)	18 (51.4)	0.685
Age, years	67.6±13.6	70.1±12.4	0.041
Smoking	56 (20.5)	7 (20.0)	0.785
Comorbidities			
Hypertension	128 (46.9)	16 (45.7)	0.563
Diabetes mellitus	63 (23.1)	10 (28.6)	0.014
Chronic kidney disease	24 (8.8)	3 (8.6)	0.896
Coronary artery disease	34 (12.4)	5 (14.3)	0.562
Cerebrovascular disease	15 (5.4)	2 (5.7)	0.368
Chronic lung disease	25 (9.2)	6 (17.1)	0.012
Heart failure	16 (5.9)	6 (17.1)	0.001
Laboratory data			
Serum creatinine, mg/dL	0.81 (0.7–1.0)	0.83 (0.7–1.0)	0.452
Hemoglobin, g/dL	12.6 (11.5–14.3)	12.7 (11.3–14.8)	0.536
Albumin, g/dL	3.8±0.65	3.5±0.54	0.029
White blood count, $\times 10^3$cells/mL	9.8±4.7	9.9±4.5	0.598
Lymphocytes, cell/mm^3	1,756±635	1,568±658	0.012
Total cholesterol, mg/dL	176.5±32.5	179.5±30.9	0.068
Nutritional status (CONUT score)			
Normal (0–1)	124 (45.4)	9 (25.7)	<0.001
Mild malnutrition (2–4)	123 (45.1)	19 (54.3)	
Moderate-severe malnutrition (≥5)	26(9.5)	7 (20)	
CONUT score	3.06±1.95	5.24±2.33	0.001
PESI	112 (75–142)	164 (130–202)	<0.001

Data are presented as mean ± standard deviation, median with the first and third quartile (Q1–Q3), or n (%).

malnutrition (CONUT score ≥5 points). The primary outcome of this study was in-hospital mortality, defined as mortality from any cause during hospitalization.

Statistical Analysis

Data were analyzed using SPSS for Windows (version 24; SPSS Inc., Chicago, IL, USA). Comparison of patients' characteristics in two groups (survivors and deceased) was done by the χ^2 test. Distribution of the analyzed continuous variables for normality was tested with the Kolmogorov-Smirnov test. Univariable and multivariable analyses with Cox proportional hazard regression were performed to identify the relationship between demographic and laboratory variables and mortality. The variables listed in Table 2 are included in the Cox models except for albumin, cholesterol, and lymphocyte counts, which are included in the CONUT score. The receiver operating characteristic curve was used to identify the optimal cutoff point of the CONUT score for the outcome.

Results

A total of 338 patients were hospitalized due to APE during the study period in our hospital. However, 30 patients who did not have cholesterol or lymphocyte count measurements in the first 24 h of admission were excluded. Hence, the study included 308 hospitalized patients with APE (mean age 68.2 ± 12.9 years, 53.9% female).

In-Hospital Mortality

A total of 35 patients (11.4%) died during the study period, of whom 17 were male, and 18 were female. Among the 35 deaths that occurred during the study period, the cause of death was cardiovascular collapse in 30, bleeding in 2, and other causes in 3 patients. Demographic and laboratory data, CONUT score, and PESI scores of the survivors and deceased patients are listed in (Table 2). Patients who died were older (70.1 ± 12.4 vs. 67.6 ± 13.6 years; p = 0.041), had higher prevalence of chronic lung disease (17.1 vs. 9.2%; p = 0.012), and heart failure (17.1 vs. 5.9%; p = 0.001). Patients who died had lower albumin and lymphocyte levels but higher PESI scores compared with patients who survived.

Nutritional Parameters

A total of 133 (43.2%) patients had normal nutritional status, 142 (46.1%) patients had mild malnutrition, 22

Table 3. Multivariate regression analysis for the prediction of in-hospital mortality

	OR	95% CI	*p* value
Age (per 1 year)	1.032	0.968–1.079	0.413
CONUT score >4	1.392	1.146–3.424	0.015
Diabetes mellitus	0.688	0.162–1.468	0.192
PESI >148	3.125	1.653–8.814	<0.001
Heart failure	1.255	1.087–1.785	0.030
Chronic lung disease	0.528	0.101–2.276	0.354

PESI, pulmonary embolism severity index.

(7.13%) patients had moderate malnutrition, and 11 (2.57%) patients had severe malnutrition according to their CONUT scores. The baseline nutritional status was different between deceased patients and survivors; deceased patients were more likely to have malnutrition (mild, moderate, and severe) compared to survivors (74.3 vs. 54.6%, $p < 0.001$).

Predictors of In-Hospital Mortality

Multivariate analysis showed that a CONUT score >4 (OR 1.39, 95% CI: 1.146–3.424, $p = 0.015$), PESI > 148 (OR 3.12, 95% CI: 1.65–8.81, $p < 0.001$), and the presence of heart failure (1.25, 95% CI: 1.08–1.78, $p = 0.03$) were independent predictors of in-hospital mortality (Table 3).

Discussion

In 308 consecutive patients with APE, we found that 56.8% of the patients had malnutrition according to their CONUT scores. Moreover, this study is the first to show that higher CONUT scores on admission were strongly associated with in-hospital mortality among APE patients.

Malnutrition is not uncommon in hospitalized adult patients, and it is associated with adverse outcomes and increased costs [21]. The prevalence of malnutrition varied from 20% to 50% in hospitalized patients depending on the method of nutritional assessment [22]. Although malnutrition has been identified with several tools in various diseases [23, 24], none of these tools has been validated in patients with APE. Therefore, the prevalence and importance of malnutrition is unclear in patients with APE. Maia and colleagues retrospectively analyzed the data of 683 patients admitted to the pulmonology unit to identify the association between undernutrition and prognosis [25]. Undernutrition was defined using the Malnutrition Universal Screening Tool and found in 34.8 of the study population [25], and patients with higher undernutrition risk were found to have a higher risk for in-hospital mortality. However, this study had a heterogeneous patient population, and most of the patients were hospitalized for chronic obstructive pulmonary disease, lung cancer, or pneumonia, with only 9 APE patients [25]. In another recent study, the medical records of 1,032 APE patients were retrospectively analyzed to identify the prevalence and importance of hypoalbuminemia [26]. The authors found that 15.5% of the patients had hypoalbuminemia at presentation, which was an independent predictor of 30- and 90-day mortality following APE [26].

Risk of malnutrition was high among older European adults according to a recent meta-analysis [27]. Additionally, comorbidities such as heart failure, cancer, and Parkinson disease were associated with higher rates of nutritional deficiency. We showed that malnutrition, older age, and heart failure were associated with mortality in APE. Elderly APE patients usually have comorbidities, and malnutrition is expected to be prevalent within this population. However, a high CONUT score and heart failure were independent predictors of mortality in APE, but age was not an independent predictor. The PESI score is used for risk stratification of pulmonary embolism after the diagnosis has been made. It has been validated for a 30-day outcome of APE patients. Our study also showed that the PESI score was an independent predictor of mortality.

Although the serum albumin level has been widely used as a marker of malnutrition in different types of diseases, some studies have suggested that malnutrition would be underdiagnosed when using hypoalbuminemia as the sole criterion [28]. Therefore, several indexes such as the prognostic nutritional index (PNI) and CONUT score have been developed for more accurate identification of malnutrition by using other biochemical markers in addition to albumin levels. The PNI is calculated with serum albumin concentration and total peripheral lymphocyte counts [19]. The only study examining the value of the PNI in APE patients showed that a lower PNI at admission was a predictor of higher in-hospital mortality [19]. The CONUT score is not only a marker of nutritional status but also reflective of immunologic status and calorie depletion as it contains albumin, lymphocyte, and total cholesterol levels in the same formula. However, the prognostic value of the CONUT score has been evaluated mostly among surgical patients [12, 13], and to our knowledge, its relation to adverse events has not been previously described in patients with APE. Although our data are preliminary and the CONUT has not been validated in APE patients, we observed significant associations between higher CONUT scores and in-hospital mortality.

Limitations of this study include the fact that it is a retrospective and single-center study without long-term follow-up. We could not assess all the hospitalized patients due to missing data which might cause a bias in our study. The CONUT score was measured within the first 24 h of admission, and this may not reflect the patient status over long periods. Since our study population included only hospitalized patients, the applicability for ambulatory patients should be evaluated. We excluded specific patient groups such as active tuberculosis, pregnancy, and malignancy; thus, our results cannot be generalized to these patient groups.

Conclusions

Our study is the first to use the CONUT score to assess malnutrition in patients with APE. We found that more than half of our patients had malnutrition, and a high CONUT score was a predictor of in-hospital mortality in patients with APE. Prospective studies involving larger numbers of patients are needed to elucidate the value of the CONUT score for predicting mortality in APE.

Statement of Ethics

All procedures involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Muğla University Ethics Committee, and all patients or their relatives gave informed written consent.

Conflict of Interest Statement

All authors declare that they have no conflicts of interest.

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Author Contributions

Birdal Yıldırım, Zeynep Karakaya, Ethem Acar, Ahmet Doğan, Kemal Gökçek, Aysel Gökçek, Volkan Doğan, and Murat Biteker conceptualized and designed the study, designed the data collection instrument, collected data, analyzed and interpreted the data, and contributed to initial manuscript drafting. Birdal Yıldırım contributed to the conceptualization and design of the study, contributed to designing data collection instruments, supervised data collection, contributed to data analysis and interpretation, and critically reviewed and revised the manuscript for important intellectual content. All the authors reviewed, revised, and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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