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Prognostic value of non-alcoholic fatty liver disease in patients with pulmonary embolism

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ABSTRACT

Objectives: Pulmonary embolism (PE) is an important disease due to its mortality and morbidity-related clinical conditions. Patients with a high risk of death within 30 days are discriminated against with the help of various clinical scores. Non-alcoholic fatty liver disease (NAFLD) has been found to be associated with atherosclerosis. We aimed to investigate the effect of NAFLD on disease severity and early death rate in patients with pulmonary embolism.

Methods: This retrospective study includes patients who applied to the emergency department with suspected pulmonary embolism and whose diagnosis was confirmed according to the results of the examination. In addition to confirming the diagnosis of PE, hepatic steatosis was detected and graded by tomographic examination of the liver and spleen. Disease severity was stratified by Simplified Pulmonary Embolism Severity Index (sPESI).

Results: A total of 165 patients (105 with sPESI≥1 and 60 with sPESI<1 controls) were included. The rate of mortality was 12% (n=13) in the sPESI≥1 group. The prevalence of NAFLD was 64% and the prevalence of hepatosteatosis was similar according to disease severity and prognosis (67% vs. 58%; P=0.28 and 69% vs. 63%; P=0.77). Besides the effect of disease severity; chronic lung disease (CLD) and chronic kidney disease (CKD) were independently associated with poor prognosis by multivariate analysis [3.71 (1.02-13.46); P=0.04 and 15.89 (2.57-98.35); P=0.003].

Conclusion: No association between disease severity and prognosis was observed with NAFLD in acute PE disease.

Keywords: Pulmonary embolism, simplified pulmonary embolism severity index, non-alcoholic fatty liver disease, hepatosteatosis

Deep vein thrombosis and pulmonary embolism (PE), with a prevalence of 1-2 per 1000 people in the world, are common causes of mortality, along with myocardial infarction and cerebrovascular events [1]. Disease-related early mortality is between 2% and 18%, and it has been shown that this risk may increase up to 30% in the long term [2]. The simplified PE severity index (sPESI) is a simplified and easier to calculate form of a previously defined index (PESI) [3]. It has as much accuracy as the original version to predict the risk of 30-day mortality in patients with acute symptomatic PE. In addition to

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these scoring methods, despite developments that positively affect disease-related diagnosis and treatment, the prognostic gain has not been at the expected level [4]. Determining the factors that negatively affect the severity of the disease may contribute positively to the prognosis of the disease and may lead to the development of new treatment strategies for PE patients.

Hepatic steatosis is defined as non-alcoholic fatty liver disease (NAFLD) in the absence of other causes for secondary hepatic fat accumulation. It is the uncontrolled storage of free fatty acids due to insulin resistance that is used in its pathogenesis [5]. Studies have reported that the prevalence of hepatosteatosis exceeds approximately 50% in the general population [6]. Recent studies have associated fatty liver disease with comorbid conditions, including an increased risk of cardiovascular disease, chronic kidney disease (CKD), and diabetes mellitus. [7]. Association of NAFLD with atherosclerosis and increased risk of thrombosis is claimed in the literature [8]. In addition to increased factor VIII activity but decreased protein C activity, the activity of various pro-coagulation factors has also been shown to be "increased in patients with NAFLD" [9, 10]. However, the relationship between clinical venous thrombo-embolism and NAFLD has not been studied much in the literature. Therefore, in this study, we aimed to evaluate the effect of NAFLD on disease severity and hospital prognosis in hospitalized PE patients.

METHODS

Data Collection

Between March 1, 2019 and September 30, 2020 patients who were examined in the emergency department for PE and whose diagnosis was confirmed after their tests were included in the study. Study eligibility required patients diagnosed with the International Classification of Diseases (ICD) should have symptomatic PE. Patients were diagnosed with PE by high-probability ventilation-perfusion scanning or spiral computed tomography (CT) according to the criteria of the Prospective Study of the Diagnosis of Pulmonary Embolism [11]. The presence of hepatic steatosis was detected and classified by defining the difference between CT imaging and liver-kidney hyperechogenicity intensities. Patient information was obtained by examining related hospitalization reports and clinical data. The patient's clinical characteristics were documented, including coronary heart disease (CAD), congestive heart failure, diabetes, chronic lung disease (CLD), CKD, and malignancy. Hospitalization details were also recorded, including referral departments and length of stay. An electronic information system was used to access the laboratory data of the patients.

Our group consisted of eligible people over the age of eighteen without covid 19 disease. Patients with missing patient registry data were excluded. Corticosteroid users, cirrhosis, or other documented chronic liver disease or imaging findings, and patients with a history of splenic diseases or recurrent venous thromboembolism or those patients with a known diagnosis of hereditary thrombophilia were excluded. Also, regular (moderate-to-severe) alcohol use of more than 2 drinks per day was another exclusion criterion.

This study was conducted in line with the principles of the Declaration of Helsinki and ethical approval has been obtained from the Local Institutional Ethics Committee.

Liver Density Evaluation

The density of different liver segments was measured in Hounsfield units (HU). Measurements of the hepatic lobular segments were made using a circular region of interest (ROI) with the maximum possible diameter per segment without including macroscopic vascular or biliary structures Previous studies have shown that the difference in liver density between different CT slices is small enough to allow valid measurement of liver fat using a single slice [12]. Spleen density was measured using HU and ROI with the maximum diameter possible without including macroscopic vascular structures. Usually, spleen density measurements were taken on the same slices used for liver density measurements (Fig. 1).

Definitions

Several non-contrast CT methods are used for the identification of hepatosteatosis: First, visual assessment attitudes of radiologists according to their professional experience [13]. Second, the liver density itself: Density <48 HU means a fatty liver and <40 HU was found to be associated with a macro-vesicular steatosis of at least 30% [14]. This measurement is a

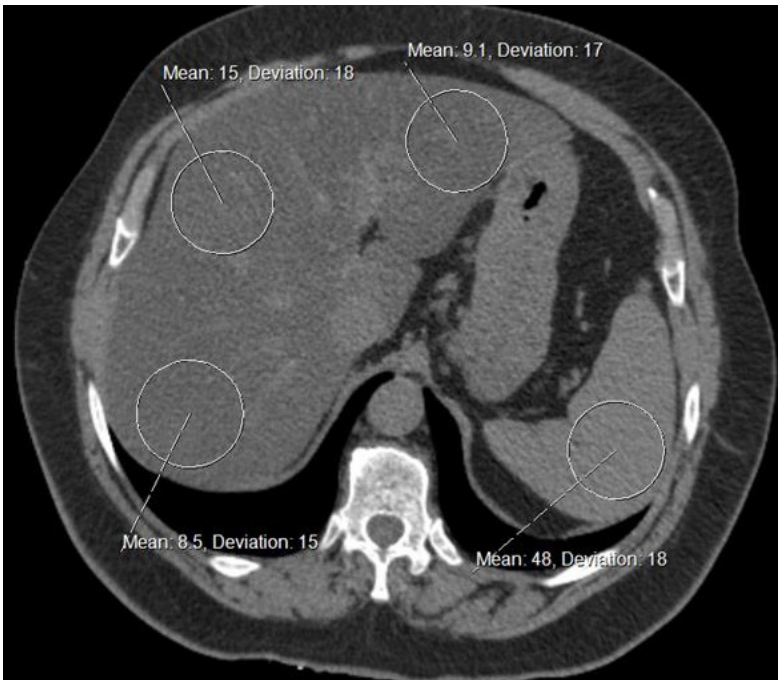

Fig. 1. Calculation of the HU values of the liver and spleen in patient with steatosis. Pay attention to the difference between the liver and the spleen HU.

strong indicator of the severity of steatosis at the histological level. Third, the ratio between liver and spleen densities (CTL/S): Using spleen density neutralizes the effect of the difference between CT scanners. A ratio of less than 0.8 between liver and spleen densities was found to be associated with at least 30% macro-vesicular steatosis [15]. Finally, the difference between liver and spleen densities (CTL-S): Normally, liver density is approximately 10 HU higher than that of the spleen. Setting the CTL-S<-9 threshold was found to have a sensitivity of 80 % and a specificity of 99 % in determining the level of high-grade hepatosteatosis [16]. This density difference method was chosen for this study and averaged over 3-segment measurements of more than nine HU inter-organ density differences defined as our dependent variable.

The sPESI, which stratifies high and low-risk patients with PE; also helps to discriminate patients who are at higher risk of death within a month. [3]. This index consists of six clinical variables including vital signs, age, and underlying comorbid conditions, each given an equal weight of one point. At least 1 point identifies high-risk patients. Low-risk patients who may benefit from early hospital discharge are also identified by this method [17].

Statistical Analysis

The Kolmogorov-Smirnov test was used to assess the normality of the distribution. Analysis of baseline features according to hepatic steatosis status, disease severity, and survival status were compared with Mann-Whitney U (for continuous variables) and Chi-square tests (for categorical parameters). Descriptive statistics were presented as median and interquartile range for continuous variables, number of cases, and (%) for categorical variables. Parameters that may have an effect on in-hospital mortality and more severe forms of disease were investigated by binary logistic regression analysis. As a result of univariate statistical analyses, the combined effects of risk factors (Age, CLD, CKD) on mortality were evaluated by multivariate regression analysis. Since we had a small number of subjects (n=13) in terms of mortality in our cohort. In order to maintain the statistical power of the regression analysis, 3 different models were created and analyzed. Chronic lung disease and CKD separately with age and CLD and CKD were evaluated together with multivariate logistic regression analysis, without including age. The SPSS 21.0 program (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was

used for performing statistical analysis. The level of significance was set as P<0.05.

RESULTS

A total of 165 patients who had been diagnosed with PE comprised the study cohort. Thus, the database was reviewed and a total of 105 (64%) patients were determined to have hepatosteatosis. Demographic, basic characteristics, laboratory, and prognostic parameters were not different between groups according to the presence of fatty liver. The more severe form of the disease was seen in men, while the prognosis was worse in elderly patients. Moreover, higher rates of hypertension, CAD, CLD, congestive heart failure, and malignancy were documented in the severe disease group. Contrary to other comorbid conditions, the presence of CLD and CKD significantly accompanied poor prognosis. The hepatic steatosis rate was also similar in both groups according to disease severity and prognosis (67% vs 58%; P=0.28 and 69% vs 63%; P=0.77). As expected Laboratory parameters related to prognosis differed significantly for all groups in our cohort (Tables 1 and 2).

The rate of mortality was 12% (n=13) in the sPESI≥1 group. Besides the effect of disease severity; CLD and CKD were independently associated with poor prognosis [3.71 (1.02-13.46), P=0.04 and 15.89 (2.57-98.35), P=0.003] (Table 3). Age was also associated significantly with mortality [1.13 (1.05-1.21), P=0.001]. When age was added to the multivariate regression analysis models, the significance of the presence of CKD persisted, while CLD lost its significance (for age; 1.20 (1.08-1.33), P=0.001; for CKD; 8.5 (154.7-2490.5 and for age; 1.12 (1.04-1.20), P=0.001; for CLD; 2.27 (0.62-8.35), P=0.22).

DISCUSSION

In this study, we demonstrated a high prevalence of NAFLD in a cohort of hospitalized patients with a diagnosis of PE. Interestingly while the frequency of comorbidities is higher in the presence of more severe disease, we did not detect any difference in the preva-

Table 1. Basic characteristics, laboratory investigations, and fatty liver status of our group according to disease severity

	Overall (n=165)	sPESI≥1 (n=105)	sPESI<1 (n=60)	P value
Age (years)	67 (56-78)	71 (64-80)	57 (40-68)	**0.0001**
Male, n (%)	91 (55)	65 (62)	26 (43)	**0.02**
Diabetes Mellitus, n (%)	42 (26)	30 (29)	12 (20)	0.22
Hypertension, n (%)	94 (57)	74 (71)	20 (33)	**0.0001**
CAD, n (%)	53 (32)	47 (45)	6 (10)	**0.0001**
Chronic lung disease, n (%)	68 (41)	61 (58)	7 (12)	**0.0001**
Chronic kidney disease, n (%)	6 (4)	5 (5)	1 (2)	0.16
Congestive heart failure, n (%)	29 (18)	25 (24)	4 (7)	**0.005**
Malignancy, n (%)	33 (20)	26 (25)	7 (12)	**0.04**
Peak troponin I (ng/dL)	38 (17-102)	80 (41-150)	15 (11-21)	**0.0001**
D-dimer (mg/L)	4.2 (1.7-10.4)	6.9 (4.2-17.4)	1.4 (1.1-2.1)	**0.0001**
Pro-BNP, ng/L	123 (42-781)	421 (123-2669)	34 (23-51)	**0.0001**
Creatinine (mg/dL)	1.0 (0.9-1.2)	1.1 (0.9-1.4)	0.9 (0.8-1.0)	**0.0001**
Fatty liver, n (%)	105 (64)	70 (67)	35 (58)	0.28

Continuous variables are presented as median (IQR), and nominal variables are presented as frequency (%). CAD=coronary artery disease, BNP=B-type natriuretic peptide

Table 2. Basic characteristics, laboratory investigations, disease severity, and fatty liver status of our group according to prognosis

	Overall (n=165)	Non-survivors (n=13)	Survivors (n=152)	P value
Age (years)	67 (56-78)	82 (80-87)	66 (54-77)	**0.0001**
Male, n (%)	91 (55)	6 (46)	85 (56)	0.49
Diabetes Mellitus, n (%)	42 (26)	5 (39)	37 (24)	0.32
Hypertension, n (%)	94 (57)	10 (77)	84 (55)	0.13
CAD, n (%)	53 (32)	4 (31)	49 (32)	0.92
Chronic lung disease, n (%)	68 (41)	9 (69)	59 (39)	**0.03**
Chronic kidney disease, n (%)	6 (4)	3 (23)	3 (2)	**0.007**
Congestive heart failure, n (%)	29 (18)	4 (31)	25 (16)	0.25
Malignancy, n (%)	33(20)	3 (23)	30 (20)	0.73
Peak troponin I (ng/dL)	38 (17-102)	451 (211-754)	32 (17-90)	**0.0001**
D-dimer (mg/L)	4.2 (1.7-10.4)	38.0 (21.4-42.0)	3.9 (1.7-7.0)	**0.0001**
Pro-BNP (ng/L)	123 (42-781)	6524 (3240-11600)	108 (38-463)	**0.0001**
Creatinine (mg/dL)	1.0 (0.9-1.2)	2.1 (1.3-3.9)	1.0 (0.9-1.2)	**0.0001**
sPESI≥1	105 (64)	13 (100)	92 (61)	**0.002**
Fatty liver, n (%)	105 (64)	9 (69)	96 (63)	0.77

Continuous variables are presented as median (IQR), and nominal variables are presented as frequency (%). CAD=coronary artery disease, BNP=B-type natriuretic peptide

lence of comorbid conditions other than chronic lung disease and CKD, in those who died and those who survived. No association was observed between NAFLD and disease severity and prognosis in acute PE disease.

Detection rates of hepatic steatosis by evaluation of the liver and spleen with CT vary according to the radiological criteria used [18]. According to the hepatosteatosis definition criteria in the literature, fatty liver rates vary and reach 80% [19, 20]. The prevalence of 64% hepatic steatosis detected in our study is in line with the literature. Recently, NAFLD was detected in 101 cases (27%) in a study in which 411 cases were evaluated by CT pulmonary angiography [6]. We think that the wide range of observed hepatosteatosis frequencies is affected by the difference in radiological criteria defined between studies. The relationship between idiopathic venous thromboembolism and NAFLD has also been investigated and it has been suggested that the presence of central obesity is particularly related to the development of PE [21, 22]. Zeina *et al*. [6], found NAFLD as a significant risk factor for PE independent of advanced age, immobilization/surgery, malignancy, obesity, diabetes, and tobacco use (HR = 4.339, P<0 .0001, and 95% CI=2.196–8.572). Also, the majority of NAFLD patients in that study had more vascular complications and other components of the metabolic syndrome. Although the incidence of malignancy was similar to that study, the NAFLD patients in our cohort were predominantly male and older, and the incidence of CAD was higher. The prevalence of diabetes was 26% in our patients, while it was 40% in this study. Our study was different from this study, in terms of its design and outcomes.

The literature suggests NAFLD as a pro-coagulant state and its contribution to the risk of thrombosis [9, 10]. Also, disturbances of hemostasis have been documented particularly in patients with hepatic steatosis and cirrhosis [23, 24]. Since the prognostic significance of NAFLD in PE disease is obscure, we find our findings valuable in terms of their scientific contribution to the literature in this context.

In parallel with our work, some clinical characteristics

Table 3. Univariate and multivariate regression analysis models for determining the predictors of in-hospital mortality

	Univariate Odds Ratio (95% CI)	P value	Multivariate Odds Ratio (95% CI)	P value
Chronic lung disease	3.55 (1.04-12.04)	**0.04**	3.71 (1.02-13.46)	**0.04**
Chronic kidney disease	14.90 (2.65-83.51)	**0.002**	15.89 (2.57-98.35)	**0.003**

CI=confidence interval

of patients with pulmonary embolism have been shown to be associated with the clinical severity of pulmonary embolism but do not affect mortality. [25, 26]. It has been found that a decrease in the estimated glomerular filtration rate (eGFR) increases the risk of in-hospital death due to venous thromboembolism by 7 times [27]. Previously published studies in the literature showed that, in addition to the negative effect of decreased eGFR on PE, advanced CKD may worsen the prognosis of patients presenting with acute PE [28]. In the literature, it has been suggested that the risk of mortality is increased in patients with PE in combination with other comorbid conditions, or in combination with other comorbidities independently of CKD [29, 30]. Similar to previous studies, the frequency of CKD was higher in non-survivors than in survivors in our study. Also, it is not surprising that CLD was more common in patients who died during the in-hospital follow-up period after acute PE [31]. However, when adjusted for age, only CKD remained as a confounding independent parameter for mortality. Elderly patients with pulmonary embolism had a higher 30-day mortality than non-elderly patients, and mortality gradually increased with age [32]. We found the effect of age on prognosis in PE similar to previous studies.

Lower serum levels of B-type natriuretic peptide (BNP), troponin, and D-dimer were associated with survival. Therefore, these indices are used to evaluate the prognosis of patients with PE [33]. PE may cause a sharp rise in pulmonary artery and right ventricular pressure. This pathophysiology affects serum levels of these parameters by increasing ventricular load and myocardial damage. It has been suggested that the combined determination of these indices improves the prognostic assessment of patients with acute PE [33]. Although these parameters show that the cardiorespiratory reserve is decreased in patients with PE, they do not affect the importance of other important clinical factors such as age, cancer, previous lung or heart disease on disease prognosis in the context of cause-effect relationship [34]. Therefore, although our findings are consistent with recent studies, these blood parameters are markers that appear early in the disease and can change in a short time. Since we are dealing with longer-term clinical conditions that may have an impact on disease severity and early prognosis, which is our main aim in the study, they were not included in the regression analysis in order not to affect the statistical power.

Limitations

Missing data and selection bias could not be eliminated due to the retrospective study design. Since we investigated early death rates, we think that our results were not affected much. Some indicators of PE severity (troponin I, BNP, D-dimer, and echocardiographic results) were not included in the final analysis. Since we think that these parameters indicate coexistence rather than causality, we think that they will not translate to a clinically significant effect on our results. Further prospective studies are needed to confirm our findings. NAFLD had no effect on disease severity and prognosis in patients with acute PE disease.

CONCLUSION

The present study demonstrated a high prevalence of NAFLD in hospitalized patients with a diagnosis of PE. Interestingly while the frequency of comorbidities is higher in the presence of more severe disease, we did not detect any difference in the prevalence of comorbid conditions other than chronic lung disease and

CKD, in those who died and those who survived. No association was observed between NAFLD and disease severity and prognosis in acute PE disease.

Authors' Contribution

Study Conception: NKK; Study Design: MK; Supervision: NKK; Funding: NÖŞ; Materials: ÖFD; Data Collection and/or Processing: MK; Statistical Analysis and/or Data Interpretation: NÖŞ; Literature Review: NKK; Manuscript Preparation: ÖFD and Critical Review: MK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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