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Pulmonary embolism risk in hospitalized patients with nonalcoholic fatty liver disease

A case-control study

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Abstract

Abundant research has associated nonalcoholic fatty liver disease (NAFLD) with atherosclerosis, but very few reports have evaluated the association between NAFLD and venous thromboembolism. We aimed to investigate the association between NAFLD and pulmonary embolism (PE) in hospitalized patients. In this retrospective case–control study, we included consecutive patients from 2 university-affiliated hospitals who were referred for CT pulmonary angiograms for a suspected PE. Patients with a history of excessive alcohol consumption, chronic liver diseases or cirrhosis were excluded. The imaging studies of the entire cohort were reviewed by 2 expert radiologists who confirmed the diagnosis of PE and examined the liver to detect and grade hepatic steatosis. Accordingly, patients were categorized into NAFLD patients and non-NAFLD controls. Patient demographics, medical history, hospitalization details as well as patients' outcomes were documented. Multivariate analysis was performed to identify predictors for developing PE and hazard ratios with corresponding 95% confidence intervals were estimated. A total of 377 patients (101 with NAFLD and 276 controls) were included. NAFLD patients had significantly higher BMI values (33.16 ± 6.78 vs 26.81 ± 5.6; $P < .001$) and prevalence of diabetes (41 (40%) vs 85 (30.8%); $P = .03$). The prevalence of PE was significantly higher in the NAFLD group (80 (79.2%) vs 147 (53.3%), $P < .001$). In a multivariate analysis, older age, recent surgery or trauma, active malignancy, smoking, and NAFLD (HR ratio = 4.339, $P < .0001$ and 95% CI = 2.196–8.572) were independently associated with PE development. Patients with NAFLD were associated with an increased risk of developing PE independent of other classical risk factors for PE.

Abbreviations: BMI = body mass index, CI = confidence interval, CTPA = computed tomography pulmonary angiogram, NAFLD = non-alcoholic fatty liver disease, NASH = nonalcoholic steatohepatitis, PE = pulmonary embolism.

Keywords: CT pulmonary angiography, nonalcoholic fatty liver disease, pulmonary embolism, risk factors, ultrasound

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) refers to hepatic steatosis when other causes for secondary hepatic fat accumulation have been excluded. Although aetiologic and pathogenic features are complex and not fully elucidated, insulin resistance from excessive accumulation of free fatty acids is thought to be a primary driver in the development of steatosis in the majority of patients with NAFLD.[1–3] In parallel to the global obesity epidemic and the increasing prevalence of diabetes and metabolic syndrome, NAFLD has become one of the most common chronic liver diseases and a leading indication for liver transplantation in adults worldwide.[4,5] Several studies have suggested a wide range of prevalence rates, with some reporting almost 50% of the general population may have NAFLD.[6–8] Thus, various medical practitioners now widely encounter NAFLD in different settings.

NAFLD represents a spectrum of chronic liver diseases that range from simple steatosis to steatohepatitis, culminating in cirrhosis. A large body of literature suggests that the clinical burden of NAFLD is not confined to liver disease but rather is a part of a multisystemic disease.[9,10] Indeed, recent literature has associated NAFLD with a broad spectrum of clinical conditions. Linked to metabolic syndrome, NAFLD has further been independently associated with an increased risk of cardiovascular disease, chronic kidney disease, and diabetes.[11–13] A possible link with increased malignancy rate was also demonstrated.[14]

Several studies have linked NAFLD to atherosclerosis and increased risk of thrombosis. NAFLD was correlated with

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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carotid atherosclerosis in one study.[15] Another report confirmed this correlation and described a direct association with coronary artery calcifications, endothelial dysfunction, and arterial stiffness.[16] These findings were translated into plentiful studies confirming the association between NAFLD and several cardiovascular conditions.[17]

Interestingly, patients with NAFLD were demonstrated to have increased activity of several pro-coagulation factors. At the same time, other reports showed NAFLD patients to have increased factor VIII activity but a decrease in protein C activity.[18,19] However, the literature is sparse in the area of clinical venous thromboembolism and NAFLD. Therefore, the current study aimed to assess the association between NAFLD in hospitalized patients and the risk of pulmonary embolism (PE) development.

2. Methods

Imaging studies of consecutive patients who were referred for CT pulmonary angiography (CTPA) in the years 2010–2019 for a suspected PE in Hillel Yaffe and EMMS medical centers, 2 university-affiliated centers in Israel, were reviewed and revised by 2 expert radiologists. The presence of fatty liver and hepatic steatosis were documented and graded based on hyperechogenicity as mild, moderate or severe, indicating the difference between liver–kidney densities. Accordingly, patients with evidence of NAFLD were included in the study group, while other patients without evidence of NAFLD on imaging studies served as controls.

Patients were excluded if they were under 18 years old, had confirmed inherited thrombophilia, had a known history of recurrent venous thromboembolism, or were on a full-dose anticoagulation treatment. We also excluded patients with history or imaging findings of cirrhosis or any other documented chronic liver diseases, as well as those with a history of moderate-excessive alcohol intake (more than 2 drinks/day).

Hospitalization reports and relevant clinical data of patients in both groups were reviewed. Patient demographics (age, sex, and ethnicity) and medical history, including ischemic heart disease, cerebrovascular accidents, diabetes, hypertension, and dyslipidemia use of antiplatelets medications, were documented. Moreover, we searched and documented background history associated with PE such as recent (<3 months) trauma or surgery, active malignancy as well as the use of hormonal therapy. Hospitalization details, including referring departments and duration of the stay, were also recorded. Body mass index (BMI) at admission was collected from electronic reports for every patient. Alcohol consumption and smoking habits were also documented. We compared the diagnosis rate of PE detected by CTPA in both groups and performed a multivariate analysis to identify an independent association between NAFLD and PE adjusting for classical risk factors for PE.

The study was approved by Hillel Yaffe and EMMS local Helsinki ethics boards, who granted exemption from informed consent in this retrospective study as data collection did not influence medical practice and patients were receiving standard care without relation to the study.

2.1. Statistical analysis

Continuous parameters were presented by means ± standard deviations and categorical parameters were expressed by using frequencies and percentages. Differences between the NAFLD and control groups were compared by *t* test for quantitative parameters and Fisher's exact test for the categorical parameters. Potential and significant variables determined in the univariate analysis were further entered in the multivariate analysis to evaluate the effects of variables on the risk of developing PE, and HRs with corresponding 95% confidence intervals (CIs) were estimated. SPSS version 25 was used for the statistical analysis and $P < .05$ was considered to be significant.

3. Results

A total of 411 patients who had undergone CTPA comprised the study cohort. Of these, 34 patients did not meet the inclusion criteria or had missing data and were excluded. Thus, the CTPA of 377 patients were reviewed by 2 expert radiologists and a total of 101 (26.8%) patients were determined to have NAFLD, while 276 (74.2%) non-NAFLD patients were included as controls. In the NAFLD group, 61.4% were considered to have mild, 24.8% moderate, and 13.8% severe hepatic steatosis. The mean age in NAFLD patients was similar to the non-NAFLD group (64.9 ± 15.9 years old vs 64.4 ± 19.6 years old; $P = .81$), but a female predominance was evident in the NAFLD group (68 (67.3%) vs 152 (55%); $P = .034$). As expected, subjects with NAFLD had significantly higher values of BMI (33.16 ± 6.78 vs 26.81 ± 5.6; $P < .001$) and obesity (BMI > 30) (62 (63.3%) vs 55 (28.9%), $P < .001$), as well as a higher rate of diabetes (41 (40.56%) vs 85 (30.8%); $P = .03$). Moreover, higher rates of hypertension, dyslipidemia, ischemic heart disease and cerebrovascular accidents were documented in the NAFLD group, but these were close to statistical significance (Table 1). The use of antiplatelet medications did not differ significantly between groups (36.6% vs 31.9%; $P = .26$). The smoking rate was also similar in both groups (18.9% vs 20.8%, $P = .66$). Hospitalization figures were similar for both groups as the average duration (days) of hospitalization (6 [3–10] vs 6 [3–12], $P = .61$) was comparable, and the majority of patients in both groups were hospitalized in the internal medicine ward (88% vs 81%, $P = .25$). Common risk factors associated with PE development, including trauma/immobility, recent surgery and hormonal therapy, were similar between the groups but patients in the NAFLD group had a higher rate of active malignancy (19.8% vs 11.6%; $P = .045$).

After the radiologists' revision, a total of 227 patients had a confirmed diagnosis of PE. Interestingly, the diagnosis rate of PE was significantly higher in the NAFLD group (80 (79.2%) vs 147 (53.3%), $P < .001$) when compared to non-NAFLD. The diagnosis rate of PE in those with mild, moderate and severe fatty liver infiltration was 79%, 80%, and 79%, respectively. Besides NAFLD, in the univariate analysis, older age, hypertension, ischemic heart disease, smoking, hospitalization duration, recent surgery or trauma, and active malignancy were all associated with PE development. In the multivariate analysis (Table 2), older age, hospitalization duration longer than 5 days, recent surgery or trauma, active malignancy, smoking, and NAFLD (HR ratio = 4.339, $P < .0001$ and 95% CI = 2.196–8.572) were independently associated with PE development.

4. Discussion

The current study has some interesting findings. First, we demonstrated that, in a cohort of hospitalized patients, more than one-quarter had NAFLD. This is not surprising as the prevalence of NAFLD is rising in concert with increasing rates of obesity and diabetes mellitus, and it is currently considered the most common chronic liver disease, particularly in western nations.[20] The majority of NAFLD patients in our cohort had other components of the metabolic syndrome and higher rates of vascular complications, indicating these conditions are related. Likewise, in concordance with other reports, lean NAFLD was not uncommon occurring in 9% of these patients.[21]

Second and foremost, the current study showed that NAFLD was a significant risk factor for PE (HR = 4.339, $P < .0001$, and 95% CI = 2.196–8.572), independent of other traditional risk factors such as advanced age, immobilization/surgery, malignancy, obesity, diabetes, and tobacco use.[22–24] Despite the growing body of literature suggesting that NAFLD is a pro-hemostatic state, we could find only 2 studies that have focused on a direct investigation of the clinical association between non-cirrhotic NAFLD patients and systemic thromboembolism. In

Table 1

Baseline characteristics of nonalcoholic fatty liver disease (NAFLD) patients and controls.

Group	No-NAFLD (n = 276)	NAFLD (n = 101)	*P* Value
Demographics			
Age (mean, range)	64.4 ± 19.6	64.9 ± 15.9	*P* = .81
Sex n (%)			***P* = .034**
Male	124 (45%)	33 (32.7%)	
Female	152 (55%)	68 (67.3%)	
Country of birth (Israel) n (%)	165 (59.8%)	58 (57.4%)	*P* = .72
BMI (mean ± SD)	26.81 ± 5.6	33.16 ± 6.78	***P* < .001**
BMI ≥ 30 n (%)	55 (28.9%)	62 (63.3%)	***P* < .001**
Hospitalization facts			
Hospital stay (d)	6 [3–10]	6 [3–12]	*P* = .61
Department			*P* = .25
Internal	225 (88%)	82 (81%)	
Surgery	22 (9%)	13 (13%)	
Genecology	9 (3%)	6 (6%)	
Background history			
Diabetes n (%)	85 (30.8%)	41 (40.5%)	***P* = .03**
Hypertension n (%)	142 (51.4%)	62 (61.4%)	*P* = .08
Dyslipidemia n (%)	118 (43%)	48 (47.5%)	*P* = .13
Ischemic heart disease n (%)	51 (18.6%)	24 (23.7%)	*P* = .09
Cerebrovascular accident n (%)	20 (7%)	11 (11%)	*P* = .19
Antiplatelet medications n (%)	87 (31.5%)	37 (36.6%)	*P* = .26
Recent surgery n (%)	16 (5.8%)	8 (7.9%)	*P* = .48
Hormonal therapy n (%)	1 (0.3%)	0 (0.0%)	*P* = .92
Recent trauma n (%)	11 (4%)	5 (5%)	*P* = .77
Active malignancy n (%)	32 (11.6%)	20 (19.8%)	***P* = .045**
Smoking n (%)	52 (18.9%)	21 (20.8%)	*P* = .66
Primary outcome			
Pulmonary embolism n (%)	147 (53.3%)	80 (79.2%)	***P* < .001**

Table 2

Predictors of pulmonary embolism development in hospitalized patients. A multivariate analysis.

			95% CI for odds ratio	
Variable	***P* value**	**Odds ratio**	**Lower**	**Upper**
Age (yr)	**.0001**	1.039	1.019	1.060
Sex (male)	.694	1.131	.613	2.088
Hospital stay > 5 d	**.003**	2.366	1.336	4.190
Hypertension	.470	1.274	.661	2.453
Diabetes	**.001**	3.357	1.595	7.066
Active malignancy	**.048**	2.151	.869	5.323
Smoking	**.043**	2.003	1.022	3.926
Obesity (BMI > 30)	.225	1.456	.793	2.674
NAFLD	**.0001**	4.339	2.196	8.572
Recent surgery/trauma	**.001**	3.432	1.647	7.152

BMI = body mass index, NAFLD = nonalcoholic fatty liver disease.

a small case–control study, Di Minno et al showed a strict link between idiopathic venous thromboembolism and NAFLD.[25] Moreover, a recent small prospective cohort study reported that de novo PVT incidence within NAFLD patients during a 9-year follow-up was 8.5%, indicating that increased central obesity, among others, was independently associated with PVT development in these patients.[26]

Indeed, the pathogenesis of the thrombophilic state in NAFLD has attracted mounting research recently, but the majority of evidence in this regard still comes from studies in cirrhotic patients where derangements in primary, secondary, and tertiary hemostasis are well documented.[27,28] Thus, our study was unique in excluding cirrhotic patients, indicating that our findings of an association with PE are relevant for noncirrhotic NAFLD patients. In fact, the pathogenesis of hypercoagulation in NAFLD, particularly in those with nonalcoholic steatohepatitis (NASH), may be driven by the chronic and continuous inflammation characterized by a lipid-based oxidative injury leading to the stimulation of the coagulation cascade and the resultant hypercoagulable condition as established elsewhere.[19,29–32] Unfortunately, as liver biopsies were of no clinical need and thus were not performed during the study period we could not obtain data on the NAFLD stage, presence or absence of inflammation, or fibrosis stage. However, some 25–30% of our cohort had multiple components of the metabolic syndrome, which are highly predictive of steatohepatitis, and we believe the frequency of NASH in our cohort is close to these estimations.

In a subgroup analysis focusing on NAFLD patients, we could not identify risk factors associated with an increased rate of PE among these patients. Interestingly, the severity of hepatic steatosis by imaging assessment in the current study did not correlate with the diagnosis rate of PE, and the frequency of PE in those with severe steatosis was similar to those with milder stages. Likewise, BMI values were not correlated with patients' outcomes.

Taken together, the findings of the current study should encourage clinicians to strictly follow hospitalized patients with known NAFLD for signs of venous thromboembolism development, identify other potential risk factors for its development, and incorporation of this data into the final decision of thromboembolism prophylaxis prescription, which might be challenging particularly in complex medical patients.

Strengths of the current study include the comprehensive demographic and clinical characterization of the study and control groups in a real-life setting. Moreover, the inclusion of non-cirrhotic NAFLD patients and the careful extraction of data on various variables correlated with the primary outcome enabled the adjustment of multiple potential confounders, drawing more reliable conclusions, and focusing the discussion on NAFLD regardless of cirrhosis.

Limitations of the current study are inherent in its retrospective design. Moreover, relevant data on venous thromboembolism prophylaxis were not incorporated and could have impacted the outcome. Likewise, although data on cancer diagnosis were extracted and adjusted for, some patients might have had venous thromboembolism related to occult cancer, affecting our analysis. In addition, histopathological data were unavailable, and thus, subgroup analyses based on simple steatosis, NASH, or fibrosis stages were not possible. Another potential point of criticism relates to the size of the study, which was not very large.

In conclusion, NAFLD in hospitalized patients was associated with PE development independent of obesity, metabolic syndrome, cirrhosis, or other classical risk factors of PE. However, large prospective studies are warranted to confirm these findings and investigate their clinical reflection on patients' follow-up and management.

Author contributions

Each individual listed as an author on the title page of the submitted manuscript (Abdel-Rauf Zeina, Yael Kopelman, Amir Mari, Helal Said Ahmad, Suheil Artul, Ali Sleman Khalaila, Randa Taher, Fernando Zertuche Villannueva, Rabea Safadi, Saif Abu Mouch, Fadi Abu Baker) have met the criteria for authorship as established by the International Committee of Medical Journal Editors (ICMJE). All authors read and approved the final version of the manuscript.

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