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ORIGINAL ARTICLE

Liver Fibrosis-4 index indicates atrial fibrillation in acute ischemic stroke

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Abstract

Background: Non-alcoholic fatty liver disease and particularly liver fibrosis are related to cardiovascular disease and may indicate an increased risk for atrial fibrillation (AF), but this association has not yet been systematically investigated in a cohort of ischemic stroke patients.

Methods: We analyzed data from a prospective single-center study enrolling all consecutive ischemic stroke patients admitted to our stroke unit over a 1-year period. All patients received a thorough etiological workup. For evaluation of liver fibrosis, we determined the Fibrosis-4 (FIB-4) index, a well-established noninvasive liver fibrosis test. Laboratory results were analyzed from a uniform blood sample taken at stroke unit admission.

Results: Of 414 included patients (mean age 70.2 years, 57.7% male), FIB-4 indicated advanced liver fibrosis in 92 (22.2%). AF as the underlying stroke mechanism was present in 28.0% (large vessel disease: 25.6%, small vessel disease: 11.4%, cryptogenic: 29.2%). Patients with FIB-4 ≥ 2.67 had higher rates of AF (53.3% vs. 20.8%, $p < 0.001$), and this association remained significant after correction for established AF risk factors (odds ratio 2.53, 95% confidence interval 1.44–4.46, $p = 0.001$). FIB-4 was further associated with worse functional outcome 3 months ($p < 0.001$) and higher mortality 4 years post-stroke ($p < 0.02$), but these relationships were no longer present after correction for age and initial stroke severity. Moreover, FIB-4 was not associated with long-term recurrent vascular events.

Conclusions: Liver fibrosis assessed by the FIB-4 index is independently associated with AF in acute ischemic stroke patients. Further studies should evaluate whether adding the FIB-4 index to AF risk scores increases their precision.

KEYWORDS
atrial fibrillation, ischemic stroke, liver fibrosis

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) is recognized as the liver disease component of metabolic syndrome and is prevalent in about a quarter of the global adult population [1]. Liver steatosis may progress to non-alcoholic steatohepatitis, leading to liver fibrosis, cirrhosis and/or hepatocellular carcinoma. In patients with NAFLD, the occurrence and stage of liver fibrosis is a critical determinant of risk for cardiovascular disease and mortality [2,3]. Various non-invasive scores have been developed for prediction of severe liver fibrosis. The most frequently used is the Fibrosis-4 index (FIB-4), which is recommended by the American Association for the Study of Liver Diseases [4] and has been shown to estimate liver fibrosis with high sensitivity and specificity [3].

NAFLD and liver fibrosis have also been identified as risk factors for ischemic stroke [5–7]. Although earlier epidemiological studies were inconsistent, a recent meta-analysis demonstrated higher rates of AF in patients with liver fibrosis [8]. However, data regarding such a potential association in stroke cohorts are lacking. Recently, we found that patients with large vessel occlusion stroke undergoing mechanical thrombectomy who had a positive FIB-4 index had a worse 3-month outcome. Moreover, in this study AF was more frequently present in patients with liver fibrosis [9]. Identification of AF risk factors is relevant in order to guide etiological workup, including long-term monitoring in stroke survivors [10]. Furthermore, a single previous study on Asian patients with ischemic stroke also indicated a higher rate of mortality and recurrent vascular events when liver fibrosis was additionally present [11].

Therefore, we aimed to investigate the association of liver fibrosis as indicated by the FIB-4 index with AF-related stroke etiology in a prospectively collected cohort of patients with ischemic stroke. Additionally, we analyzed whether the FIB-4 index would relate to a higher long-term risk for recurrent vascular events and worse clinical outcome.

METHODS

Study cohort

All consecutive patients with ischemic stroke admitted to our stroke unit were prospectively included in this study over a 1-year period (April 2017 to April 2018). The study cohort was devised for an in-depth investigation of stroke etiology; therefore, a thorough and standardized diagnostic workup was performed, as previously reported [12]. Laboratory data were taken from a standardized blood sample which was drawn at stroke unit admission. AF was defined as previously documented in the patient's medical history, detected on admission ECG or during in-patient cardiac rhythm monitoring (with at least 48 h of electrocardiogram [ECG] monitoring at the stroke unit plus a 24-h Holter ECG during further in-patient stay). Cryptogenic stroke was defined according to published criteria [13]. At discharge, stroke etiology was defined based on the entire stroke workup; in cases of multiple possible stroke etiologies, consensus for the most likely cause was reached in team discussions [12].

A clinical follow-up at our stroke outpatient department 3 months post-stroke was scheduled for all patients – if a physical consultation was not possible, a telephone interview was performed instead. Recurrent vascular events and mortality were assessed approximately 4 years post-stroke (median 4.1 years, range 3.6–4.7 years) using patients' electronical health records, which encompass all hospitals providing acute care for vascular events in the larger administrative region. The mentioned health records were first searched for respective International Classification of Diseases, Tenth Edition (ICD-10) diagnosis codes of arterial vascular events (stroke, myocardial infarction, peripheral arterial embolism), then manually examined by a trained physician for plausibility.

Patients with missing or incomplete laboratory data were excluded from this study ($n = 11$). We did not exclude patients with preexisting liver disease or chronic alcohol abuse as we aimed for a coherent "real-world" ischemic stroke cohort. Chronic alcohol abuse was defined as ≥2 drinks or ≥20 g of ethanol on at least 5 days per week [14]. Chronic heart disease was defined as coronary artery disease, heart failure, cardiomyopathy or clinically apparent valve disease.

Liver fibrosis was assessed using the well-validated and clinically established FIB-4 index [4,15]. FIB-4 is calculated as follows: FIB-4 = age (years) × aspartate aminotransferase (U/L)/[platelet count (10^9/L) × √alanine aminotransferase (U/L)]. The cut-off value for prediction of advanced liver fibrosis (i.e. bridging fibrosis or cirrhosis) was used as established in current literature (≥2.67). Additionally, we analyzed the lower cut-off value of FIB-4 (<1.30), which excludes advanced liver fibrosis with a high probability [16,17].

Statistical analysis

We performed statistical analysis using IBM SPSS Statistics for Windows, version 26 (IBM Corp.). Normally distributed continuous variables were compared by the unpaired Student's *t*-test. For other distributions, non-parametric tests such as the Mann–Whitney U-test were used. Categorical variables were investigated by Pearson's chi-square test. Additionally, a multivariable logistic regression model for prediction of AF was calculated, using FIB-4 together with known clinical predictors of AF according to the $CHADS_2$ score [18] (age, diabetes, chronic heart disease, arterial hypertension) and sex. History of stroke/transient ischemic attack (TIA) was not used in the multivariable model as it was present in all patients. *P* values of less than 0.05 were considered statistically significant.

Ethical approval

The study was approved by the ethics committee of the Medical University of Graz (approval number 29–285 ex 16/17), and written informed consent was obtained in all patients.

TABLE 1 Clinical characteristics of study participants categorized by the Fibrosis-4 index (FIB-4) liver fibrosis index

Characteristic	Study cohort ($n = 414$)	FIB-4 positive ($n = 92$; 22.2%)	FIB-4 negative ($n = 322$; 77.8%)	*P* value
Clinical data				
Age (years)	70.2 ± 13.4	80.4 ± 8.6	67.3 ± 13.1	**<0.001**
Male sex	239 (57.7%)	44 (47.8%)	195 (60.6%)	**0.03**
Arterial hypertension	347 (83.8%)	83 (90.2%)	264 (82.0%)	0.06
Dyslipidemia	231 (55.8%)	45 (48.9%)	186 (57.8%)	0.13
Chronic heart disease*	90 (21.7%)	29 (31.5%)	61 (18.9%)	**0.01**
Diabetes mellitus	88 (21.3%)	16 (17.4%)	72 (22.4%)	0.30
History of stroke	86 (20.8%)	15 (16.3%)	71 (22.0%)	0.32
Alcohol abuse	43 (10.4%)	9 (9.8%)	34 (10.6%)	0.86
Body mass index	26.6 ± 4.0	27.1 ± 3.9	26.5 ± 4.0	0.20
NIHSS at admission (median, IQR)	4 (1–9)	7 (3.25–14.75)	3 (1–7)	**<0.001**
Intravenous thrombolysis	74 (17.9%)	26 (28.3%)	48 (14.9%)	**0.01**
Stroke etiology				
Cardioembolism	128 (30.9%)	51 (55.4%)	77 (23.9%)	**<0.001**
Atrial fibrillation	116 (28.0%)	49 (53.3%)	67 (20.8%)	**<0.001**
Large vessel disease	106 (25.6%)	19 (20.7%)	87 (27.0%)	0.22
Small vessel disease	47 (11.4%)	5 (5.4%)	42 (13.0%)	0.05
Other determined	12 (2.9%)	0	12 (3.7%)	0.06
Cryptogenic stroke	121 (29.2%)	17 (18.5%)	104 (32.3%)	**0.01**
Laboratory parameters (median, IQR)				
Alanine aminotransferase (U/L)	19 (13)	20 (15)	18.5 (13)	0.56
Aspartate aminotransferase (U/L)	22 (11)	30 (22)	20 (8)	**<0.001**
Gamma-glutamyl transferase (U/L)	29 (32)	31 (53)	28 (29)	0.26
NT-proBNP (pg/mL)	542 (1547)	1625 (3060)	384 (1025)	**<0.001**
Platelet count (10^9/L)	208 (76)	160 (44)	220 (71)	**<0.001**
Outcome parameters				
mRS at discharge (median, IQR)	2 (1–4)	4 (2–5)	2 (1–4)	**<0.001**
mRS after 3 months (median, IQR)	1 (0–3)	3 (0.75–5)	1 (0–2)	**<0.001**
mRS 0–2 at 3 months post-stroke	241 (69.3%)	30 (42.9%)	211 (75.9%)	**<0.001**
Recurrent stroke	42 (10.1%)	7 (7.6%)	35 (10.9%)	0.36
Recurrent vascular events	55 (13.3%)	10 (10.9%)	45 (14.0%)	0.44
Mortality 4 years post-stroke	62 (15.0%)	21 (22.8%)	41 (12.7%)	**0.02**

Abbreviations: FIB-4, Fibrosis-4; IQR, interquartile range; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NT-proBNP, N-terminal pro-brain natriuretic peptide.

*Defined as coronary artery disease, heart failure, cardiomyopathy or clinically apparent valve disease.

The Significance of Bold values indicates p values < 0.05.

RESULTS

We included 414 patients with acute ischemic stroke in this study (mean age 70.2 years, 57.7% male). Median admission National Institutes of Health Stroke Scale (NIHSS) was 4 (interquartile range: 1–9), and 17.9% of patients were treated with intravenous thrombolysis. Chronic alcohol abuse was reported in 10.4% of patients (Table 1).

Atrial fibrillation was the presumed cause of stroke in 28.0% of patients, and overall cardioembolism was determined as the underlying stroke etiology in 30.9%. Large vessel disease was found in 25.6%, small vessel disease in 11.4% and other determined causes in 2.9%, while stroke etiology remained cryptogenic in 29.2% of patients (Table 1).

Liver fibrosis indices

A high FIB-4 index indicating severe liver fibrosis (cut-off ≥ 2.67) was present in 22.2% of patients. Those patients were older, more

frequently women, had higher NIHSS scores at admission and higher rates of intravenous thrombolysis. There was no difference in the frequency of alcohol abuse. FIB-4 was further associated with higher levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) (Table 1).

Patients with FIB-4 ≥ 2.67 had higher rates of AF (53.3% vs. 20.8%, $p < 0.001$) and subsequently cardioembolic stroke etiology, while cryptogenic stroke was less common in this subgroup (Table 1). The association between FIB-4 index values and AF is visualized in Figure 1.

In a multivariable model including age, sex, arterial hypertension, diabetes and chronic heart disease as covariates, FIB-4 index ≥ 2.67 was still significantly related to AF (odds ratio 2.51, 95% confidence interval 1.44–4.40, $p = 0.001$; Table 2). Adding NT-proBNP as a well-known marker of AF into the model did not change the significance of the association between FIB-4 and AF (data not shown).

Patients with an FIB-4 index below the cut-off of 1.30 (excluding advanced liver fibrosis with high probability) conversely had a much lower AF rate (11.3% vs. 35.5%, $p < 0.001$) and higher rates of small vessel disease (16.1% vs. 8.7%, $p = 0.03$) as well as other determined stroke causes (6.5% vs. 1.4%, $p = 0.01$).

When analyzing FIB-4 index as a continuous variable, we found a strong association with AF with a moderate effect size ($r = 0.34$, $p < 0.001$).

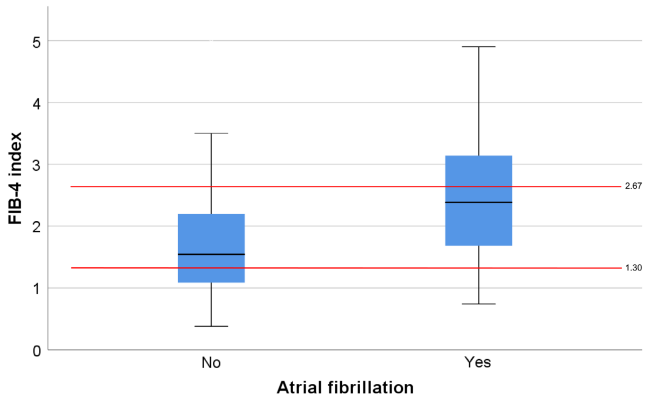

FIGURE 1 Boxplot of Fibrosis-4 index (FIB-4) and atrial fibrillation in the study cohort. Red lines depict the established upper (2.67) and lower (1.30) cut-off values for inclusion and exclusion of liver fibrosis, respectively. The black line depicts the median value and the blue boxes indicate the 25th and 75th percentiles [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Multivariable regression model regarding atrial fibrillation as target variable

Variable	OR	95% CI	*P* value
Age (per year)	1.04	1.02–1.07	**0.001**
Male sex	1.23	0.75–2.0	0.41
Arterial hypertension	3.53	1.31–9.48	**0.01**
Chronic heart disease*	1.98	1.14–3.44	**0.02**
Diabetes mellitus	0.91	0.54–1.71	0.91
Positive FIB–4 index (≥2.67)	2.51	1.44–4.40	**0.001**

Abbreviations: CI, confidence interval; FIB-4, Fibrosis-4; OR, odds ratio.

*Defined as coronary artery disease, heart failure, cardiomyopathy or clinically apparent valve disease.

The Significance of Bold values indicates *p* values < 0.05.

Clinical outcomes and recurrent vascular events

At the prespecified follow-up 3 months post-stroke, 69.3% of patients had a favorable functional outcome (determined as mRS values of 0–2). Patients with FIB-4 ≥ 2.67 had a much lower rate of favorable outcome (42.9% vs. 75.9% in patients without, $p < 0.001$). However, after correction for age and initial stroke severity (NIHSS at admission), this association was no longer statistically significant ($p = 0.21$).

During long-term follow-up of median 4.1 years (range 3.6–4.7 years) post-stroke, recurrent strokes occurred in 10.1%, the overall rate of recurrent vascular events (myocardial infarction, peripheral arterial embolism or stroke) was 13.3%. FIB-4 ≥ 2.67 was not associated with recurrent vascular events (Table 1). Mortality 4 years post-stroke was higher in patients with FIB-4 ≥ 2.67 (22.8% vs. 12.7%, $p = 0.02$), but again after correction for age and stroke severity this association was no longer present ($p = 0.55$).

DISCUSSION

In this prospective study on consecutive patients with acute ischemic stroke, liver fibrosis according to the well-established FIB-4 index was associated with AF-related stroke etiology. Importantly, FIB-4 remained predictive for AF after correction for factors known to be related to AF ($CHADS_2$ score variables, sex and NT-proBNP).

An association between NAFLD and AF has already been shown in a meta-analysis including population-based study cohorts, [8] and a large Korean study found that among patients with NAFLD, liver fibrosis determined by FIB-4 was associated with higher rates of AF [19]. To the best of our knowledge, this is the first study investigating the relationship of FIB-4 with AF in an unselected cohort of patients with acute ischemic stroke treated at a stroke unit. The present findings are in line with the results of an earlier study from our group on patients with large vessel occlusion stroke similarly showing an increased AF rate in patients with elevated FIB-4 index [9]. However, this study considered a selected group of stroke patients and was not designed to further explore this potential relationship in more detail.

While NAFLD and AF share common risk factors (including dyslipidemia, diabetes, hypertension and obesity), NAFLD has additionally been associated with diastolic dysfunction, [20,21] remodeling of the left ventricle [22] and systemic inflammation, [23] predisposing to AF development. Furthermore, autonomic dysfunction has been described in patients with NAFLD and affected

patients had higher ectopic fat burden including pericardial fat, which in turn is associated with AF [24]. Notably, after ablation therapy, NAFLD has been identified as an independent predictor for AF recurrence [25]. These factors together with our findings imply that NAFLD and particularly liver fibrosis may also be a so far under-recognized factor associated with the detection of paroxysmal AF after ischemic stroke beyond the initial hospital stay. Unfortunately, our study was not designed to analyze this potential relationship. Further studies should investigate whether liver fibrosis may help in the selection of ischemic stroke patients with high risk for paroxysmal AF and consecutive indication for long-term heart rhythm monitoring.

Patients with liver fibrosis indicated by FIB-4 had higher NIHSS scores at admission, which in turn could be attributed to the higher rates of AF known to be associated with more severe strokes [26]. Accordingly, the univariable associations between high FIB-4 values and functional outcome at 3 months as well as mortality at 4 years were no longer significant in multivariable analysis correcting for age and stroke severity. Noteworthy, we did not find differences regarding the risk of recurrent vascular events in patients with elevated FIB-4 index ≥ 2.67. However, this comparison is limited due to the different severity of stroke between those two groups and the higher mortality in patients with elevated FIB-4 indices. Further limitations of our study include the single-center design, limiting generalizability. Although the FIB-4 index is easy to use in clinical practice and has high sensitivity and specificity for liver fibrosis, incorporation of transient liver elastography might have added to improve diagnostic precision [27].

However, our findings prompt further research into this liver-heart-brain axis and indicate that patients with ischemic stroke and liver fibrosis might require more thorough screening for AF. Further studies should investigate whether the FIB-4 index adds to previously proposed risk scores of occult AF in stroke workup.

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None.

CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHOR CONTRIBUTIONS

Simon Fandler-Höfler: Conceptualization (lead); Data curation (lead); Formal analysis (lead); Investigation (lead); Methodology (lead); Writing – original draft (lead). **Markus Kneihsl:** Conceptualization (equal); Data curation (equal); Methodology (equal); Writing – review & editing (lead). **Rudolf E. Stauber:** Data curation (equal); Methodology (equal); Writing – review & editing (equal). **Egbert Bisping:** Conceptualization (supporting); Methodology (supporting); Writing – review & editing (supporting). **Harald Mangge:** Conceptualization (supporting); Data curation (supporting); Writing – review & editing (supporting). **Gerit Wünsch:** Data curation (equal); Investigation (supporting); Writing – review & editing (supporting). **Melanie Haidegger:** Data curation (equal); Writing – review & editing (supporting). **Linda Fabisch:** Data curation (equal); Writing – review & editing (supporting). **Isra Hatab:** Data curation (equal); Writing – review & editing (supporting). **Peter Fickert:** Conceptualization (equal); Methodology (equal); Writing – review & editing (supporting). **David Werring:** Conceptualization (equal); Writing – review & editing (equal). **Christian Enzinger:** Supervision (equal); Writing – review & editing (equal). **Thomas Gattringer:** Conceptualization (lead); Data curation (equal); Investigation (equal); Methodology (lead); Supervision (lead); Writing – review & editing (lead).

DATA AVAILABILITY STATEMENT

Anonymized datasets generated during this study are available from the corresponding author upon reasonable request.

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