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ORIGINAL ARTICLE

A higher FIB-4 index is associated with an increased incidence of renal failure in the general population

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Abstract

The Fibrosis-4 index (FIB-4) is a recommended noninvasive fibrosis test in patients at risk of liver fibrosis. Chronic liver diseases are often associated with kidney diseases. This study aimed to investigate the association between FIB-4 and the development of renal failure among the general population. For this study, we used the Disease Analyzer database, which includes diagnoses and basic medical and demographic data of patients followed in general practices in Germany. Using these data, we extensively matched patients with a FIB-4 index ≥ 1.3 (n = 66,084) to patients with a FIB-4 index < 1.3 (n = 66,084). The primary outcome was the incidence of renal failure or chronic renal failure during a 10-year period. Within 10 years of the index date, 9.2% of patients with a FIB-4 < 1.3 and 10.6% of patients with a FIB-4 ≥ 1.3 were diagnosed with renal failure ($p = 0.007$). The endpoint chronic renal failure was reached by 7.9% with a FIB-4 < 1.3 and 9.5% with a FIB-4 ≥ 1.3 ($p < 0.001$). A FIB-4 index ≥ 1.3 was associated with a slight increase in renal failure incidence (hazard ratio [HR]: 1.08, $p = 0.009$). There was an increasing association between an increase in FIB-4 index and the incidence of renal failure with the strongest association for a FIB-4 index ≥ 2.67 (HR: 1.34, $p = 0.001$). In sensitivity analyses, a significant association was found for the age group of 51–60 years (HR: 1.38, $p < 0.001$), patients with arterial hypertension (HR: 1.15, $p < 0.001$), obese patients (HR: 1.25, $p = 0.005$), and patients with lipid metabolism disorders (HR:1.22, $p < 0.001$). *Conclusion*: A higher FIB-4 index is associated with an increased incidence of renal failure. Therefore, the FIB-4 index may be useful in identifying patients who are at risk not only for liver-related events but also for renal disease.

Karel Kostev and Christian Labenz share senior authorship.

INTRODUCTION

Patients with advanced liver fibrosis have a high risk of disease progression resulting in decompensation and an increased mortality.[1] Several studies are currently in progress or have been completed (e.g., LiverScreen [NCT03789825] or SEAL) to determine the best strategy for fibrosis screening in the general population.[2,3] As of today, liver biopsy still remains the gold standard for the grading of fibrosis. However, there is a great need for noninvasive procedures based on imaging or laboratory values because of the invasive nature of biopsy and the potential risks associated with the procedure.[4–6] Although liver stiffness measurement by transient elastography is a cost-effective screening tool, its availability is limited in primary care settings.[7–9] Another cheap alternative to estimate the risk of advanced fibrosis is the Fibrosis-4 index (FIB-4). It relies on readily available blood tests (aminotransferases and platelet count). Initially, it was developed as a noninvasive test to predict liver fibrosis in patients with human immunodeficiency virus/hepatitis C virus coinfection.[10] The European Association for the Study of the Liver recommends the implementation of the FIB-4 as a noninvasive fibrosis test in populations at risk of liver fibrosis.[6] There is evidence that the FIB-4 is not only relevant for hepatic diseases and liver-related events but also for extrahepatic comorbidities such as depression.[11,12] Given the fact that advanced liver fibrosis also appears to be linked to a higher risk of incidental chronic kidney disease (CKD), the FIB-4 may have merit to identify high-risk patients in the general population.[13,14] Therefore, it was the aim of this study to investigate the association between a higher FIB-4 and the incidence of renal failure over a 10-year period in the general population in Germany.

METHODS

Database

This study was based on data from the Disease Analyzer database (IQVIA), which contains drug prescriptions, diagnoses, and basic medical and demographic data obtained directly and in an anonymous format from computer systems used in the practices of general practitioners and specialists.[15] The database covers approximately 3% of all outpatient practices in Germany. Diagnoses (according to the International Classification of Diseases, 10th revision [ICD-10]), prescriptions (according to the Anatomical Therapeutic Chemical Classification System), and the quality of reported data are monitored by IQVIA. It has previously been shown that the panel of practices included in the Disease Analyzer database is representative of general and specialized practices in Germany.[15] This database has already been used in previous studies focusing on the FIB-4.[12,16]

Study population

This retrospective cohort study included adult patients (≥18 years) in 924 general practices in Germany with available laboratory values for FIB-4 calculation between January 2005 and December 2019. The index date was the first documentation of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelet count in this period (Figure 1). Further inclusion criteria were an observation period of at least 6 months before the index date and a follow-up time of at least 6 months after the index date. Patients with renal diseases including renal tubulo-interstitial diseases (ICD-10: N10–N16), renal failure (ICD-10: N17–N19), diabetic renal complications (ICD-10: E10.2, E11.2, E12.2, E13.2, and E14.2), and dialysis (ICD-10: Z49) before the index date were excluded.

The FIB-4 was calculated using the following formula: age (years) × AST (U/L)/(PLT [10^9/L] × ALT$^{1/2}$ [U/L]). Each patient included in the study had on average 3.2 FIB-4 values. FIB-4 was calculated per patient for the whole follow-up time. Patients with a FIB-4 of < 1.3 were 1:1 matched to patients with a FIB-4 of ≥1.3 by age, sex, and diagnoses known as risk factors for renal failure (diabetes mellitus [ICD 10:

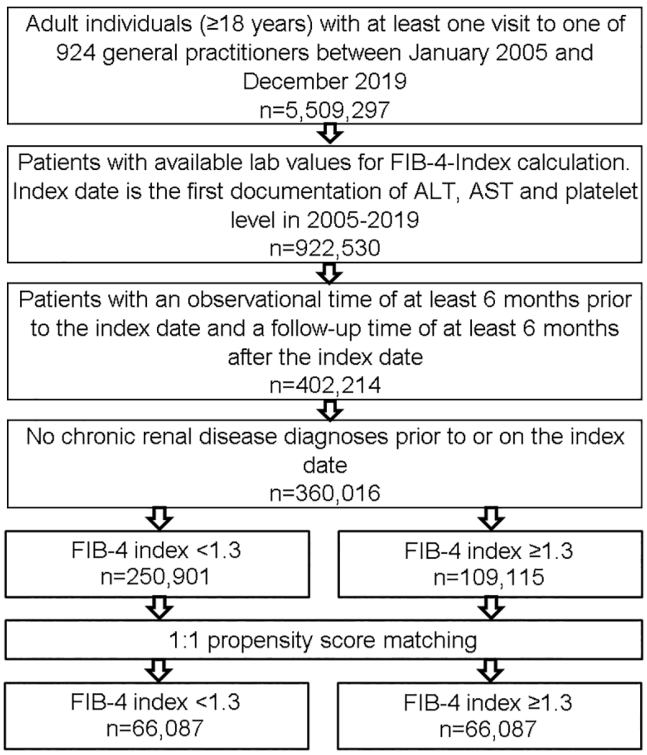

FIGURE 1 Selection of the study patients. ALT, alanine aminotransferase; AST, aspartate aminotransferase; FIB-4, Fibrosis-4 index.

E10–E14]), hypertension [ICD-10: I10], obesity [ICD-10: E66], lipid metabolism disorders [ICD-10: E78], coronary heart diseases [ICD-10: I24 and I25], and cancer [ICD-10: C00–C97]. This matching was necessary due to a very strong age, sex, and comorbidity difference among patients with a FIB-4 < 1.3 and ≥1.3. Additionally, the distribution of the three most frequent liver codes (nonalcoholic fatty liver disease [NAFLD] ICD-10: K75.8 and K76.0; chronic viral hepatitis ICD-10: B18; and liver cirrhosis ICD-10: K70.3 and K74) as well as alcohol dependency (ICD-10: F10) were displayed.

In a secondary analysis, we investigated the association between a higher AST-to-platelet ratio index (APRI) and renal failure during follow-up. The APRI was calculated using the following formula: ([AST/ULN AST] × 100)/platelets ($\times 10^9$/L). For these analyses, the same kind of matching process as described previously was applied.

Study outcomes and covariates

The primary outcome of the study was the incidence of renal failure as a function of average FIB-4 indices calculated per patient for the whole follow-up time (<1.3 vs. ≥1.3). In sensitivity analysis, we performed matching and regression analysis for other higher FIB-4 index cutoffs (<1.0 vs. ≥1.0, <1.7 vs. ≥1.7, <2.0 vs. ≥2.0). Renal failure was defined as the occurrence of either chronic renal failure (ICD-10: N18 and N19), acute renal failure (ICD-10: N17), or diabetic renal failure (ICD-10: E10.2, E11.2, E12.2, E13.2, and E14.2).

Additionally, in a second analysis, we investigated the incidence of chronic renal failure (ICD-10: N18 and N19) as a function of average FIB-4 calculated per patient for the whole follow-up time (<1.3 vs. ≥1.3). In sensitivity analysis, we performed matching and regression analysis for other FIB-4 index cutoffs (<1.0 vs. ≥1.0, <1.7 vs. ≥1.7, <2.0 vs. ≥2.0).

Finally, we investigated the incidence of renal failure as a function of average APRI calculated per patient for the whole follow-up time. Here, we performed matching and regression analysis for different APRI cutoffs (APRI ≥ 0.5 vs. <0.5 and ≥1.5 vs. <1.5).

Statistical analyses

Differences in the sample characteristics between those with a FIB-4 index < 1.3 and those with a FIB-4 index ≥ 1.3 were tested using chi-squared tests for categorical variables and Wilcoxon tests for continuous variables. Kaplan–Meier curves were used to analyze the time to renal failure diagnosis or chronic renal failure. Univariable Cox regression models were conducted to study the ratio of two incidence rates (FIB-4 ≥1.3 vs. <1.3). Regression analyses were performed separately for women and men, four age groups (age ≤ 50, age 51–60, age 61–70, and age > 70), and patients with predefined co-diagnoses. Additionally, several sensitivity analyses for different FIB-4 cutoffs were conducted. The same analyses were also repeated for the endpoint of chronic renal failure. Moreover, we calculated the respective sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of the different FIB-4 cutoffs for the prediction of renal failure within 10 years from the index date.

To investigate the potential association between the FIB-4 as a continuous variable and renal failure, we conducted a multivariable Cox regression model adjusted for age (as a continuous variable), sex, diabetes mellitus, hypertension, obesity, lipid metabolism disorders, coronary heart diseases, cancer, and alcohol dependency (all categorical variables).

In a secondary analysis, we conducted additional univariable Cox regression models including the dichotomized APRI to study the potential association between a higher APRI and renal failure during follow-up (APRI ≥ 0.5 vs. <0.5 and ≥1.5 vs. <1.5).

To counteract the problem of multiple comparisons, p-values < 0.01 were considered statistically significant. Analyses were carried out using SAS version 9.4 (SAS Institute).

RESULTS

Basic characteristics of the study cohort

In total, 66,087 patients with a FIB-4 ≥ 1.3 and 66,087 matched patients with a FIB-4 < 1.3 were included.

More than 95% of patients with a FIB-4 ≥ 1.3 had a FIB-4 between 1.3 and 3.25. The baseline characteristics of study patients are displayed in Table 1. There were no significant differences in the mean age (61.4 years), sex (49% women), and the prevalence of comorbidities between both groups (Table 1). The most frequently coded underlying liver disease was NAFLD, with a frequency of 4.4% in patients with a FIB-4 < 1.3 and a frequency of 4.9% in patients with a FIB-4 ≥ 1.3.

Incidence of renal failure

Within 10 years of the index date, 9.2% of patients with a FIB-4 < 1.3 and 10.6% of patients with a FIB-4 ≥ 1.3 were diagnosed with renal failure (log-rank p = 0.007) (Figure 2). Of the 4925 patients with an initial renal failure diagnosis, 86.8% had chronic renal failure (ICD-10: N18 and N19), 4.0% had acute renal failure (ICD-10: N17), and 8.0% had diabetic renal failure (ICD-10: E10.2, E11.2, E12.2, E13.2, and E14.2). Dialysis was

TABLE 1 Baseline characteristics of the study sample after 1:1 matching

Variable	Proportion affected among patients with FIB-4 < 1.3 (%); N = 66,087	Proportion affected among patients without FIB-4 ≥ 1.3 (%); N = 66,087	*p*
Age (mean, SD)	61.4 (11.1)	61.4 (11.1)	0.983
Age ≤ 50 years	14.8	14.8	0.887
Age 51–60 years	30.7	30.6	
Age 61–70 years	35.1	35.2	
Age > 70 years	19.4	19.4	
Women	49.2	48.9	0.237
Men	50.8	51.1	
Comorbidities			
Diabetes	11.8	12.0	0.320
Obesity	7.0	7.1	0.293
Lipid metabolism disorder	23.2	23.5	0.191
Hypertension	33.2	33.4	0.517
Coronary heart disease	7.7	7.9	0.223
Cancer	8.1	8.3	0.074
NAFLD	4.4	4.9	<0.001
Chronic viral hepatitis	0.2	0.7	<0.001
Liver cirrhosis	0.3	1.3	<0.001
Alcohol dependency	2.7	5.5	<0.001

Note: Proportions of patients in percentage given, unless otherwise indicated.
Abbreviation: NAFLD, nonalcoholic fatty liver disease.

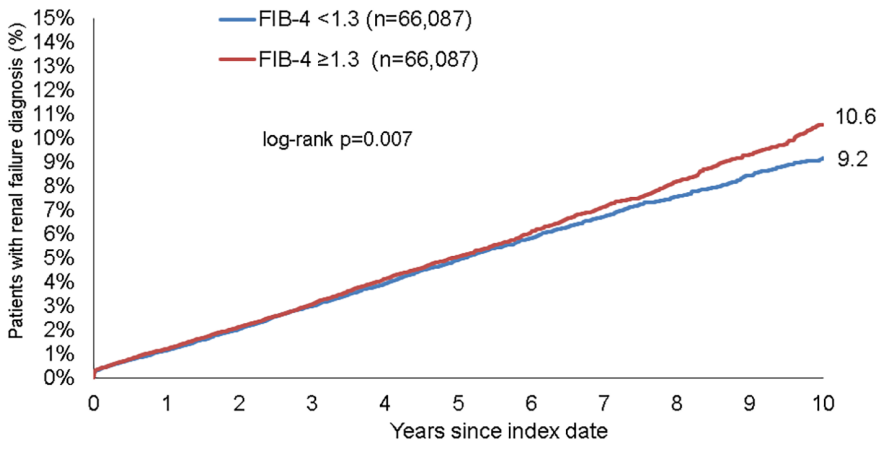

FIGURE 2 Kaplan–Meier curves for time to renal failure diagnosis depending on FIB-4.

not documented before renal failure diagnosis but during the follow-up time after the renal failure diagnosis in 72 (1.5%) of the renal failure patients. This low number of events precluded further analysis regarding the impact of the FIB-4 index on the need for dialysis.

Regarding the endpoint chronic renal failure, 7.9% of patients with a FIB-4 < 1.3 and 9.5% of patients with a FIB-4 ≥ 1.3 were diagnosed with these disease codes within 10 years of the index date (log-rank $p < 0.001$) (Figure 3).

Association of FIB-4 ≥ 1.3 and renal failure

In regression analyses, a FIB-4 ≥ 1.3 was significantly associated with an increased renal failure incidence (hazard ratio [HR]: 1.08, $p = 0.009$) (Table 2). In sensitivity analyses based on the same matched cohorts, a significant positive association was observed for the age group 51–60 years (HR: 1.38, $p < 0.001$), patients with arterial hypertension (HR: 1.15, $p < 0.001$), obese patients

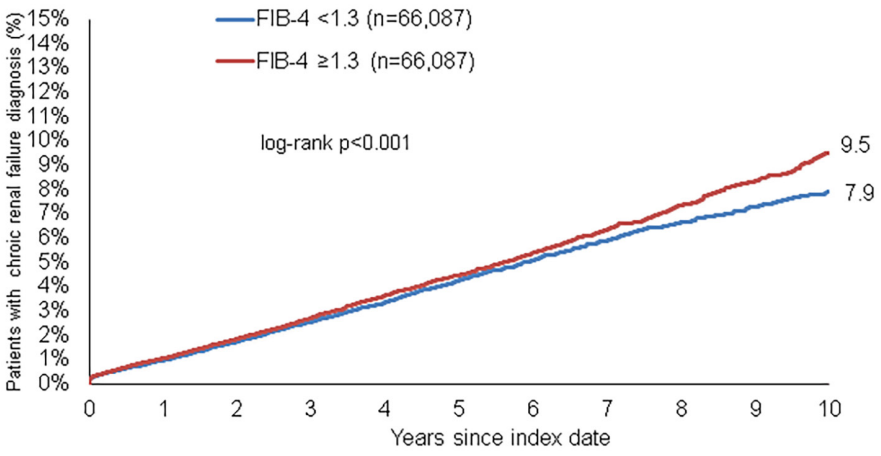

FIGURE 3 Kaplan–Meier curves for time to chronic renal failure diagnosis depending on FIB-4.

(HR: 1.25, $p = 0.005$), and patients with lipid metabolism disorders (HR: 1.22, $p < 0.001$) (Table 2).

In another regression analysis that included the FIB-4 as a continuous variable and adjusted for these mentioned demographic characteristics and comorbidities, the association between a higher FIB-4 and renal failure remained significant (HR: 1.098 per 1-point increase in FIB-4; 95% confidence interval [CI]: 1.064–1.133; $p < 0.001$) (Table S1).

Sensitivity analyses with different FIB-4 measurements for the endpoint renal failure

Table 3 lists the results of regression analyses for matched pairs with a FIB-4 < 1.0 versus ≥1.0, <1.7 versus ≥1.7, <2.0 versus ≥2.0, and <2.67 versus ≥2.67. There was no significant association between a FIB-4 ≥ 1.0 and renal failure. The association between a FIB-4 ≥ 1.7 was very similar to that of a FIB-4 ≥ 1.3. However, a FIB-4 ≥ 2.0, and especially ≥2.67, were more strongly associated with renal failure than lower scores. The respective sensitivity and specificity of all FIB-4 cutoffs for predicting the incidence of renal failure are displayed in Table S2.

Association of a FIB-4 ≥ 1.3 and chronic renal failure

In regression analyses, FIB-4 ≥ 1.3 was significantly associated with an increased chronic renal failure incidence (HR: 1.11, $p < 0.001$) (Table 2). In sensitivity analyses based on the same matched cohorts, a significant positive association was observed for age groups 51–60 years (HR: 1.41, $p < 0.001$) and 61–70 years (HR: 1.18, $p = 0.001$), patients with diabetes (HR: 1.18, $p = 0.011$), patients with arterial hypertension (HR = 1.21, $p < 0.001$), obese patients (HR: 1.35, $p < 0.001$), patients with lipid metabolism disorder (HR: 1.30, $p < 0.001$), and patients with coronary heart disease (HR: 1.23, $p = 0.009$) (Table 2).

Sensitivity analyses with different FIB-4 measurements for the endpoint chronic renal failure

Table 4 lists the results of regression analyses for matched pairs with a FIB-4 < 1.0 versus ≥1.0, <1.7 versus ≥1.7, <2.0 versus ≥2.0, and <2.67 versus ≥2.67. There was no significant association between a FIB-4 ≥ 1.0 and chronic renal failure. The association between a FIB-4 ≥ 1.7 was very similar to that of a FIB-4 ≥ 1.3. However, a FIB-4 ≥ 2.0 was more strongly associated with chronic renal failure (HR: 1.17, $p < 0.001$). The strongest association between FIB-4 and chronic renal failure was observed for a FIB-4 ≥ 2.67 (HR: 1.35, $p < 0.001$).

Due to the fact that the FIB-4 is more inaccurate in the older population, and the traditional cutoffs may not apply to these patients, we repeated our sensitivity analyses in patients with age ≥ 65 years. Table 4 provides the results of regression analysis for matched pairs (≥65 years) with a FIB-4 < 1.0 versus ≥1.0, <1.7 versus ≥1.7, <2.0 versus ≥2.0, and <2.67 versus ≥2.67.

Association of different APRI cutoffs and renal failure

For the analyses on the potential association between a higher APRI and renal failure, the same matching process as for the analyses on the FIB-4 were applied. In regression analyses, an APRI ≥ 0.5 (vs. 0.5) was significantly associated with an increased renal failure incidence (HR: 1.32, 95% CI: 1.23–1.41; $p < 0.001$; 56,065

TABLE 2 Association between FIB-4 ≥ 1.3 and incident renal failure within 10 years of index date in patients followed in general practices in Germany by age and sex, and co-diagnoses (univariable regression models)

	Outcome: renal failure		Outcome: chronic renal failure	
	Incidence rate ratio (FIB-4 ≥ 1.3 vs. <1.3) (95% CI)	*p*	Incidence rate ratio (FIB-4 ≥ 1.3 vs. <1.3) (95% CI)	*p*
Total	1.08 (1.02–1.14)	0.009	1.11 (1.05–1.18)	<0.001
Age ≤ 50 years	1.33 (1.02–1.74)	0.039	1.22 (0.91–1.64)	0.175
Age 51–60 years	1.38 (1.51–1.58)	<0.001	1.41 (1.22–1.64)	<0.001
Age 61–70 years	1.11 (1.02–1.21)	0.028	1.18 (1.07–1.29)	0.001
Age > 70 years	0.89 (0.82–0.98)	0.021	0.02 (0.84–1.01)	0.091
Women	1.05 (0.97–1.13)	0.228	1.09 (1.00–1.18)	0.059
Men	1.10 (1.02–1.19)	0.014	1.14 (1.04–1.24)	0.003
Patients with diabetes	1.07 (0.97–1.18)	0.193	1.18 (1.04–1.33)	0.011
Patients with arterial hypertension	1.15 (1.06–1.25)	<0.001	1.21 (1.11–1.33)	<0.001
Obese patients	1.25 (1.07–1.47)	0.005	1.35 (1.13–1.61)	<0.001
Patients with lipid metabolism disorder	1.22 (1.11–1.35)	<0.001	1.30 (1.16–1.46)	<0.001
Patients with coronary heart disease	1.14 (0.99–1.31)	0.067	1.23 (1.05–1.44)	0.009
Patients with cancer	1.01 (0.85–1.20)	0.873	1.06 (0.88–1.28)	0.528
Patients with alcohol dependency	1.12 (0.85–1.46)	0.428	1.18 (0.88–1.59)	0.278

Abbreviation: CI, confidence interval.

TABLE 3 Association between FIB-4 and incident renal failure diagnosis within 10 years of index date depending on different FIB-4 cutoffs (univariable regression models)

FIB-4 cutoffs	Number of matched pairs	Incidence rate ratio (higher vs. lower FIB-4) (95% CI)	*p*
≥1.0 vs. <1.0	73,569	0.96 (0.90–1.03)	0.338
≥1.3 vs. <1.3	66,087	1.08 (1.02–1.14)	0.009
≥1.7 vs. <1.7	48,033	1.09 (1.03–1.15)	0.003
≥2.0 vs. <2.0	34,665	1.17 (1.10–1.24)	<0.001
≥2.67 vs. <2.67	14,146	1.34 (1.22–1.46)	<0.001

matched patient pairs). In another regression analysis including 3762 matched pairs with an APRI ≥ 1.5 or <1.5, the association with renal failure during follow-up became stronger (HR: 1.64, 95% CI: 1.23–2.18; $p < 0.001$). The respective sensitivity and specificity of both APRI cutoffs for predicting the incidence of renal failure are displayed in Table S2.

DISCUSSION

In this study, we found a mild association between a higher FIB-4, a surrogate and composite score for the potential prevalence of advanced liver fibrosis, and the development of renal failure as a composite endpoint or chronic renal failure. Additionally, we were able to demonstrate an increasing association between a higher FIB-4 and the risk of renal failure or chronic renal failure during follow-up. The association between a higher FIB-4 and renal failure was more pronounced in middle-aged patients (51–60 years) and patients with metabolic comorbidities such as arterial hypertension or lipid metabolism disorders. Moreover, our findings regarding an association between noninvasive tests (NITs) for detection of liver fibrosis and renal failure were validated by secondary analyses demonstrating an additional robust association between the APRI and renal failure.

Liver diseases and especially liver cirrhosis are among the most lethal diseases worldwide, and cirrhosis itself accounts for about 2 million deaths per year.[17] Given the importance of chronic liver disease

TABLE 4 Association between FIB-4- and incident chronic renal failure diagnosis within 10 years of index date depending on different FIB-4 cutoffs (univariable regression models)

	All patients			Patients ≥ 65 years		
Fib-4 cutoffs	Number of matched pairs	Incidence rate ratio (higher vs. lower FIB-4) (95% CI)	*p*	Number of matched pairs	Incidence rate ratio (higher vs. lower FIB-4) (95% CI)	*p*
≥1.0 vs. <1.0	73,569	1.00 (0.93–1.08)	0.978	9713	0.85 (0.75–0.97)	0.012
≥1.3 vs. <1.3	66,087	1.11 (1.05–1.18)	<0.001	25,663	1.01 (0.94–1.09)	0.855
≥1.7 vs. <1.7	48,033	1.09 (1.04–1.16)	0.001	32,922	1.04 (0.99–1.10)	0.187
≥2.0 vs. <2.0	34,665	1.17 (1.10–1.24)	<0.001	26,380	1.12 (1.05–1.19)	<0.001
≥2.67 vs. <2.67	14,146	1.35 (1.22–1.48)	<0.001	10,778	1.29 (1.17–1.43)	<0.001

for overall health and prognosis, it is a surprising finding that <10% of our patients with a FIB-4 ≥ 1.3 had a coded diagnosis of chronic liver disease. In part, this may be explained by the more or less mediocre PPV of FIB-4 or other composite scores for the presence of advanced fibrosis.[2] Although the FIB-4 is a validated and independent predictor of mortality and liver-related outcomes in patients with known chronic liver disease, such as NAFLD, current evidence suggests that the predictive value of the FIB-4 is not sufficient for screening of fibrosis in the general population.[11,18] In this context, a study by Hagström et al. in the Swedish general population demonstrated that about 50% of severe liver disease outcomes had consistently low or intermediate FIB-4 values despite repeated measurements.[11] This limited PPV of traditional NITs is confirmed by the recently published SEAL study.[3] Here, only 45 of 245 participants (18.4%) with elevated aminotransferase activities and an APRI > 0.5 suffered from advanced fibrosis or liver cirrhosis after advanced diagnostic workup. Nevertheless, our findings underscore the low awareness for potentially advanced chronic liver diseases among the German population as well as physicians. This lack of awareness is a worrisome finding, as according to Schreiner et al., a FIB-4 with indeterminate risk (FIB-4 1.3–2.67) and high risk (FIB-4 > 2.67) is associated with an increased incidence of severe liver disease in primary care patients without known chronic liver disease.[19] Therefore, calculation of the FIB-4 in primary care may serve as a signal to pursue a diagnosis of chronic liver disease.[20] In addition, there is evidence that repeating measurements of FIB-4 within a 5-year period can, in comparison with a single measurement, help to identify individuals who are at higher risk of developing severe liver disease.[11] A Swedish epidemiological study found that an elevated FIB-4 predicted the 10-year risk of liver-related events in the general population; however, 65% of those events occurred in participants with a low FIB-4 index.[21] Moreover, a recently published study by Shi et al. demonstrated that the FIB-4 is also associated with clinical outcomes in critically ill patients with acute kidney injury.[22]

Our current study expands the existing literature, which focuses primarily on the predictive ability of FIB-4 regarding liver-related outcomes by demonstrating a mild association between a higher FIB-4 and key extrahepatic events such as renal failure as a composite endpoint and chronic renal failure. Although the association between a higher FIB-4 and the development of renal failure was comparably weak, the results are strengthened by a clear risk increase for renal failure in patients with a higher FIB-4. Our findings regarding the usefulness of the calculation of the FIB-4 index in a general population to predict relevant outcome measures are well in line with previous studies indicating an association between FIB-4 and

the occurrence of depression or anxiety disorders.[12] Moreover, several studies indicated that the presence of NAFLD and especially advanced fibrosis in these patients is associated with an increased risk of developing CKD.[23–27] Seo et al. found that among patients with NAFLD, advanced liver fibrosis was associated with an increased risk of CKD, although there was no increased risk of incident CKD in the NAFLD group compared with the non-NAFLD group.[24] Our study adds to this evidence by indicating the value of FIB-4 measurements in the general population, not only to identify patients at higher risk for liver-related events but also to identify patients at higher risk of renal failure. In this context, our data indicate that FIB-4 may have merit especially in middle-aged patients with metabolic comorbidities such as arterial hypertension or lipid metabolism disorders. Using the FIB-4 routinely in these patients could potentially help to enable screening measures to finally identify patients at an early stage of their disease.

There are well-known pathophysiological relations that link advanced fibrosis, as reflected by higher FIB-4 values, and the development of renal failure. First and foremost, advanced fibrosis is linked to (subclinical) systemic inflammation, which has a proven impact on the risk of developing renal failure.[13,28] The underlying mechanisms are not fully understood; however, the systemic release of multiple mediators including pro-inflammatory, pro-fibrogenic, and anti-fibrinolytic molecules (e.g., fibroblast growth factor-21, tumor necrosis factor-α, transforming growth factor-β [TGF-1β]) can promote renal failure.[14,29–31]

Overexpression of active TGF-1β in the liver of mice caused the development of severe renal fibrosis, and thus plays a key role in the development of CKD.[31–33] Second, the renin-angiotensin-system (RAS) may constitute a potential link, as RAS activation has been implicated in the production of pro-inflammatory cytokines, in particular interleukin-6, which promotes oxidative stress.[34] Therefore, RAS activation may support subclinical organ dysfunctions potentially leading to renal failure in the long run. Additionally, systemic and hepatic insulin resistance, atherogenic dyslipidemia, and fibrosis progression may be indicators of a decreased overall metabolic health status that feature the increased risk of the development of CKD.[26]

Our study has several strengths such as the large patient cohort, reflecting a real-world scenario in Germany, a long follow-up period, and careful matching. Especially the large number of patients allowed us to perform sensitivity analyses and to give robust estimates of the association between FIB-4 and renal failure. However, we have to acknowledge several limitations that need to be considered when interpreting our data. First, because of our study design, we were only able to identify associations; causality has to be proven in future prospective studies. Second, our study was based on the retrospective analysis of ICD-10 codes. Therefore, we were unable to adjust for lifestyle-related factors such as chronic alcohol consumption or nutritional aspects. Moreover, we were unable to adjust our models for disease severity of comorbidities, which may be a potential bias. Additionally, there may be some bias due to undercoding or miscoding that has to be kept in mind when interpreting our data. This may be especially true for the prevalence of NAFLD. Third, some important laboratory parameters, such as creatinine or hemoglobin A1c, are only available in a small subset of our cohort. Therefore, we cannot compare the usefulness of FIB-4 for predicting renal failure with other risk factor–based models, which is a limitation. Finally, due to the fact that the follow-up period varied among individual patients, our analyses regarding the respective sensitivity and specificity of different FIB-4 and APRI cutoffs for predicting the incidence of renal failure within 10 years from the index date have to be interpreted with caution. This may introduce some bias into these analyses.

CONCLUSIONS

We found a mild and dose-dependent association between a higher FIB-4, a surrogate and composite score for the potential prevalence of advanced liver fibrosis, and the development of renal failure as a composite endpoint or chronic renal failure. Strikingly, the association between a higher Fib-4 and renal failure was more pronounced in middle-aged patients and patients with metabolic comorbidities such as arterial hypertension or lipid metabolism disorders. Especially in patients with metabolic comorbidities, the use of FIB-4 may help to identify patients at higher risk of renal failure.

AUTHOR CONTRIBUTIONS

Research: Eva Maria Schleicher, Karel Kostev, and Christian Labenz. *Study design and data analysis*: Eva Maria Schleicher, Karel Kostev, and Christian Labenz. *Reagents/materials/analysis tools contribution*: Karel Kostev. *Manuscript draft*: Eva Maria Schleicher, Karel Kostev, and Christian Labenz. *Critical revision of the manuscript*: Simon Johannes Gairing, Jörn M. Schattenberg, Julia Weinmann-Menke, and Peter Robert Galle. *Statistical analysis*: Karel Kostev. All authors approved the final version of the manuscript and the authorship list. Guarantor of the article: Christian Labenz.

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CONFLICT OF INTEREST

Karel Kostev is Scientific Principal-Epidemiology Research at IMS Health (IQVIA) in Frankfurt (Germany). However, IQVIA has no influence on the content or publication of this manuscript. All other authors disclose no potential financial or nonfinancial conflicts of interest. JS consults for Apollo Endosurgery, Albireo Pharma Inc, Bayer, BMS, Echosens, GSK, Intercept Pharmaceuticals, Ipsen, Inventiva Pharma, Madrigal, MSD, and Novarti. He is on the speakers' bureau of MedPublico GmbH. He received grants from Nordic Bioscience and Siemens Healthcare GmbH. He consults and receives grants from Gilead Sciences. He consults, received grants from, and is on the speakers' bureau of Boehringer Ingelheim.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon reasonable request from K.K. after approval by IQVIA.

ETHICS

This study was conducted according to the ethical guidelines of the 1964 Declaration of Helsinki (amended, 2013). We used anonymous electronic medical records for research purposes with no directly identifiable data. Accordingly, this study did not collect informed consent from individual patients, and according to German regulations no ethical approval is needed. Anonymized data were analyzed as aggregates with no protected health information available.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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