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Utility of non-invasive liver fibrosis markers to predict the incidence of chronic kidney disease (CKD): A systematic review, meta-analysis, and meta-regression

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ABSTRACT

Background and aims: Chronic kidney disease (CKD) and non-alcoholic fatty liver disease (NAFLD) share common risk factors and pathogenesis mechanisms. However, the association between the degree of liver fibrosis and the incidence of CKD remains unclear. This study aims to examine the utility of non-invasive fibrosis markers to predict the occurrence of CKD.

Methods: Cochrane Library, Scopus, and Medline were searched up to May 20th, 2023 using combined keywords. Literature that analyzes FIB-4, NFS, and APRI to predict CKD incidence was included in this review. We used random-effect models of odds ratio (OR) with 95% confidence intervals (CI) to express the outcomes in this review.

Results: Twenty-one studies were included. Our meta-analysis showed that high FIB-4 was associated with a higher incidence of CKD (OR 2.51; 95%CI: 1.87−3.37, $p < 0.00001$, $I^2 = 96\%$). Further regression analysis revealed that this association was significantly influenced by hypertension ($p = 0.0241$), NAFLD ($p = 0.0029$), and body mass index (BMI) ($p = 0.0025$). Our meta-analysis also showed that high NFS (OR 2.49; 95%CI: 1.89−3.30, $p < 0.00001$, $I^2 = 96\%$) and high APRI (OR 1.40; 95%CI: 1.14−1.72, $p = 0.001$, $I^2 = 26\%$) were associated with a higher incidence of CKD.

Conclusions: This study suggests that these non-invasive liver fibrosis markers can be routinely measured both in NAFLD patients and the general population to enable better risk stratification and early detection of CKD.

1. Introduction

Chronic Kidney Disease (CKD) is a kidney disease in which there is a decline in kidney function over a period of months to years and is characterized by a slow decline in glomerular filtration rate (GFR) over a long period [1]. Until now, CKD still become a major public health problem, both in developed and developing countries [2]. Globally, there are an estimated 843.6 million cases of CKD stages 1−5 worldwide [2]. Based on the data from the Global Burden of Disease (GBD), CKD has become the leading cause of worldwide mortality with a mortality rate that continues to increase by about 41.5% from 1990 to 2017 [3]. Therefore, early identification and management of CKD can reduce the risk of life-threatening complications and reduce the burden of this disease [2,3].

In recent years, evidence has shown that non-alcoholic fatty liver disease (NAFLD) may be associated with the risk of developing CKD [4]. An international consensus has also recently been published which stated that there is an interconnected relationship between NAFLD and CKD where both NAFLD and CKD share similar risk factors and pathogenesis mechanisms, such as hypertension, insulin resistance, dyslipidemia, and obesity [5,6]. Physicians should be made aware of this relationship so that the management can also focus on shared risk factors between NAFLD and CKD [5]. Numerous studies have demonstrated a link between severe liver

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disease, such as fibrosis in those with biopsy-proven NAFLD, with a higher risk of CKD [4,7]. Despite the fact that liver biopsy remains the gold standard for identifying liver fibrosis, this procedure has several limitations, such as an invasive method that may cause discomfort to the patients and higher risks of complications [8]. Other methods for determining the degree of liver fibrosis such as transient elastography (FibroScan) are not available in all health-care facilities, especially in resource-limited areas, relatively expensive, and operator-dependent [9]. Non-invasive fibrosis markers, such as the fibrosis-4 index (FIB-4), non-alcoholic fatty liver disease fibrosis score (NFS), and aspartate aminotransferase (AST) to platelet ratio index (APRI) have been developed to replace liver biopsy in evaluating the severity of liver fibrosis [10]. Unfortunately, studies on these non-invasive fibrosis markers still showed inconsistent results in predicting the incidence of CKD [11–13]. For instance, Kuma et al.'s [11] study employing the Japanese population indicated that a high FIB-4 score (≥1.30) was not an independent risk factor for CKD after propensity score matching. Another study by Machida et al. [12] also supported this evidence by showing no significant relationship between high FIB-4 and CKD. On the other side, a study by Cao et al. [13] showed that a high FIB-4 score (≥1.30) was significantly associated with CKD. Given these inconsistencies, a systematic review and meta-analysis study is needed to resolve this problem. This study aims to assess the ability of non-invasive fibrosis markers (FIB-4, NFS, and APRI) to predict the occurrence of CKD.

2. Materials and methods

2.1. Eligibility criteria

A systematic review and meta-analysis of observational studies was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. This study has been previously registered in the PROSPERO (CRD42022376481). We compiled the inclusion criteria in this study based on the PECOS formulation as follows:

(1) adult patients aged over 18 years with or without a diagnosis of non-alcoholic fatty liver disease (NAFLD) (Population);
(2) has data regarding (a) the fibrosis-4 index (FIB-4) with a cut-off value of 1.30 or classified into low (<1.30), intermediate (1.30–2.67), and high (>2.67) risk of liver fibrosis; (b) the NAFLD fibrosis score (NFS) with classification into low (<-1.455), intermediate (−1.455 to 0.676), and high (>0.676); (c) the AST to platelet ratio index (APRI) with a cut-off value of 0.50 (Exposure and Control);
(3) assessing the incidence of chronic kidney disease in various groups of FIB-4, NFS, and APRI (Outcome);
(4) has an observational design (can be cohort, case-control, or cross-sectional) (Study Design).

Meanwhile, the exclusion criteria were as follows: (1) study in pediatric population/children (age <18 years); (2) the study population already had an eGFR value of 60 mL/min/1.73 m2 or a diagnosis of CKD at the start of the study; (3) studies in patients with alcoholic fatty liver disease; (4) clinical trials, case-series, case-reports, correspondence, letters to editors, or review articles; (5) studies that are not available in the full-text form or studies that have not been published.

2.2. Search strategy and study selection

A literature search was conducted on English-language articles up to May 20th, 2023 in 3 international databases: Medline, Scopus, and the Cochrane Library. The keywords used for the literature search were as follows: "(fibrosis-4 index OR FIB-4 OR fibrosis-4 score OR non-alcoholic fatty liver disease fibrosis score OR NAFLD fibrosis score OR NFS OR aspartate aminotransferase to platelet ratio index OR AST to platelet ratio index OR APRI) AND (chronic kidney disease OR CKD OR chronic renal failure OR chronic renal disease OR chronic renal insufficiency)". More details regarding the search strategy used for each database can be seen in Supplementary Table 1. First, the screening process was begun by looking at the suitability of the titles and/or abstracts against our eligibility criteria. Any original publications that were cited in the systematic reviews or meta-analyses but missed by the initial search would also be included if they were suitable with our inclusion/exclusion criteria. All duplicate articles were removed. The process was then followed by a comprehensive assessment of full-text articles. All of these processes were carried out independently by two reviewers. If disagreement was found during the screening process, it will be resolved by seeking the opinion of a third reviewer.

2.3. Data extraction

The data extraction process was carried out independently by two reviewers. The extracted data were as follows: author's name, study's year, design of the study, number of samples, type of participants, age, gender, comorbidities, BMI, number of participants in each group, and outcome of interest.

FIB-4 values in the existing studies were calculated using the formula: age × AST (IU/L)/platelet count (× 10^9/L) × $\sqrt{}$ALT (IU/L) [12]. NFS values in the existing studies were calculated using the formula: −1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × diabetes (yes = 1, no = 0) + 0.99 × AST/ALT ratio - 0.013 × platelet count (x10^9/L) - 0.66 × albumin (g/dL). APRI score was calculated as AST (IU/L)/platelet count (× 109/L) × 100. Chronic kidney disease (CKD), which was the outcome of interest in this study, was defined based on the criteria from the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, namely eGFR <60 mL/min/1.73 m2 and/or urinary albumin-to-creatinine ratio (ACR) ≥3 mg/mmol [1].

2.4. Risk of bias assessment

Assessment of the risk of bias from each study was carried out independently by two reviewers using standardized tools. To evaluate the quality of each observational study, we used the Newcastle-Ottawa Scale (NOS) which encompasses assessments on the selection of study subjects, comparability between study groups, as well as the outcomes of each study [15]. The total scores that can be obtained using this tool were 0–9 where research with a total score of ≥7 was considered to have good quality [15]. Meanwhile, for the quality assessment of the cross-sectional studies included in this study, we used the Modified Newcastle-Ottawa Scale (modified NOS) which was an adaptation of the original NOS but with some adjustments to obtain a comprehensive assessment of cross-sectional studies [16]. The total scores ranged from 0 to 9 where a value ≥ 7 was considered good quality research [16].

2.5. Statistical analysis

We calculated the incidence of CKD in each FIB-4, NFS, and APRI group by using the Generic Inverse-Variance formula to obtain the odds ratio (OR) along with the 95% confidence interval (95% CI). Due to the various participant characteristics, the study design, and the time points at which the follow-up was conducted, there was a

significant level of heterogeneity that needed to be accounted for, and this was done by using random-effect models. I-squared (I^2; Inconsistency) statistic was used to measure the heterogeneity between studies, with values of more than 50% corresponding to high or significant heterogeneity [17]. To determine how non-invasive fibrosis markers and pre-specified variables, such as age, sex, hypertension, diabetes, NAFLD, and body mass index (BMI), interacted to affect the incidence of CKD, meta-regression with a restricted-maximum likelihood random-effects model was carried out. We also performed subgroup analysis based on the geographical region and studies' population. In case of more than 10 studies were combined in the meta-analysis, a funnel plot would be used to assess the publication bias. The Cochrane Collaboration's Review Manager 5.4 and Comprehensive Meta-Analysis 3 tools were used for all analyses in this study.

3. Results

3.1. Study selection and characteristics

A literature search of the database yielded 397 studies. After screening titles/abstracts and removing duplicates, we assessed 80 full-text articles based on the eligibility criteria of this study. Out of a total of 80 full-text articles, 59 articles were excluded from this study because of the following reasons: twenty-eight articles had no data on FIB-4, NFS, or APRI, twenty-five articles did not have data on the outcome of interest, three were review articles, two articles used different cut-off values, and one article was not available in English. Ultimately, the remaining 21 articles [10–12,18–35] with a total of 306,633 patients were included in the final analysis (Fig. 1). Out of 21 articles, 11 articles had a cross-sectional design, while the remaining 10 articles were retrospective cohort studies. The majority of included studies were studies conducted on the adult general population, whereas 5 articles only included patient populations with non-alcoholic fatty liver disease (NAFLD). A more detailed description of the characteristics of each included study can be seen in Table 1.

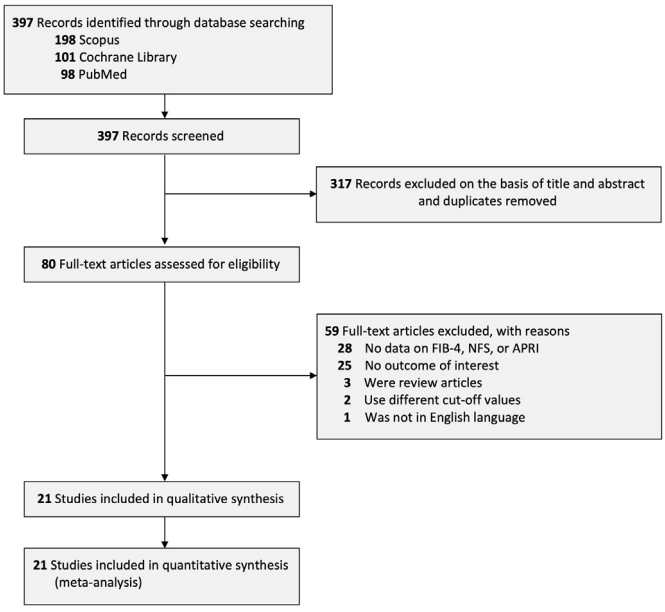

Fig. 1. PRISMA diagram of the detailed process of selection of studies for inclusion in the systematic review and meta-analysis.

3.2. Quality of study assessment

All cohort studies included in this analysis showed good quality according to the Newcastle Ottawa Scale (NOS), with scores ranging from 7 to 8 (Table 2). Meanwhile, all cross-sectional studies in this study also had good quality based on the modified NOS scale with a total score of 7–9 (Table 3). All studies were deemed eligible for inclusion in the meta-analysis.

3.3. FIB-4 and incidence of CKD

Our meta-analysis showed that a high FIB-4 score was associated with a higher incidence of CKD when compared with a low FIB-4 score (OR 2.51; 95%CI: 1.87–3.37, $p < 0.00001$, $I^2 = 96\%$, random-effect model) (Fig. 2). Sub-group analysis based on the FIB-4 cut-off still showed significant results in each sub-group and a positive correlation between FIB-4 values and the incidence of CKD where higher FIB-4 cut-off values are being used, the risk of developing CKD will also be higher. From a total of 7 studies, it was revealed that FIB-4 values > 1.30 were significantly associated with a higher incidence of CKD compared to FIB-4 values < 1.30 (OR 1.28; 95%CI: 1.06–1.56, $p = 0.01$, $I^2 = 70\%$, random-effect model). There were 6 studies that report data regarding the relationship between the intermediate risk of liver fibrosis and the incidence of CKD. From a meta-analysis based on these 6 studies, it was shown that an intermediate risk of liver fibrosis (defined as FIB-4 = 1.30–2.67) was associated with a higher incidence of CKD than a low risk of liver fibrosis (FIB-4 <1.30) (OR 2.93; 95%CI: 2.48–3.46, $p < 0.00001$, $I^2 = 38\%$, random-effect model). Finally, 8 studies reported data regarding the high risk of liver fibrosis with the incidence of CKD. From a pooled analysis based on these 8 studies, it has been demonstrated that those with a high risk of liver fibrosis (FIB-4 score >2.67) will have a higher incidence of CKD than those with a low risk of liver fibrosis (FIB-4 <1.30) (OR 3.53; 95%CI: 2.12–5.90, $p < 0.00001$, $I^2 = 90\%$, random-effect model).

3.4. NFS and incidence of CKD

Our meta-analysis showed that a high NFS score was associated with a higher incidence of CKD when compared with a low NFS score (OR 2.49; 95%CI: 1.89–3.30, $p < 0.00001$, $I^2 = 96\%$, random-effect model) (Fig. 3). Sub-group analysis based on the NFS cut-off still showed significant results in each sub-group and a positive correlation between NFS values and the incidence of CKD where higher NFS cut-off values are being used, the risk of developing CKD will also be higher. There were 11 studies that report data regarding the relationship between the intermediate risk of liver fibrosis and the incidence of CKD. From a meta-analysis based on these 11 studies, it was shown that an intermediate risk of liver fibrosis (defined as NFS = −1.455 to 0.676) was associated with a higher incidence of CKD than a low risk of liver fibrosis (NFS < -1.455) (OR 1.83; 95%CI: 1.37–2.46, $p < 0.0001$, $I^2 = 95\%$, random-effect model). Finally, 12 studies reported data regarding the high risk of liver fibrosis with the incidence of CKD. From a pooled analysis based on these 12 studies, it has been demonstrated that those with a high risk of liver fibrosis (NFS >0.676) will have a higher incidence of CKD than those with a low risk of liver fibrosis (NFS < -1.455) (OR 3.43; 95%CI: 2.06–5.72, $p < 0.00001$, $I^2 = 93\%$, random-effect model).

3.5. APRI and incidence of CKD

Our meta-analysis from 4 studies showed that a high APRI score

Table 1
Characteristics of included studies.

Study	Country	Design	Sample size	Type of participants	Age (years)	Male (%)		Diabetes (%)	NAFLD (%)	BMI (kg/m^2)
Cao et al. [12] 2021	China	Cross-sectional	3,872	General population aged >18 years old	60	76.4%	48.8%	23.5%	49.2%	25.6
Chen et al. [18] 2020	Taiwan	Retrospective cohort	29,797	General population aged >18 years old	52.2	54%	N/A	7.7%	44.5%	23.8
Choi et al. [19] 2019	South Korea	Cross-sectional	11,836	Non-institutionalized population aged >20 years old	44.4	41.3%	N/A	N/A	N/A	23.7
Ciardullo et al. [20] 2020	Italy	Retrospective cohort	2,770	Patients aged >18 years with a diagnosis of type 2 diabetes	68	59%	75.5%	100%	65%	30.2
Deng et al. [21] 2021	USA	Cross-sectional	4,869	General population aged >20 years old	51.7	48.6%	31.4%	16.2%	56.8%	N/A
Han et al. [22] 2022	South Korea	Cross-sectional	9,444	General population aged >20 years old	48.8	43.4%	36.3%	9.7%	38%	23.6
Hsieh et al. [23] 2020	Taiwan	Retrospective cohort	11,376	General population aged >40 years old	52	39.8%	67.2%	N/A	N/A	24.8
Hu et al. [24] 2022	China	Cross-sectional	8,226	General population aged >18 years old	44.3	60%	22.3%	8.5%	53.5%	24.1
Kotoku et al. [25] 2021	Japan	Cross-sectional	806	Middle-aged and older subjects (aged 29–72 years)	49.9	73.1%	89.1%	96.9%	N/A	N/A
Kuma et al. [10] 2022	Japan	Retrospective cohort	5,353	Metabolically healthy men	38	100%	3%	1.7%	4.5%	22.9
Lombardi et al. [26] 2020	Italy	Retrospective cohort	351	Patients aged >18 years with a diagnosis of type 2 diabetes and NAFLD	68.3	46.1%	N/A	100%	100%	28.8
Machida et al. [11] 2022	Japan	Cross-sectional	11,867	General population aged >20 years old	56.9	49.8%	22.5%	3.8%	35.8%	23.1
Onnerhag et al. [27] 2019	Sweden	Retrospective cohort	144	Patients with biopsy-proven primary NAFLD without liver disease of other etiologies	53.2	57.6%	45.8%	22.2%	100%	28
Schleicher et al. [28] 2022	Germany	Retrospective cohort	132,174	Adults (age >18 years) general population	61.4	50.9%	33.3%	11.9%	4.7%	N/A
Seko et al. [29] 2020	Japan	Retrospective cohort	344	Patients with biopsy-proven NAFLD without other liver diseases	56.8	48%	42.2%	41.6%	100%	27.2
Seo et al. [30] 2022	South Korea	Retrospective cohort	3,188	Patients aged >20 years old with a diagnosis of type 2 diabetes	56.7	46.9%	27.7%	100%	54.2%	24.3
Sesti et al. [31] 2014	Italy	Cross-sectional	570	Patients with ultrasonography-diagnosed NAFLD	54.1	55.9%	71.1%	49.8%	100%	32.3
Sinn et al. [32] 2017	South Korea	Retrospective cohort	41,430	Patients aged >18 years old	48.9	60.9%	24%	7.4%	34.3%	23.9
Sun et al. [33] 2021	USA	Cross-sectional	12,571	General population aged 20–74 years old	43.8	46.9%	24.7%	11.5%	30.1%	27.2
Wijarnpreecha et al. [34] 2017	USA	Cross-sectional	4,142	Adults aged 20–74 years with abdominal ultrasound consistent with fatty liver with no significant alcohol consumption and without other causes of liver diseases.	45.3	50.1%	31.5%	7.5%	100%	29
Xiong et al. [35] 2023	China	Cross-sectional	11,503	General population aged >35 years old	53.9	46.3%	50.6%	10.4%	N/A	24.8

BMI = body mass index; NAFLD = non-alcoholic fatty liver disease; USA = United States of America.

Table 2
Newcastle-Ottawa quality assessment of observational studies.

First author, year	Study design	Selection[a]	Comparability[b]	Outcome[c]	Total score	Result
Chen et al. [18] 2020	Cohort	***	**	**	7	Good
Ciardullo et al. [20] 2020	Cohort	***	**	***	8	Good
Hsieh et al. [23] 2020	Cohort	***	**	***	8	Good
Hu et al. [24] 2022	Cohort	***	**	***	8	Good
Kuma et al. [10] 2022	Cohort	***	**	**	7	Good
Lombardi et al. [26] 2020	Cohort	***	**	**	7	Good
Onnerhag et al. [27] 2019	Cohort	***	**	***	8	Good
Schleicher et al. [28] 2022	Cohort	***	**	***	8	Good
Seko et al. [29] 2020	Cohort	***	**	***	8	Good
Seo et al. [30] 2022	Cohort	***	**	**	7	Good
Sinn et al. [32] 2017	Cohort	***	**	**	7	Good

[a] (1) representativeness of the exposed cohort; (2) selection of the non-exposed cohort; (3) ascertainment of exposure; (4) demonstration that outcome of interest was not present at the start of the study.
[b] (1) comparability of cohorts on the basis of design or analysis, (maximum two stars).
[c] (1) assessment of outcome; (2) was follow-up long enough for outcomes to occur; (3) adequacy of follow-up of cohorts.

(≥0.5) was associated with a higher incidence of CKD when compared with a low APRI score (<0.5) (OR 1.40; 95%CI: 1.14–1.72, $p = 0.001$, $I^2 = 26\%$, random-effect model) (Fig. 3).

3.6. Meta-regression

Identification of risk factors that influence the relationship

Table 3
Modified Newcastle-Ottawa quality assessment of cross-sectional studies.

First author, year	Study design	Selection[a]	Comparability[b]	Outcome[c]	Total score	Result
Cao et al. [12] 2021	Cross-sectional	***	*	***	7	Good
Choi et al. [19] 2019	Cross-sectional	***	**	***	8	Good
Deng et al. [21] 2021	Cross-sectional	***	**	***	8	Good
Han et al. [22] 2022	Cross-sectional	***	**	***	8	Good
Kotoku et al. [25] 2021	Cross-sectional	***	**	***	8	Good
Machida et al. [11] 2022	Cross-sectional	****	**	***	9	Good
Sesti et al. [31] 2014	Cross-sectional	***	**	***	8	Good
Sun et al. [33] 2021	Cross-sectional	***	**	***	8	Good
Wijarnpreecha et al. [34] 2017	Cross-sectional	***	**	***	8	Good
Xiong et al. [35] 2023	Cross-sectional	****	**	***	9	Good

[a] (1) representativeness of the sample; (2) sample size; (3) non-respondents; (4) ascertainment of exposure (maximum four stars).
[b] (1) comparability of subjects in different outcome groups, (maximum two stars).
[c] (1) assessment of outcome; (2) statistical test (maximum three stars).

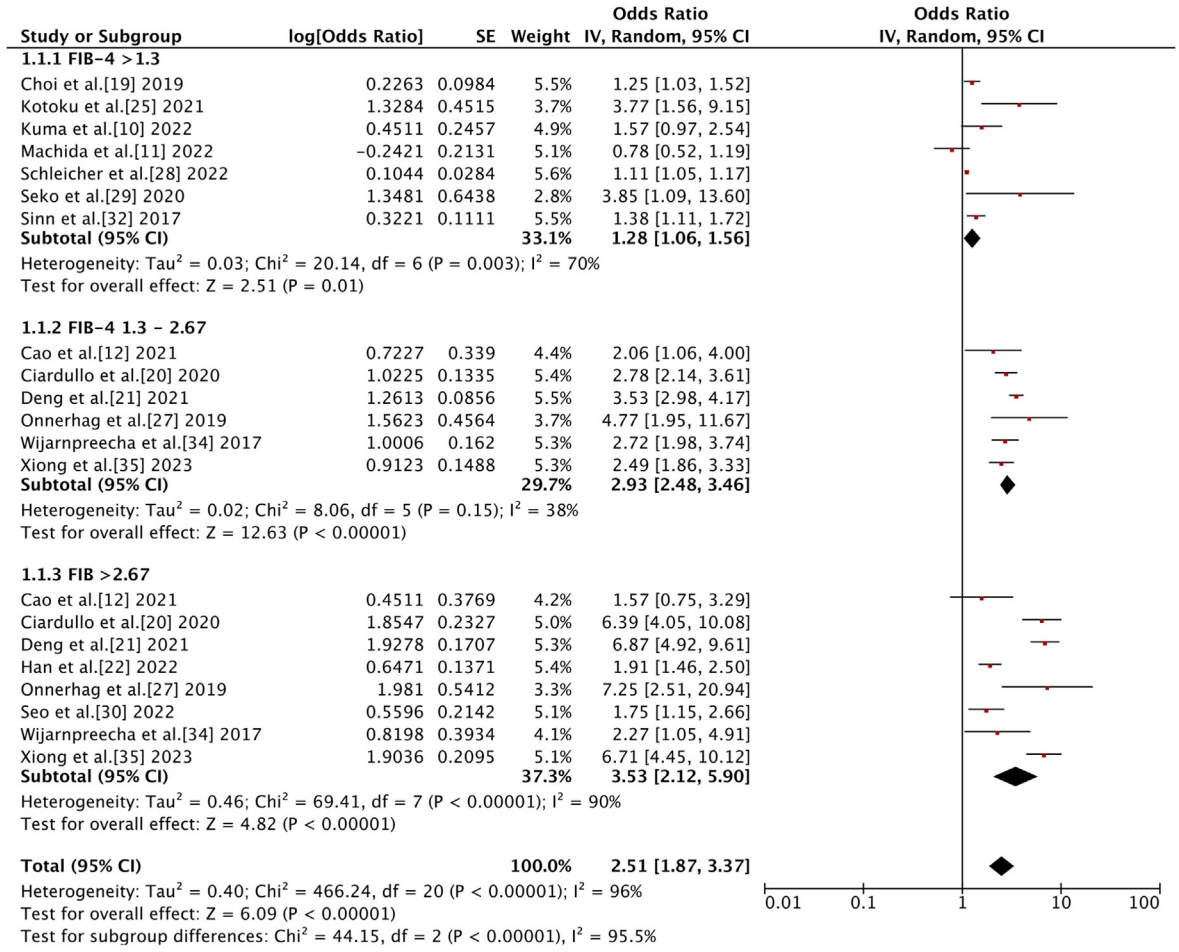

Fig. 2. Forest plot that demonstrates the association between high fibrosis-4 index (FIB-4) with the incidence of chronic kidney disease (CKD).

between non-invasive fibrosis markers (FIB-4, NFS, APRI) and the incidence of chronic kidney disease (CKD) was done with meta-regression. Our meta-regression revealed that variability in that outcome can be explained by known patient factors associated with predictors of CKD outcomes (Supplementary Table 2).

For the relationship between FIB-4 and the incidence of CKD, statistically significant associations were present for hypertension (beta coefficient: 0.0154; 95% CI: 0.0020–0.0288; $p = 0.0241$) (Supplementary Fig. 1A), NAFLD (beta coefficient: 0.0132; 95% CI: 0.0045–0.0219; $p = 0.0029$) (Supplementary Fig. 1B), and BMI (beta coefficient: 0.1477; 95% CI: 0.0519–0.2435; p=0.0025) (Supplementary Fig. 1C). From our meta-regression analysis, it was also revealed that the incidence of CKD was not significantly influenced by age (p = 0.5051) (Supplementary Fig. 1D), male sex (p = 0.6846) (Supplementary Fig. 1E), nor diabetes (p = 0.2781) (Supplementary Fig. 1F).

For the relationship between NFS and the incidence of CKD, variables such as age ($p = 0.3573$) (Supplementary Fig. 2A), male sex ($p = 0.2925$) (Supplementary Fig. 2B), hypertension (p=0.9057) (Supplementary Fig. 1C), diabetes (p = 0.1694) (Supplementary Fig. 1D), NAFLD (p = 0.0754) (Supplementary Fig. 1E), nor BMI (p = 0.2147) (Supplementary Fig. 1F) were not significantly

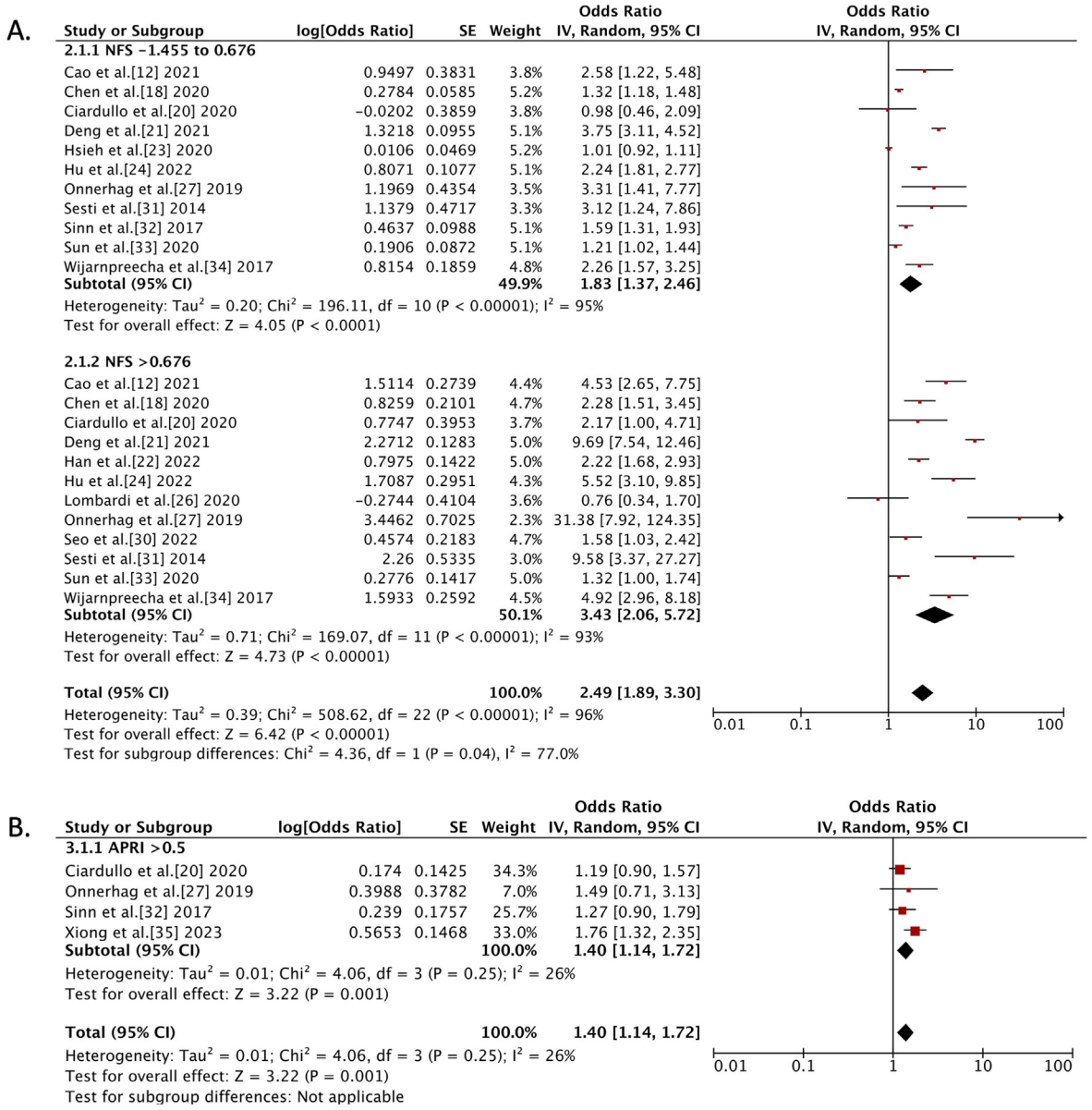

Fig. 3. Forest plot that demonstrates the association between high non-alcoholic fatty liver disease fibrosis score (NFS) (A) and aspartate aminotransferase to platelet ratio index (APRI) (B) with the incidence of chronic kidney disease (CKD).

influenced that relationship.

For the relationship between APRI and the incidence of CKD, meta-regression cannot be performed due to insufficient data and the insufficient number of included studies.

3.7. Subgroup analysis

3.7.1. Fibrosis-4 index (FIB-4)

We performed subgroup analysis based on the geographical region and populations of included studies. Subgroup analysis based on geographic region revealed that the association between high FIB-4 and incidence of chronic kidney disease (CKD) was stronger in the studies from non-Asian countries (OR 3.74; 95% CI 1.26−11.06, $p = 0.02$, $I^2 = 98\%$, random-effect modeling) than in the studies from Asian countries (OR 1.88; 95% CI 1.33−2.65, $p = 0.0003$, $I^2 = 88\%$, random-effect modeling) (Supplementary Fig. 3). Meanwhile, subgroup analysis based on the studies' populations revealed a higher odds ratio for the relationship between high FIB-4 and incidence of CKD in the NAFLD-only population (OR 3.68; 95% CI 1.80−7.53, $p = 0.0004$, $I^2 = 34\%$, random-effect modeling) than in the general population (OR 2.26; 95% CI 1.57−3.24, $p < 0.00001$, $I^2 = 96\%$, random-effect modeling) (Supplementary Fig. 4).

3.7.2. Non-alcoholic fatty liver disease fibrosis score (NFS)

We performed subgroup analysis based on the geographical region and populations of included studies. Subgroup analysis based on geographic region revealed that the association between high NFS and incidence of chronic kidney disease (CKD) was stronger in the studies from non-Asian countries (OR 4.12; 95% CI 1.65−10.26, $p = 0.002$, $I^2 = 96\%$, random-effect modeling) than in the studies from Asian countries (OR 2.18; 95% CI 1.44−3.28, $p = 0.0002$, $I^2 = 94\%$, random-effect modeling) (Supplementary Fig. 5). Meanwhile, subgroup analysis based on the studies'

populations revealed a higher odds ratio for the relationship between high NFS and incidence of CKD in the NAFLD-only population (OR 5.35; 95% CI 1.43−20.06, $p = 0.01$, $I^2 = 89\%$, random-effect modeling) than in the general population (OR 2.46; 95% CI 1.47−4.10, $p = 0.0006$, $I^2 = 97\%$, random-effect modeling) (Supplementary Fig. 6).

3.8. Publication bias

We used Funnel plot analysis for the publication bias assessment. This analysis showed a relatively symmetrical inverted plot for the incidence of CKD outcome in the FIB-4 and NFS groups (Supplementary Figs. 7A and B), indicating no publication bias. Meanwhile, for the association between APRI and incidence of CKD, publication bias assessment was not performed due to the insufficient number of studies (<10 included studies), thus assessment of publication bias is not as robust as when there were more than 10 studies.

4. Discussion

Our meta-analysis based on 21 studies has shown that the fibrosis-4 index (FIB-4), non-alcoholic fatty liver disease fibrosis score (NFS), and AST to platelet ratio index (APRI) can all be used to predict the occurrence of chronic kidney disease (CKD), where the highest odds ratio (OR) for CKD prediction was found in FIB-4, followed by NFS, and finally APRI. Further regression analysis also showed that the relationship between FIB-4 and CKD incidence was significantly influenced by hypertension, non-alcoholic fatty liver disease (NAFLD), and body mass index (BMI). Meanwhile, the relationship between NFS and CKD incidence was not influenced by confounding factors such as age, sex, hypertension, diabetes, NAFLD, or BMI. Sub-group analysis based on the studies' population showed that the relationship between high non-invasive liver fibrosis markers (FIB-4 and NFS) and the CKD incidence was found to be stronger in the NAFLD-only population than in the general population. Sub-group analysis based on the geographic region also showed that the relationship between both high FIB-4 and high NFS with CKD incidence was stronger in studies from non-Asian countries than in studies from Asian countries.

To the best of our knowledge, this is the first systematic review and meta-analysis that comprehensively discusses the ability of the non-invasive marker of liver fibrosis, namely FIB-4, NFS, and APRI to predict the occurrence of CKD. A recent updated meta-analysis by Mantovani et al. [36] only analyzed the relationship between NAFLD and CKD where the authors have found that NAFLD may increase the long-term risk of incident CKD stage ≥3 by approximately 1.45 times. However, in their study, no further analysis was carried out regarding non-invasive fibrosis markers, such as FIB-4, NFS, and APRI in predicting the occurrence of CKD [36]. Their research has also stated that further studies were still needed to see the relationship between the severity of NAFLD and the risk of CKD incidence [36]. Therefore, our research presents to fill the remaining knowledge gaps from the existing meta-analyses. Another meta-analysis by Ciardullo et al. [37] analyzed the relationship between non-invasive liver fibrosis assessment using vibration-controlled transient elastography (VCTE) and the incidence of CKD in patients with NAFLD. However, there was no data regarding FIB-4, NFS, and APRI in their study [37]. Even though VCTE is considered a non-invasive method, not all institutions or hospitals have this tool. In addition, the relatively expensive price may also limit the use of this tool to determine the degree of liver fibrosis.

On the other hand, fibrosis-4 index (FIB-4) is another non-invasive marker of liver fibrosis that has higher applicability because it only requires data on age, platelet count, AST, and ALT which can be obtained through a simple laboratory test so that it can be done in almost all healthcare facilities [13]. The same is also true for NFS and APRI which only require data on demographic characteristics such as age, BMI, and simple laboratory values [13]. There are several reasons underlying the relationship between liver fibrosis and CKD. First, in NAFLD with significant fibrosis, activation of the NF-κB pathway can enhance the transcription of pro-inflammatory genes that cause systemic inflammation and may lead to CKD [38,39]. Second, an increased risk of atherosclerotic diseases, such as renal endothelial dysfunction and renovascular damage, is closely linked to atherogenic dyslipidemia, a key feature of NAFLD that is characterized by increased small, dense LDL cholesterol, low high-density lipoprotein (HDL) cholesterol, and high levels of triglycerides [39−42]. Finally, increased procoagulant and profibrogenic factors in NAFLD can contribute to the development of CKD by increasing vascular endothelial damage and accelerated atherosclerosis [39−42].

5. Limitations

This study is not without limitations. First, the observational design used in the included research precludes the establishment of causation. Second, although the majority of the studies that were included in the analysis corrected the findings for age, gender, hypertension, diabetes, obesity, and other traditional CKD risk factors, it is still possible that some residual confounding from unmeasured variables could have occurred. Finally, notable heterogeneity was found in the outcome of interest in this study which may be due to differences in the proportion of patients with NAFLD or metabolic disorders as well as differences in the duration of follow-up. Therefore, the results from this meta-analysis should be interpreted with caution. Nevertheless, we still believe that the results from our systematic review and meta-analysis can provide further insight into better risk stratification and management of both NAFLD and CKD.

6. Conclusions

Our systematic review and meta-analysis have shown that the fibrosis-4 index (FIB-4), non-alcoholic fatty liver disease fibrosis score (NFS), and AST to platelet ratio index (APRI) can be used to predict the incidence of chronic kidney disease (CKD) where a high value of these scores are associated with a higher risk of CKD, especially in non-Asian populations and populations of patients with NAFLD.

Our study suggests that these non-invasive liver fibrosis markers can be routinely measured to enable better risk stratification and early detection of CKD, especially in the populations of patients with NAFLD.

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Ethics approval

This is a systematic review and meta-analysis study. The Faculty of Medicine, Pelita Harapan University Research Ethics Committee has confirmed that no ethical approval is required.

Consent to participate

Not applicable.

Consent to publish

Not applicable.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article [and/or] its supplementary materials.

Author contributions

Conceptualization: Rudi Supriyadi, Theo Audi Yanto, Timotius Ivan Hariyanto; Methodology: Timotius Ivan Hariyanto; Formal analysis and investigation: Rudi Supriyadi, Theo Audi Yanto, Timotius Ivan Hariyanto; Writing - original draft preparation: Timotius Ivan Hariyanto; Writing - review and editing: Rudi Supriyadi, Theo Audi Yanto; Funding acquisition: Rudi Supriyadi, Theo Audi Yanto; Resources: Timotius Ivan Hariyanto; Supervision: Rudi Supriyadi, Theo Audi Yanto.

Declaration of competing interest

The authors declare no conflict of interest regarding this article.

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None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2023.102814.

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