

Fibrosis-4 index and mortality in coronavirus disease 2019: a meta-analysis

Raymond Pranata^a, Emir Yonas^b, Ian Huang^c, Michael Anthonius Lim^a, Sally Aman Nasution^d and Raden Ayu Tuty Kuswardhani^e

Background/aims In this meta-analysis, we aimed to evaluate the prognostic value of fibrosis-4 index (FIB-4) in COVID-19.

Methods We performed a comprehensive literature search of PubMed, Embase, and Scopus databases on 26 November 2020. FIB-4 was calculated by $[\text{age (years)} \times \text{AST (IU/L)}] / [\text{platelet count (10}^9/\text{L)} \times \sqrt{\text{ALT (U/L)}}]$. A value above cutoff point was considered high and a value below cutoff point was considered low. The main outcome was mortality, the association between high FIB-4 and mortality was reported in odds ratio (OR). Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic OR (DOR), area under the curve (AUC) were generated.

Results There were 963 patients from five studies included in this systematic review and meta-analysis. Meta-analysis showed that high FIB-4 was associated with increased mortality [OR 3.96 (2.16–7.27), $P < 0.001$; I^2 : 41.3%]. High FIB-4 was associated mortality with a sensitivity of 0.56 (0.40–0.70), specificity of 0.80 (0.72–0.86), PLR 2.8 (1.8–4.2), NLR 0.55 (0.39–0.78), DOR 5 (2–10), and AUC of 0.77 (0.73–0.81). Fagan's nomogram indicated that for a pre-test probability (mortality) of 30%, a high FIB-4 was associated with 54% post-test probability and a low FIB-4 was associated with 19%, respectively. The funnel-plot analysis was asymmetrical, trim-and-fill analysis by imputation of a study on the left side using linear estimator resulted in an OR of 3.48 (1.97–6.14). Egger's test showed no indication of small-study effects ($P = 0.881$).

Conclusion High FIB-4 was associated with mortality in patients with COVID-19. *Eur J Gastroenterol Hepatol* 33: e368–e374
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Introduction

Coronavirus disease 2019 (COVID-19) has a broad spectrum of clinical manifestations, ranging from asymptomatic to mild and severe conditions, which could culminate into acute respiratory distress syndrome (ARDS) and lethal multi-organ failure. With the current COVID-19 pandemic, reports show approximately 2% of patients with COVID-19 had underlying chronic liver disease. As with other preexisting comorbidities such as obesity, diabetes, and heart failure, this condition is also thought to influence the outcome of COVID-19 [1–3]. Additionally, SARS-CoV-2 is thought to interact with liver tissue, as data from previous SARS family of virus outbreak shows liver damage as one of the complications of infections [4,5]. Liver injury is of concern because it is shown to be associated with severe COVID-19 and poor outcomes [6].

Using a simple noninvasive clinical scoring system that could help identify and predict disease severity is crucial

in this pandemic. Early identification of high-risk patients could help clinicians in triage and respiratory support allocation. The fibrosis-4 index (FIB-4) scoring system was initially developed as an efficient and readily available tool to identify liver fibrosis in patients with chronic viral hepatitis [7]. This system uses routine laboratory values and clinical measurement to calculate the severity of liver impairment, the variables are age, AST, ALT, and platelet count [8]. This scoring system was superior to NFS and BARD scores in assessing NAFLD patients, with a 80% positive predictive value and 90% negative predictive value [9]. With these potential benefits, this scoring will serve as an ideal noninvasive test for assessment of hepatic fibrosis, which is sensitive, specific, and applicable across all chronic liver diseases. Interestingly, FIB-4 has been shown to be a useful risk stratification tool in patients with known liver disease and various extra-hepatic associated conditions, including atrial fibrillation and intracerebral hemorrhage [10,11]. Moreover, this simple scoring system has been recently reported to be associated with ICU admission in patients with COVID-19 [12].

This meta-analysis aimed to explore the association between the FIB-4 index and the risk of mortality among COVID-19 patients. We seek to evaluate whether the FIB-4 index could serve as a simple and effective prognostication tool in patients with COVID-19.

Material and methods

This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses reporting guidelines. The protocol for this study is registered in PROSPERO (CRD42020223023).

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Keywords: COVID-19, death, fibrosis-4 index, prognosis, severe

^aFaculty of Medicine, Universitas Pelita Harapan, Tangerang, ^bFaculty of Medicine, Universitas YARSI, Jakarta, ^cDepartment of Internal Medicine, Faculty of Medicine, Universitas Padjadjaran, Hasan Sadikin General Hospital, Bandung, ^dDivision of Cardiology, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia/Cipto Mangunkusumo National General Hospital, Jakarta and ^eDivision of Geriatrics, Department of Internal Medicine, Faculty of Medicine, Udayana University, Sanglah Teaching Hospital, Denpasar - Bali, Indonesia

Correspondence to Raymond Pranata, MD, Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Banten 15810, Indonesia
Tel: +6282112918892; e-mail: raymond_pranata@hotmail.com

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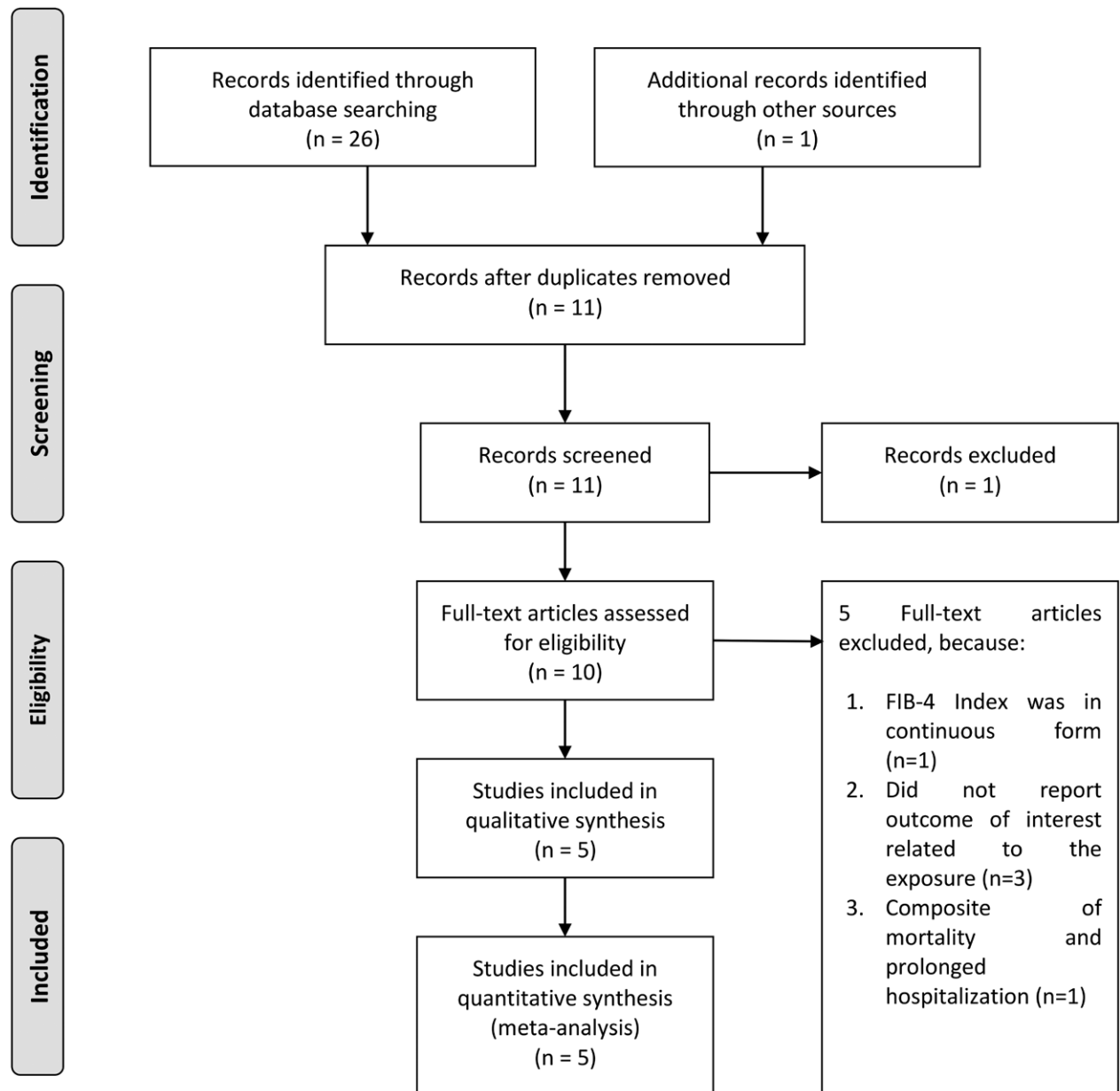


Fig. 1. PRISMA flowchart. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

Table 1. Baseline characteristics of the included studies

Authors	Design	Population	Sample	FIB-4 cutoff value	Mean/median age (years)	Male (%)	CLD (%)	NOS
Forlano et al. (2020)	RO	OR was calculated for NAFLD Cohort	61 (NAFLD)	>3.25	60	60	NAFLD	8
Li et al. (2020)	RO	COVID-19 patients	202	>2.67	58	54	32.2	8
Lopez-Mendez et al. (2020)	RO	COVID-19 >18 years old	155	>3.25	51	72	1.3	6
Park et al. (2020)	RO	COVID-19 receiving respiratory support (low or high dose oxygen)	289	>4.95	72	46	5.2	8
Sterling et al. (2020)	RO	COVID-19 patients	256	>2.67	58	43	5.9	8

CLD, chronic liver disease; FIB-4, fibrosis-4 index; NAFLD, nonalcoholic fatty liver disease; NOS, Newcastle–Ottawa Scale; RO, retrospective observational.

Eligibility criteria

The inclusion criteria were prospective and retrospective observational studies in the form of research articles or research letters, reporting (1) COVID-19 patients, (2) FIB-4, and (3) mortality as an outcome. The main outcome was mortality, defined as death/non-survivor. The

key exposure was high FIB-4, and the control was low FIB-4.

The exclusion criteria were commentaries, review articles, preprints, non-research letters, case reports, studies that did not report the outcome/exposure, and articles in non-English Language. Preprints were excluded due to varying credibility [13].

Fibrosis-4 Index and Mortality

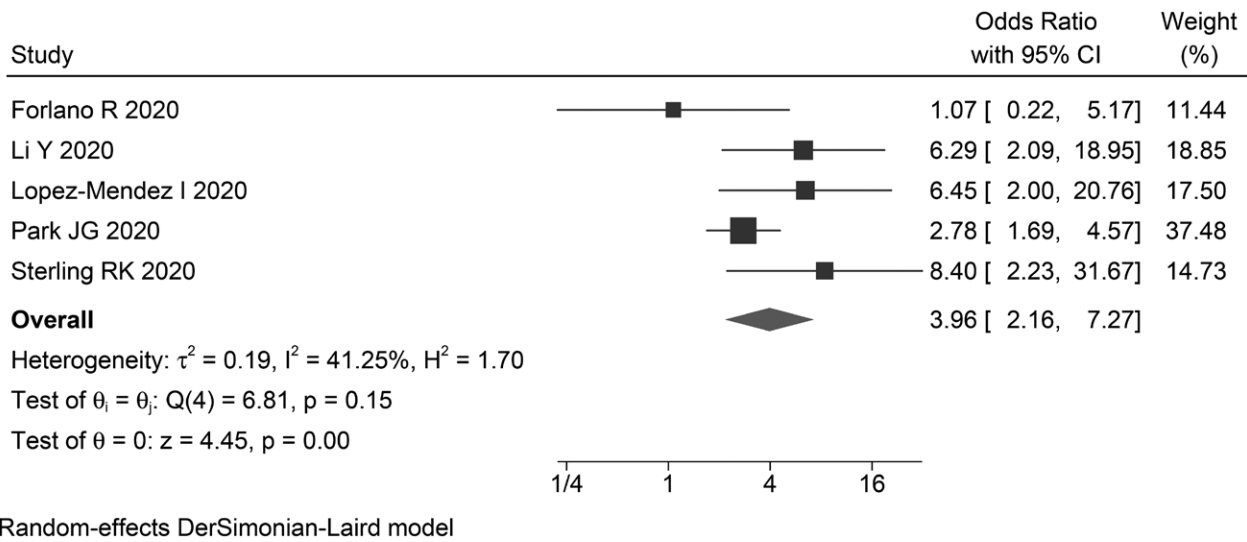


Fig. 2. Fibrosis-4 Index (FIB-4) and mortality in COVID-19.

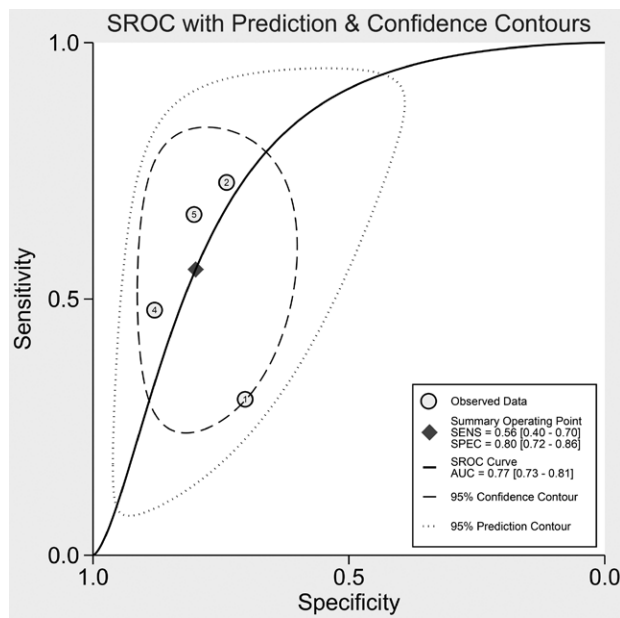


Fig. 3. SROC with prediction & confidence contours for high FIB-4 and mortality.

Search strategy and study selection

We performed a comprehensive literature search of PubMed, Embase, and Scopus databases using keywords ‘SARS-CoV-2’ OR ‘COVID-19’ OR ‘2019-nCoV’ AND ‘fibrosis-4 index’ OR ‘FIB-4’ on 26 November 2020. The PubMed (MEDLINE) search strategy was [(SARS-CoV-2) OR (COVID-19) OR (2019-nCoV)] AND [(fibrosis-4) OR (FIB-4)]. Two independent authors screened the title/abstracts after the removal of duplicates. Ineligible studies were excluded, and the full-texts of potentially relevant articles were assessed.

Data extraction

Data extraction from the eligible studies was performed by two independent authors using standardized extraction forms containing information on first author, study

design, year of publication, patients’ characteristics, FIB-4 cutoff value, and mortality.

FIB-4 was calculated by [age (years) × AST (IU/L)]/[platelet count (10⁹/L) × √ALT (U/L)]. A value above cutoff point was considered high and a value below cutoff point was considered low. The main outcome was mortality, the association between FIB-4 and mortality was reported in odds ratio (OR). Sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic OR (DOR), area under the curve (AUC) were generated for the association between FIB-4 and mortality.

Risk of bias and quality assessment was performed using the Newcastle–Ottawa Scale by two independent authors. Any discrepancies were resolved by discussion.

Statistical analysis

STATA 16 (StataCorp LLC, College Station, Texas, USA) was used to perform meta-analysis. A meta-analysis of proportion was performed for mortality in the included studies. We pooled the ORs using the DerSimonian and Laird random-effects model, regardless of heterogeneity, and the effect estimate was reported in ORs and its 95% confidence interval. A *P*-value of ≤0.05 was considered statistically significant. Heterogeneity among the included studies was assessed using the *I*² and Cochrane *Q* test, where a value of >50% or *P*-value <0.10 indicates heterogeneity. Publication bias and small-study effects were assessed by funnel-plot analysis and Egger’s test. Trim-and-fill analysis was performed using linear estimator. Sensitivity analysis was performed by excluding studies with 100% liver disease. Sensitivity, specificity, PLR, NLR, DOR, AUC, and corresponding Fagan’s nomogram were generated.

Results

There were 963 patients from five studies included in this systematic review and meta-analysis (Fig. 1) [14–18]. Baseline characteristics of the included studies are displayed in Table 1. All studies reported mortality as their outcome. The mortality rate in the included studies was 30%.

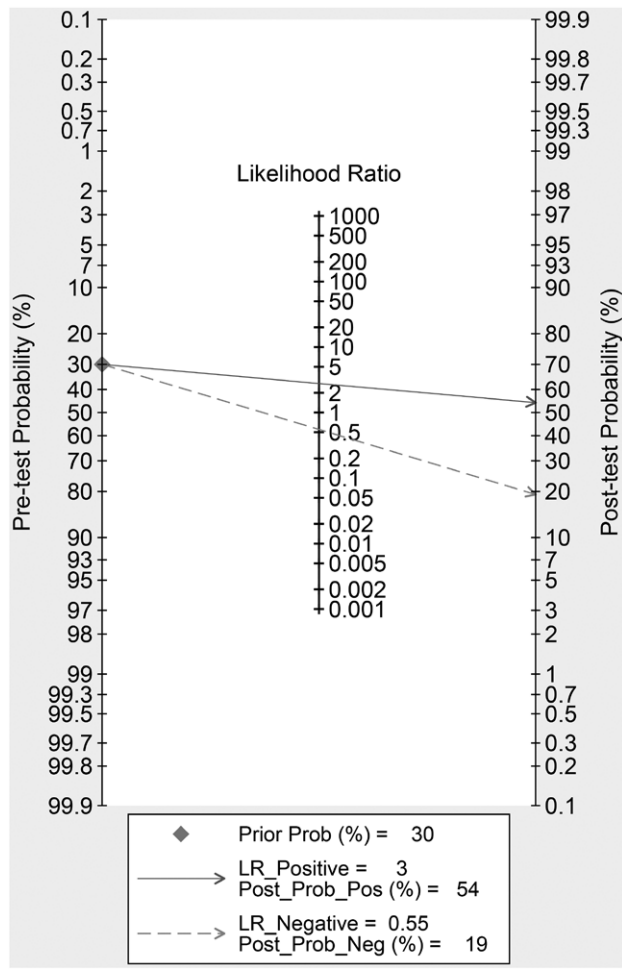


Fig. 4. Fagan's nomogram for high FIB-4 and mortality

Meta-analysis showed that high FIB-4 was associated with increased mortality [OR 3.96 (2.16–7.27), $P < 0.001$; $I^2: 41.3\%$, $P = 0.146$] (Fig. 2). Sensitivity analysis by excluding Forlano *et al.*, whose study include only patients with NAFLD, high FIB-4 remained significant [OR 4.49 (2.53–7.98), $P < 0.001$; $I^2: 33.1\%$, $P = 0.214$]. High FIB-4 was associated mortality with a sensitivity of 0.56 (0.40–0.70), specificity of 0.80 (0.72–0.86), PLR 2.8 (1.8–4.2), NLR 0.55 (0.39–0.78), DOR 5 (2–10), and AUC of 0.77 (0.73–0.81) (Fig. 3). Fagan's nomogram indicate that for a pre-test probability (mortality) of 30%, a high FIB-4 was associated with 54% post-test probability and a low FIB-4 was associated with 19% post-test probability (Fig. 4). Deek's asymmetry test was NS for publication bias ($P = 0.26$). The funnel-plot analysis showed asymmetrical shape, indicating possible publication bias (Fig. 5a). Trim-and-fill analysis by imputation of a study on the left side using linear estimator resulted in an OR of 3.48 (1.97–6.14) (Fig. 5b). Egger's test showed no indication of small-study effects ($P = 0.881$).

Discussion

This meta-analysis indicates that high FIB-4 was associated with increased mortality in patients with COVID-19 with 56% sensitivity and 80% specificity. The finding has a moderate heterogeneity possibly due to (1) different

cutoff points and (2) different proportions of patients with comorbidities.

COVID-19 primarily causes organ damage due to the exaggerated immune response to the virus [19]. High liver function tests, including AST, ALT, GGT, and total bilirubin, are often reported in hospitalized patients with SARS-CoV-2 infection, reinforcing suspicion of varying degree of liver damage in patients with COVID-19 [20,21]. These simple parameters are among the most frequently offered on admission as well as complete blood count, in which a decrease in leukocyte and thrombocyte counts is commonly found in COVID-19 patients [22,23]. Such abnormalities in laboratory values are associated with increased severity and mortality in patients with COVID-19 diagnosis. Cytokine storm, characterized by the excessive release of inflammatory cytokines, such as interleukins, lactate dehydrogenase, C-reactive protein, and D-dimer, are postulated as an underlying mechanism for the development of life-threatening complications, such as ARDS, coagulopathy, and multi-organ dysfunction [6,19,24]. Elderly population is at a higher risk of developing severe SARS-CoV-2 infection, partly because of increasing age and the high prevalence of comorbidities and frail conditions [25–27].

The use of various scoring systems has been increasingly popular to predict the outcomes of COVID-19. Considering the high incidence of liver injury associated with SARS-CoV-2, simple parameters such as De Ritis Ratio and FIB-4 are often utilized to predict the need for mechanical ventilation or ICU stay [12,14,28].

The results of this meta-analysis confirm that the presence of liver impairment is associated with a poorer prognosis in COVID-19 patients. This impairment can be further quantified and staged using FIB-4 scoring system, even though this scoring system was initially designed for chronic liver disease population secondary to viral infection. In this study, we repurpose the use of FIB-4 as a prognostication tool in patients with COVID-19. Despite the limited amount of studies available for our meta-analysis and difference in cutoff points, we did not encounter a significant amount of heterogeneity in our analyses.

We found that the study by Forlano *et al.* displays unequivocal results related to mortality. It is interesting to note that all of the subjects included in this study have NAFLD. Due to the differing characteristic in Forlano *et al.*, we performed sensitivity analysis by excluding this study. An in-depth assessment of this particular study reveals that NAFLD was not associated with mortality in COVID-19 patients. FIB-4 score >1.45 and >3.25 were also not associated with mortality in COVID-19 patients. However, data for both of these scoring results were impaired by the significant amount of missing data for FIB-4 scores in subjects of this study (37%) [18]. The amount of missing data in this variable exceeded the threshold of missing data of 10% in which there is a high possibility that the results of this analysis will be statistically biased [29]. In patients with chronic liver disease, an inherent perpetual inflammation occurs in the liver, which ultimately causes fibrosis in the end-stage of the disease. This inflammation is further exaggerated with SARS-CoV-2 virus, which might explain liver damage in some patients, and poorer prognosis in COVID-19 patients with chronic liver disease

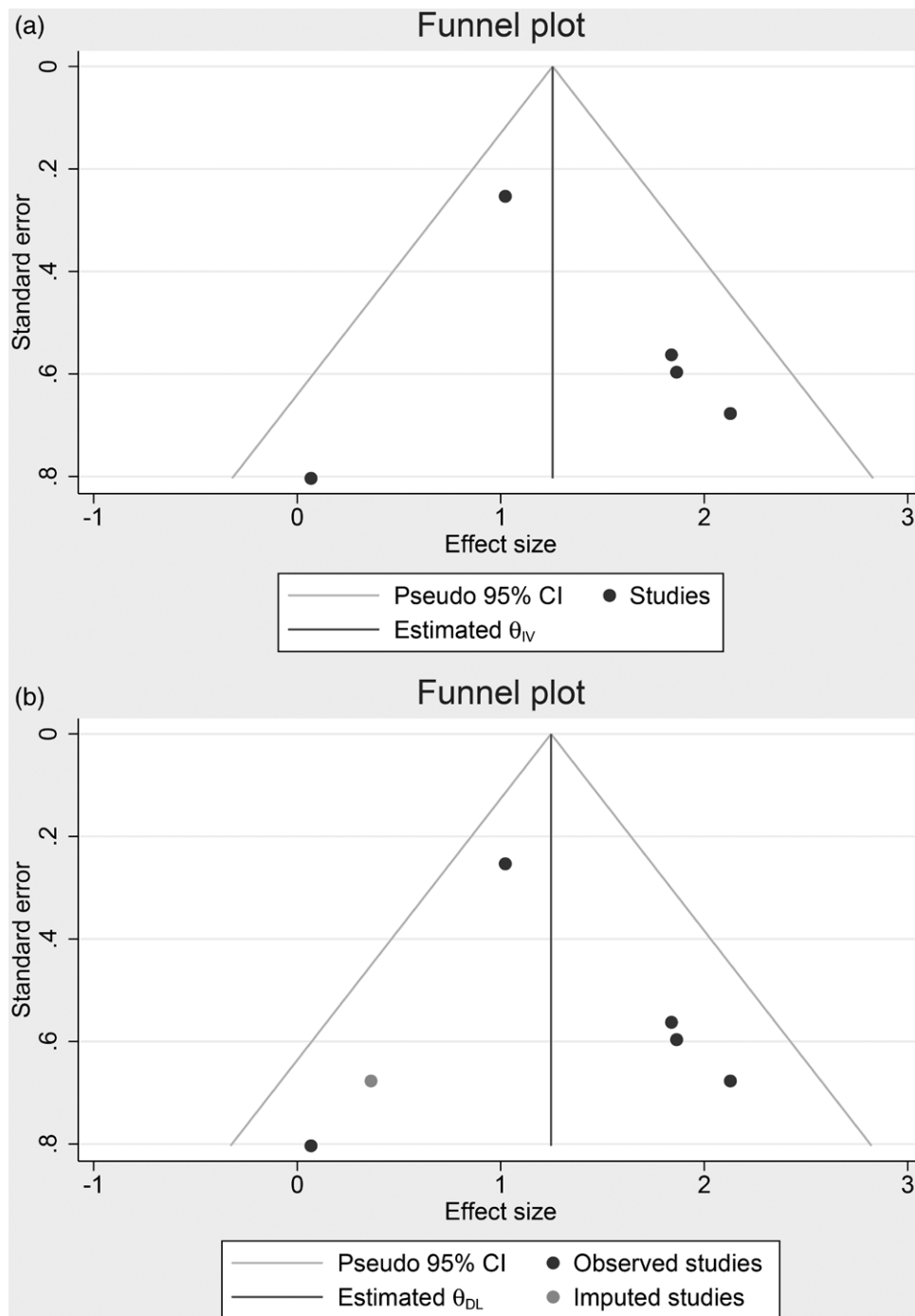


Fig. 5. Publication bias. Funnel-plot (a) and trim-and-fill analysis (b).

[30]. However, the study by Forlano *et al.* indicates that the COVID-19 severity in NAFLD patients was not due to the underlying liver disease’s severity but instead attributed to other factors. FIB-4 use was applicable in studies with a low proportion of chronic liver disease patients. The strongest association between FIB-4 and mortality is found in Sterling *et al.*, who enrolled only 5.9% of patients with chronic liver disease. One of the excluded studies was Xiang *et al.* which was excluded due to composite endpoint (death or prolonged hospitalization), rather than death/mortality alone. The study indicated that FIB-4 was independently associated with progression to severe disease and death or prolonged hospitalization [31]. Thus

FIB-4 might be repurposed for COVID-19 prognostication, regardless of the presence or absence of liver diseases.

Clinical implications

FIB-4 is a marker of liver fibrosis, however, it can be repurposed into a prognostication tool for patients with COVID-19 regardless of prior history of liver disease. Determining the optimal FIB-4 cutoff point requires further investigation. The studies included in this meta-analysis indicates that a cutoff point of as low as >2.67 is adequate for prognostication in patients with COVID-19. Despite varying cutoff points, the heterogeneity was not

substantial. There is a potential difficulty in interpreting FIB-4 because platelet count often varies in patients with COVID-19 due to other causes than liver fibrosis, nevertheless, this repurposed score has shown to be useful regardless of prior history of liver disease.

Limitations

Our analysis has several limitations, we were unable to dismiss the possibility of publication bias using our funnel-plot analysis, however, our egger's test showed no indication of small-study effects. Trim-and-fill analysis indicates that hypothetical studies' imputation to achieve a symmetrical funnel-plot resulted in a significant association, albeit slightly weaker. We also acknowledge the limited data and studies available to use in this meta-analysis.

Conclusion

High FIB-4 was associated with mortality in patients with COVID-19.

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Data availability: Available on reasonable request.

The guidelines of the PRISMA 2009 Statement have been adopted; the protocol for this review is registered in PROSPERO (CRD42020223023).

All data generated or analyzed during this study are included in this published article.

Conflicts of interest

There are no conflicts of interest.

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