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Review Article

Serum YKL-40 Levels as a Non-Invasive Potential Biomarker for Liver Fibrosis Patients: A Systematic Review and Meta-Analysis

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Abstract

Background: This research's comprehensive review and meta-analysis seek to offer additional non-invasive techniques for diagnosing and monitoring liver fibrosis, thereby serving as a dependable resource for clinical practice and scientific investigation.

Methods: To find pertinent research on the use of serum YKL-40 levels in liver fibrosis patients, databases including PubMed, Web of Science, WILEY ONLINE LIBRARY, Scopus, Embase, Cochrane Library, Science Direct, CNKI, Wanfang Data, VIP Information, and the China Biology Medicine Library System were searched. The search was conducted up to May 2024.

Results: In studies comparing serum YKL-40 levels in patients with hepatic fibrosis and controls, the overall combined difference was 1.37 (0.66, 2.08), with the Chinese subgroup showing high heterogeneity, while the Egyptian study did not show heterogeneity. A total of 17 studies, including 2554 patients, were included. The combined sensitivity for diagnosing advanced fibrosis and severe fibrosis was 0.80 and 0.78 respectively, with specificities of 0.88 and 0.82. The AUC for advanced fibrosis and severe fibrosis were 0.91 and 0.87 respectively.

Conclusion: Serum YKL-40 shows potential value in diagnosis of liver fibrosis, but further clinical research is needed to confirm and improve its utility.

Keywords: Liver fibrosis; Biomarkers; Meta-analysis

Introduction

Liver fibrosis, a significant issue arising from long-term liver conditions, often necessitates invasive procedures like liver biopsies for accurate diagnosis. Nonetheless, identifying non-invasive biomarkers is essential for the early detection and tracking of liver fibrosis progression. Blod concentrations of YKL-40 (Chitinase-3-like protein 1) have been identified as a valuable indicator for evaluating the status of individuals with liver fibrosis (1). YKL-40 is an extracellular matrix protein whose level is closely associated with inflammatory response and cell proliferation. YKL-40 plays a crucial role in various biological functions, including tissue repair, pathogen defense, and the differentiation of macrophages (2). Higher serum YKL-40 levels are associated with in-

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creased severity and advancement of liver fibrosis, implying it could be a non-invasive biomarker for diagnosing liver fibrosis in patients (3). Tracking YKL-40 concentrations enables physicians to identify liver fibrosis sooner and modify treatment strategies promptly, thereby enhancing patient survival rates and quality of life (4). Serum YKL-40 levels hold significant potential as a non-invasive biomarker for liver fibrosis patients. However, additional research is required to confirm their precision and dependability, thereby enhancing their use in medical practice.

According to the WHO, about 200 million people worldwide are affected by chronic liver disease, and about 20% of those with chronic liver disease develop liver fibrosis (5). According to data from global epidemiological studies, the prevalence of liver fibrosis varies significantly across regions and populations. The Asia-Pacific region, especially China and India, has a high prevalence of liver fibrosis and cirrhosis, and hepatitis B and C virus infections remain one of the leading causes of liver fibrosis. According to a China-based national survey, the prevalence of fibrosis is about 2.85%, and China is projected to have the largest number of NAFLD patients by 2030, with 314.58 million cases (6).

Despite the recent advances in the use of serum markers in the diagnosis of hepatic fibrosis, there are still many gaps and uncertainties in the existing literature regarding the use of YKL-40 in hepatic fibrosis. The potential of YKL-40 as a marker in some chronic diseases has been initially demonstrated, but there is still a lack of sufficient systematic studies and comprehensive evaluation of its diagnostic efficacy in hepatic fibrosis.

This research sought to systematically review and conduct a Meta-analysis to determine the significance of serum YKL-40 levels as a non-invasive biomarker for liver fibrosis in patients. The particular aims of the study were: 1) to compile and evaluate existing research to determine variations in serum YKL-40 levels among liver fibrosis patients; 2) to investigate the correlation between YKL-40 concentrations and the extent of liver fibrosis; 3) to evaluate the diagnostic precision and potential clinical applications of YKL-40 as a biomarker for liver fibrosis.

Methods

Search strategy

This systematic review has been performed and written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (7). Electronic searches were conducted on PubMed, Web of Science, Wiley Online Library, Scopus, Embase, Cochrane Library, Science Direct, CNKI, Wanfang Data, VIP Information, and the China Biology Medicine Library System, utilizing both subject-specific and free-text terms tailored to each database's features. The search was conducted from the time of database construction to May 2024. The English search formula: ("Serum YKL-40 levels" OR "YKL-40" OR "Chitinase-3-like protein 1" OR "CHI3L1") AND ("Liver Fibrosis" OR "Cirrhosis") AND ("Diagnosis" OR "Biomarker"). A manual search of the reference lists of potentially relevant studies was conducted to determine if any studies may have been overlooked.

Exclusion Criteria

Eligible studies were those involving patients with liver fibrosis, utilizing both YKL-40 testing and liver biopsy as a reference standard, and published in peer-reviewed journals or presented at conferences. Prognostic studies were excluded. The research exclusively focused on adult individuals (18 yr and older) diagnosed with liver fibrosis. Study groups consisting of patients with mixed etiologies were excluded if data on patients with liver fibrosis were not reported separately. The possibility of patient group overlap across studies was carefully examined and verified with the researchers. If patient groups overlapped between studies, the largest study was selected. Eligible studies were those that utilized liver biopsy as the clinical reference standard. This study included research that offered information on true-positive (TP), false-positive (FP), true-negative

(TN), and false-negative (FN) outcomes of YKL-40 assays or permitted data reconstruction from classification tables.

According to the METAVIR scoring system similar to the fibrosis scoring system, which consists of 5 stages: stage 0 = no fibrosis, stage 1 = any localized fibrosis but no septa, stage 2 = few septa, stage 3 = many septa, and stage 4 = cirrhosis. The METAVIR and Batts-Ludwig scoring systems define severe fibrosis and advanced fibrosis as F2-F4, and F3-F4 (8).

Data extraction as well as quality assessment

Two authors independently reviewed the identified titles and abstracts to determine potential eligibility of the studies. The two writers subsequently assessed complete articles detailing potentially qualifying studies to reach a final inclusion decision. The title and abstract screening phase were conducted using ENDNOTE X9. Any disagreements were discussed and resolved by the two lead authors, and when inconclusive, the judgment of the third author was decisive. One author extracted the subsequent information from the included studies, then verified by another author: details of the studies, characteristics of the study groups, attributes of the reference tests, features of the index tests, and the data necessary for reconstructing the 2×2 concordance tables (TP, FP, TN, FN).

Risk of bias assessment

Two primary authors independently evaluated the potential bias and relevance of each study included, utilizing the QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies) instrument within Review Manager 5.4 (9). Any conflicts of opinion were discussed and resolved or discussed with a third author. In this study, we used the Version 1 of the Cochrane Risk of Bias Assessment Tool (ROB 1) to classify the risk of bias of the included studies. We assessed six aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete data reporting, and selective reporting, and judged the overall risk of bias of each study based on the results of the assessment of each aspect, and the overall risk of bias was low if the majority of the aspects were low-risk; it was judged as high risk if there were multiple high-risk aspects; and it was judged as unclear risk if there were multiple unclear or mixed risks, so as to ensure the scientific and accurate risk classification of the studies and enhance the reliability of the results. If there are multiple high-risk aspects, the risk is judged as high risk; if multiple aspects are unclear risk or mixed risk, the risk is judged as unclear risk, so as to ensure the scientific and accuracy of the risk classification of the study, and to enhance the reliability of the study results.

Statistical analysis

All meta-analyses were performed by RevMan 5.4 software. Continuous data using different scales or units were summarized using Standard mean deviation (SMD) and 95% confidence interval (CI). Data from eligible studies were synthesized using a random-effects model because random-effects models are considered to be more conservative and reliable than fixed-effects models and produce wider 95% CI for combined-effects estimates and reduce the probability of type I error. In this study, the SMD of 95% CI was calculated to investigate the difference between serum YKL-40 concentrations between patients with liver fibrosis and non-hepatic fibrosis controls. Heterogeneity between studies was assessed using Q-test and I^2 statistical test. I^2 values greater than 50% or *P*-values less than 0.05 indicated significant heterogeneity.

Publication bias was evaluated using Deeks' funnel plot asymmetry test and STATA software. When the funnel plot showed significant asymmetry or Deeks' test indicated a *P*-value less than 0.05, it suggested the presence of publication bias. Pooled likelihood ratios were used to determine the posttest probability.

Ethical approval

As this study involves the summary and analysis of other studies, it does not involve medical ethics approval or patient-informed consent.

Results

Basic characteristics of the included literature

Out of 495 papers initially reviewed, 341 were removed due to duplication, 92 were excluded after evaluating titles and abstracts, 62 underwent full-text screening, and ultimately, 17 papers qualified for meta-analysis, as detailed in Table 1 (10-26). The sample size comprised 2554 specimens, with 14 in English and 3 in Chinese; 13 studies originated from China, 2 from Japan, 1 from Brazil, and 1 from Egypt; the average age was 46 yr, and the majority were men. Sensitivity and specificity of hepatic fibrosis S1 was documented in one document (10), hepatic fibrosis S2 in one document (10), hepatic fibrosis S4 in two documents (12, 19), hepatic fibrosis S2-S3 in two documents (12, 15), hepatic fibrosis S2-S4 in seven documents (11, 13, 22, 23, 24), and another five documents documented hepatic fibrosis S3 -S4 sensitivity and specificity (10, 14, 17, 18, 20) (Fig. 1).

Table 1: Basic characteristics of the included literature

Author	Year	Country	Years of research	Sample size	Age(yr)	Gender (male)	Type of research
Bao J(10)	2022	China	2019-2020	96	49.00	49	-
Zhang F(11)	2023	China	2017-2021	105	45.51	48	Cross-Sectional Study
Li H(12)	2018	China	2015-2017	228	42.27	-	-
Li Y(13)	2022	China	2018-2019	78	41.73	47	-
Yan L(14)	2018	China	2015-2017	307	37.54	224	RCT
Jiang Z(15)	2020	China	2018-2019	50	39.83	15	-
Jin X(16)	2020	China	2016-2018	134	39.00	90	-
Huang H(17)	2015	China	2012-2013	98	-	-	prospectively enrolled
Kumagai E(18)	2016	Japan	-	111	55	-	Multivariate analysis
Schiavon LL(19)	2008	Brazil	-	85	44.9	-	-
Qiu H(20)	2022	China	2018-2019	132	57	85	RCT
Saitou Y(21)	2005	Japan	-	109	54	62	-
Hu Z(22)	2024	China	2018-2019	69	42.81	45	prospectively enrolled
Lin C(23)	2021	China	2018-2019	524	56.25	302	prospectively enrolled
Li Y(24)	2021	China	2019	70	-	-	RCT
Huang Q(25)	2021	China	2019-2020	270	36.6	72.6	RCT
Toson E(26)	2016	Egypt	-	91	-	-	-

Quality assessment

For the four randomized clinical trials included in this study, we utilized the Cochrane Risk of Bias Assessment Tool to classify the risk of bias as shown in Fig. 2. For the remaining non - randomized studies, we employed the Newcastle - Ottawa Scale (NOS) for cross - sectional studies to assess their quality (Table 2).

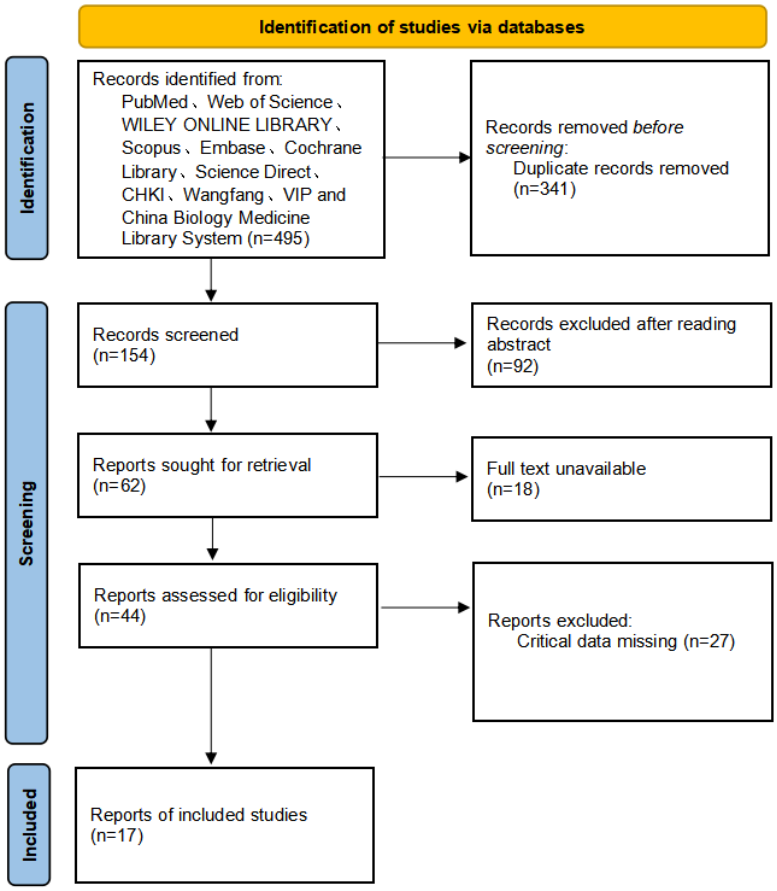

Fig. 1: Flowchart for inclusion of literature

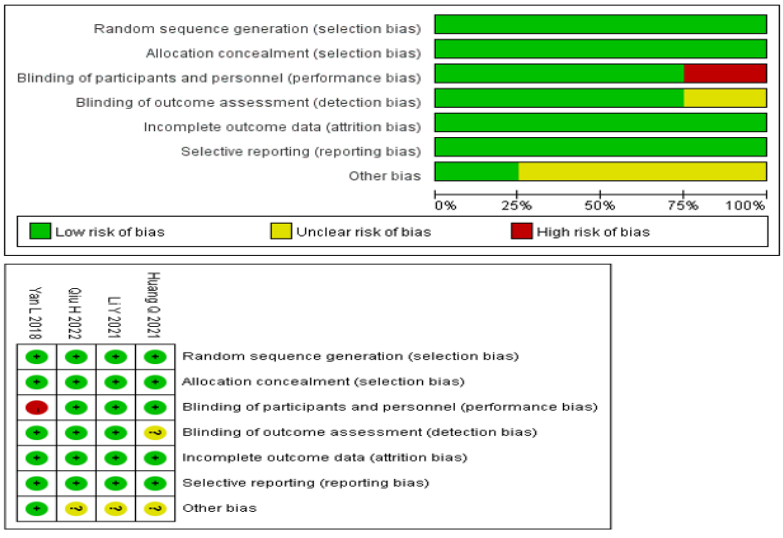

Fig. 2: Quality assessment of included studies

Table 2: Literature quality assessment (NOS scale)

Author	Selection				Comparability	Exposure			Quality scores
	1	2	3	4		A	B	C	
Bao J 2022(10)	*	*	*	*	*	*	*		7
Zhang F 2023(11)	*			*	*	*	*	*	6
Li H 2018(12)	*	*	*	*	*	*	*	*	8
Li Y 2022 (13)	*	*		*	**	*	*	*	8
Jiang Z 2020(15)	*	*		*	*	*	*		6
Jin X 2020(16)	*	*		*		*	*		5
Huang H 2015(17)	*	*	*	*	*	*	*	*	8
Kumagai E 2016(18)	*	*	*	*	*	*	*	*	8
Schiavon LL 2008(19)	*	*	*	*	*	*	*		7
Saitou Y 2005(21)	*	*	*	*	*	*	*		7
Hu Z 2024(22)	*			*	*	*	*	*	6
Lin C 2021(23)	*	*	*	*	*	*	*	*	8
Toson E 2016(26)	*	*	*	*	*	*	*	*	8

Differences in serum levels of YKL-40 in controls and patients with liver fibrosis

Seven articles (10, 15, 20, 22, 24, 25, 26) were included to record the serum levels of YKL-40 in patients with liver fibrosis and controls (liver fibrosis S0 or S0-S1), and after meta-analysis, the difference between the two groups combined was found to be 1.37(0.66,2.08). There were 6 studies in China with SMDs ranging from 0.11-5.27, with a subgroup combined SMD of 1.19 and high heterogeneity (I^2 = 94.0%), and 1 study in Egypt with an SMD of 2.30 and 0 heterogeneity (I^2 = 0.0%). Overall analysis showed heterogeneity between groups (P = 0.019), with a combined SMD of 1.37 and high overall heterogeneity. YKL-40 serum levels were significantly different between the two groups, as shown in Fig. 3. However, significant heterogeneity was detected (I^2 = 94.7%, P <0.001).

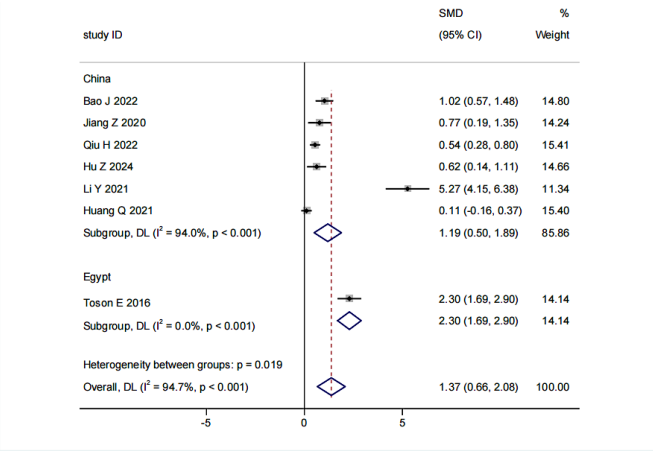

Fig. 3: Forest plot of the subgroup analysis of the differences in serum YKL-40 levels between the control group and patients with liver fibrosis

YKL-40 in the Diagnosis of Advanced Liver Fibrosis (Stages S3-S4)

Five studies were included, and the combined sensitivity: 0.80 (95% CI: 0.67-0.88) demonstrated the good performance of YKL-40 in diagnosing the correct S3-S4 stage of liver fibrosis. Specificity: 0.88 (95% CI: 0.77-0.94), which demonstrated the very high accuracy of YKL-40 in diagnosing correct hepatic fibrosis stages S3-S4 (Fig. 4A). The Summary Receiver Operating Characteristic (SROC) curve, along with the 95% confidence interval of the combined points and prediction region, shows an Area Under the Curve (AUC) of 0.91 (ranging from 0.88 to 0.93), where values nearer to 1 signify superior diagnostic accuracy. Overall sensitivity and specificity values were high, but inter-study heterogeneity was high, as shown in Fig. 4B. Clinicians found the initial posterior probability significant, thus likelihood ratios were employed to ascertain the posterior probability for both positive and negative outcomes of the index test. Initially, the likelihood of identifying liver fibrosis at stages S2-S4 was 20%. However, after a positive serum YKL-40 test, this probability increased to 63%, while a negative result reduced it to 5% (Fig. 4C).

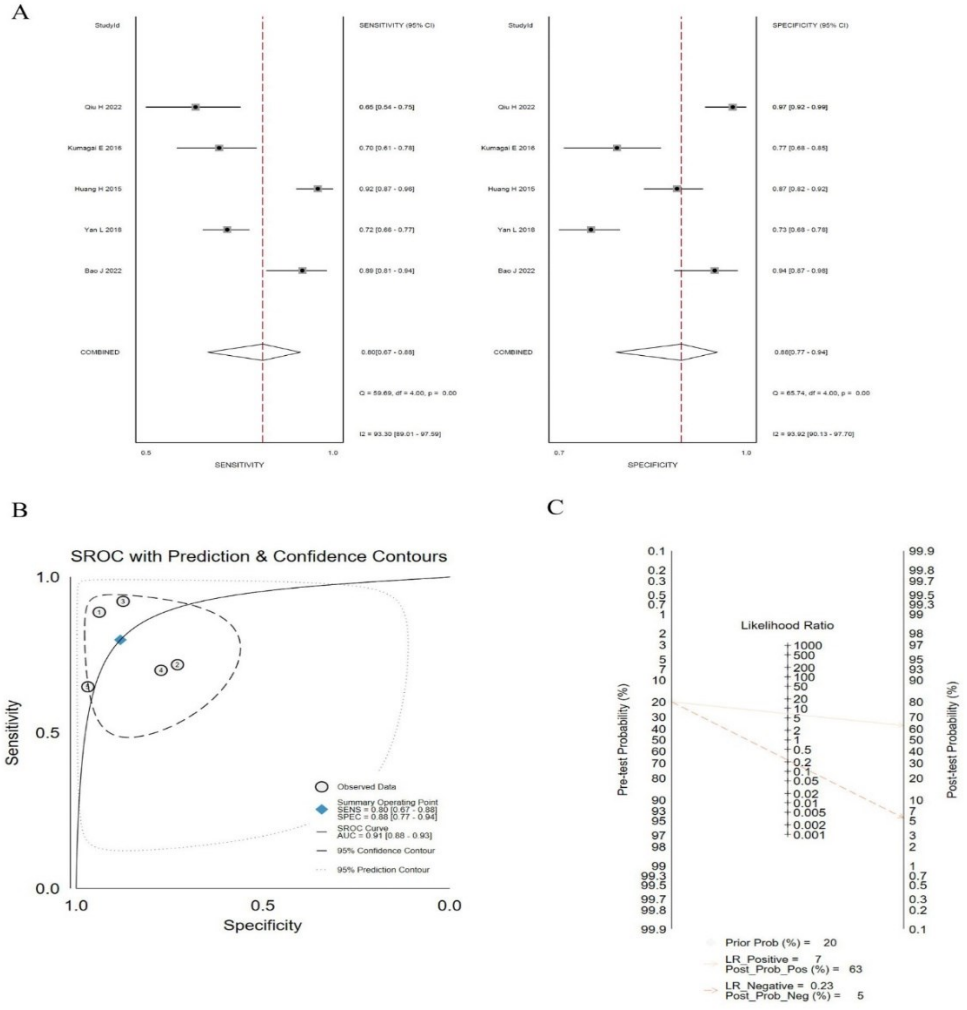

Fig. 4: Meta-Analysis of YKL-40 in the Diagnosis of Advanced Liver Fibrosis (Stages S3-S4). A. Forest plot of sensitivity and specificity. B. SROC curve. C. Fagan plot

YKL-40 in the Diagnosis of Severe Liver Fibrosis (Stages S2-S4)

A total of 5 studies were included, and the combined sensitivity: 0.78 (95% CI: 0.60-0.89) demonstrated the good performance of YKL-40 in diagnosing the correct S2-S4 stage of liver fibrosis. Specificity: 0.82 (95% CI: 0.72-0.89), demonstrated that YKL-40 had a very high accuracy in diagnosing correct hepatic fibrosis S2-S4 stages (Fig. 5A). The SROC curves, as well as the pooled-point 95% CI and AUC = 0.87 (0.83-0.89), the closer to 1 indicated better diagnostic performance. Overall sensitivity and specificity values were high, but inter-study heterogeneity was high (Fig. 5B). Clinicians found the initial posterior probability significant, thus likelihood ratios were employed to ascertain the posterior probability for both positive and negative outcomes of the index test. As illustrated in Fig. 5C, the initial likelihood of identifying liver fibrosis at stages S2-S4 was 20% with a positive serum YKL-40 test result, increasing to 51% after the test. Conversely, the initial probability dropped to 6% with a negative result.

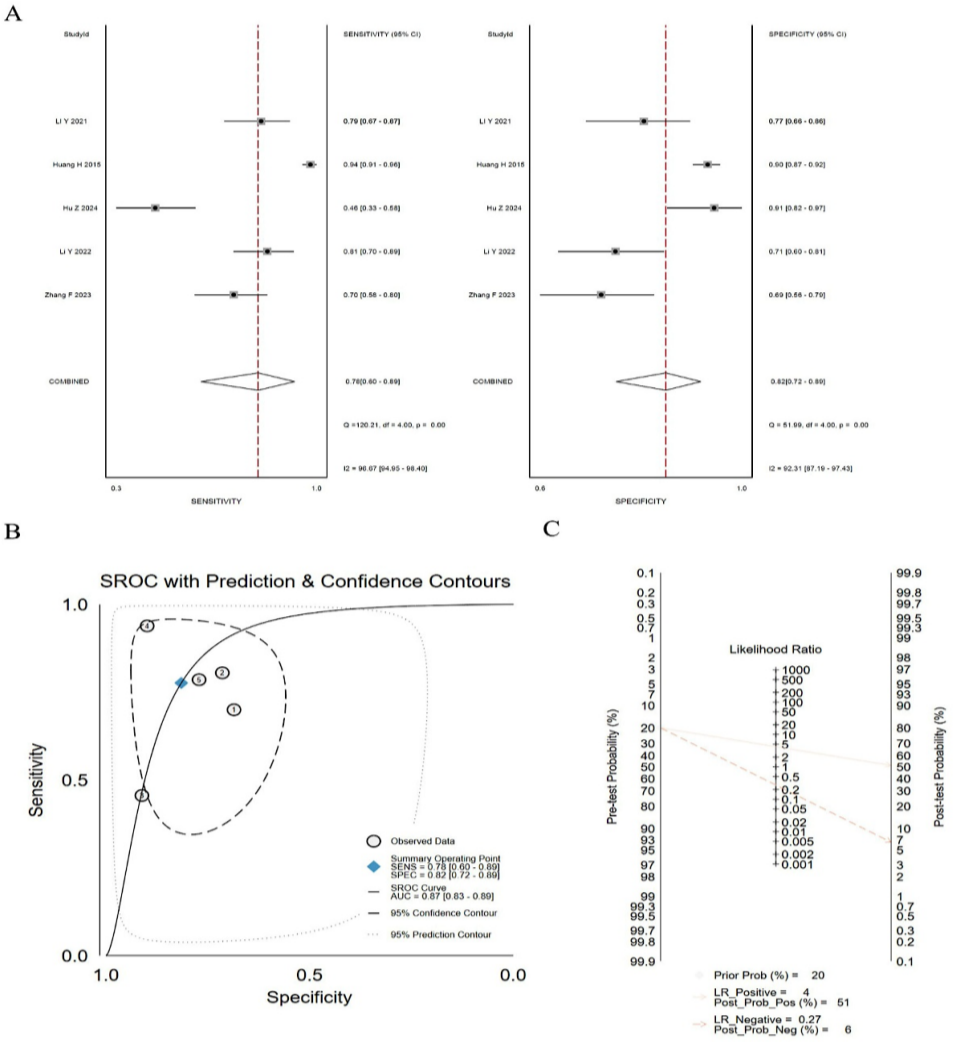

Fig. 5: Meta-Analysis of YKL-40 in the Diagnosis of Severe Liver Fibrosis (Stages S2-S4). A. Forest plot of sensitivity and specificity. B. SROC curve. C. Fagan plot

Estimation of bias

The Deeks funnel plot asymmetry test and STATA software were utilized to detect publication bias, with a *P*-value below 0.05 deemed statistically significant. Serum YKL-40 diagnosis of severe liver fibrosis stage S3-S4 did not have publication bias, with a P value of 0.34, respectively. Serum YKL-40 diagnosis of severe liver fibrosis stage S2-S4 had publication bias, with a *P*-value of 0.00, respectively, and the source of the bias was Li Y2022 (Fig. 6A and 6B).

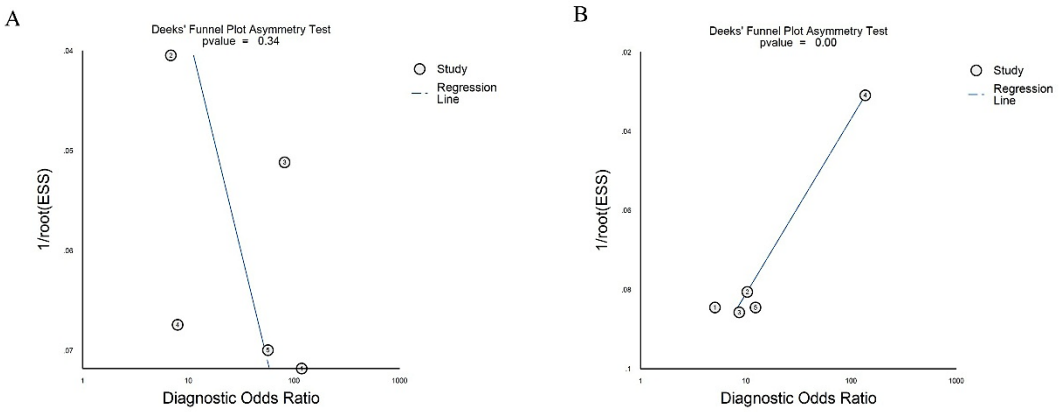

Fig. 6: Estimation of bias. A. Deeks funnel plot of YKL-40 in diagnosing S3-S4 stages of liver fibrosis; B. Deeks funnel plot of YKL-40 in the diagnosis of S2-S4 stages of liver fibrosis

Discussion

Early diagnosis is crucial for liver fibrosis. This review evaluates the effectiveness of serum YKL-40 as a potent and noninvasive indicator for diagnosing liver fibrosis. So far, various clinical diagnostic methods including liver biopsy, B-mode ultrasound, transient elastography (TE), and traditional serum markers like type III procollagen, type IV collagen, laminin, and hyaluronidase have been developed to diagnose and assess liver fibrosis (27, 28). However, the disadvantages of these methods include invasiveness, high-cost burden and lack of specificity. Consequently, it is essential to develop an effective screening technique that aligns with contemporary principles of safety, cost-effectiveness, and ease of use.

In recent years, serum YKL-40 has gained attention as a potential non-invasive marker for the diagnosis of hepatic fibrosis.YKL-40, as a glycosylated protein, has been shown to play an important role in the onset and progression of hepatic fibrosis (29,30). YKL-40 exhibits high sensitivity and specificity in the early stages of liver fibrosis, which provides a theoretical basis for its use as an early diagnostic tool. In addition, YKL-40 is believed to act as an upstream signaling molecule involved in the regulation of liver fibrosis, further supporting its potential as a biomarker of liver fibrosis.

This systematic evaluation and meta-analysis conducted an extensive and comprehensive study of serum YKL-40 level as a non-invasive potential biomarker for patients with liver fibrosis. The study's findings indicated that serum YKL-40 levels exhibited high sensitivity and specificity for diagnosing both advanced and severe fibrosis, highlighting its strong diagnostic utility. SMDs ranged from 0.11-5.27 for the Chinese subgroup, with a combined SMD of 1.19 and high heterogeneity, while the Egyptian subgroup had a SMD of 2.30 and zero heterogeneity, and there was overall intergroup heterogeneity, with a combined SMD of 1.37. The AUC values for the subjects' operational characteristics were 0.91 and

0.87, respectively, which further confirms its efficacy as a non-invasive biomarker.

Studies demonstrated the important diagnostic and monitoring potential of YKL40 as a biomarker in chronic viral hepatitis. This biomarker excels in differentiating between different fibrosis stages and are more accurate compared to traditional indicators such as the aspartate aminotransferase to platelet ratio index (APRI) and fibrosis-4 index (FIB-4) (31). This further supports its role as a promising biomarker for liver fibrosis. Moreover, gene polymorphisms have been discovered to be strongly linked to YKL-40 levels and the progression of liver fibrosis (32, 33). In metabolism-related liver diseases, such as non-alcoholic fatty liver disease (NAFLD) and type 2 diabetes (T2D), YKL40 expression showed diagnostic and assessment value (34). Consequently, these results underscore the significance of YKL40 in diagnosing liver fibrosis and open up new possibilities for personalized treatment and tracking of the disease. Utilizing these biomarkers can help refine noninvasive liver fibrosis diagnostics, enhance the accuracy of fibrosis staging, and offer more precise diagnostic and therapeutic choices for liver disease patients.

The limitations of this study were, first, the sample size of the included literature and studies was small. Second, the heterogeneity was high, and its due to the limited number of articles that Meta-regression analysis could not be performed to explore the heterogeneity. Third, most of the included articles were from China, limiting the extrapolation of the results. Additionally, significant publication bias in analysis of severe liver fibrosis stage S2-S4 was detected, which may influence the reliability of the findings. Results Contrary to previous meta-analysis, YKL-40 has a higher diagnostic value for advanced fibrosis (35). The results of the previous analysis of YKL-40, which included 11 studies, reported high sensitivity and specificity for significant fibrosis, advanced fibrosis were 0.79 and 0.82 with AUC values of 0.85 and 0.91, and 0.81 and 0.83 with an AUC of 0.91, respectively. This paper was inconsistent with the liver fibrosis staging it used, and the analysis herein was strictly based on the original staging of the included literature.

Conclusion

This study's findings introduced novel concepts and techniques for diagnosing and tracking liver fibrosis, serving as a crucial reference for both clinical application and research. However, although serum YKL-40 levels show some potential application value in the diagnosis of hepatic fibrosis, more clinical studies are needed to validate and improve its application in clinical practice. Upcoming research might delve deeper into the connection between serum YKL-40 concentrations and liver fibrosis progression, along with its possible utility in tracking liver disease treatment.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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