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Original Article

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Protein Induced by Vitamin K Absence or Antagonist-II Versus Alpha-Fetoprotein in the Diagnosis of Hepatocellular Carcinoma: A Systematic Review With Meta-Analysis

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Abstract

Background: Protein induced by vitamin K absence or antagonist-II (PIVKA-II) and α-fetoprotein (AFP) are promising tumor markers for the diagnosis of hepatocellular carcinoma (HCC). Yet, their diagnostic performance differs throughout HCC investigations. The aim of this meta-analysis was to assess the effectiveness of PIVKA-II and AFP in the diagnosis of HCC.

Methods: A systematic literature search was performed to identify relevant studies from eight databases, which were published up to February 2023, in order to compare the diagnostic performance of PIVKA-II and AFP for HCC. Pooled sensitivity and specificity were calculated. Summary receiver operating characteristic (SROC) curve was performed to assess the diagnostic accuracy of each biomarker.

Results: Fifty-three studies were identified. The pooled sensitivity (95% confidence interval (CI)) of PIVKA-II and AFP was 0.71 (0.70 - 0.72) and 0.64 (0.63 - 0.65), respectively in diagnosis of HCC, and the corresponding pooled specificity (95% CI) was 0.90 (0.89 - 0.90) and 0.87 (0.87 - 0.88), respectively. The area under the ROC curve (AUC) of PIVKA-II and AFP was 0.89 (0.88 - 0.90) and 0.78 (0.77 - 0.79), respectively. Subgroup analysis demonstrated that PIVKA-II presented higher AUC values compared to AFP in terms of ethnic group (African, European, Asian, and American patients), etiology (mixed-type HCC, hepatitis C virus (HCV)-related, and hepatitis B virus (HBV)-related) and sample size of cases (≤ 100 and > 100).

Conclusion: This study reveals that PIVKA-II is a promising biomarker for identifying and tracking HCC, exhibiting greater accuracy than AFP. Our findings indicate that PIVKA-II outperforms AFP in detecting HCC across diverse racial groups and sample sizes, as well as in cases of HBV-related, HCV-related, or mixed-etiology HCC.

Keywords: Vitamin K absence or antagonist-II; Alpha-fetoprotein; Hepatocellular carcinoma; Hepatitis B virus; Hepatitis C virus

Introduction

Liver cancer accounts for 841,000 new cases and 782,000 fatalities annually, making it the sixth most prevalent cancer overall [1]. In all primary liver malignancies, hepatocellular carcinoma (HCC) accounts for more than 90% of cases. It is still becoming more common, ranking as the second most common reason for cancer-related deaths [2]. The most frequent etiological causes of HCC include alcoholic liver disease, non-alcoholic fatty liver disease, and hepatitis B virus (HBV) or hepatitis C virus (HCV) infection [3]. The early stages of HCC are typically asymptomatic and have a propensity for intravascular and invasive behavior. Due to a lack of efficient diagnostic methods, more than two-thirds of patients do not receive a diagnosis until an advanced stage [4]. The prognosis of HCC varies significantly depending on the tumor stage at the time of diagnosis; as a result, early detection is essential to enable therapeutic methods and hence increase patient survival [5]. Presently, abdominal ultrasonography (US) is the mainstay of monitoring programs for HCC diagnosis in high-risk populations. The US is a non-invasive and cost-effective screening

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approach. However, it has sub-optimal sensitivity [6]. Moreover, the presence of a coarse liver echo pattern, obesity, meteorism, chest wall abnormalities, prior abdominal surgery, a lack of patient participation, and the operator's skill are some other factors that may affect the US examination [7]. As a result, alternative non-invasive techniques must be used in conjunction with the US to enhance the detection of possible malignant tumors such as serum biomarkers. However, the use of serum biomarkers is still up for debate and lack of trustworthy blood biomarkers is, in fact, a serious problem with HCC surveillance [6]. Alpha-fetoprotein (AFP) has received the most attention among non-invasive biomarkers and has been shown to have a diagnostic accuracy of 0.767 (0.732 - 0.803) for HCC diagnosis [8]. AFP-L3, an AFP variant, holds significant importance in diagnosing HCC. AFP-L3 is a specific isoform of AFP associated with malignant liver tumors, particularly HCC. It provides higher specificity than total AFP, making it a valuable biomarker for detecting and differentiating HCC from other liver diseases early [8-10].

In the same context, Trevisani et al revealed that AFP showed 60-80% sensitivity at a cut-off value of 20 ng/mL [9]. However, data on the effectiveness of AFP combined with US in a surveillance situation are still inconclusive [10].

Also known as "des-gamma-carboxy prothrombin" (DCP), protein induced by vitamin K absence or antagonist-II (PIVKA-II) is a prothrombin protein that is aberrant as a result of an acquired deficiency in the post-translational carboxylation of the prothrombin precursor in cancerous cells [11]. Several research articles demonstrated that PIVKA-II presents a high sensitivity (up to 90%) and specificity (up to 100%) at distinguishing HCC from other chronic liver disorders [11-13]. Many studies have compared the diagnostic value of PIVKA-II and AFP, but findings are conflicting and, data about whether PIVKA-II and AFP perform differently in diagnosing HCC of different etiologies should be updated.

Therefore, this systematic review and meta-analysis was conducted to provide up-to-date evidence on the diagnostic performance of PIVKA-II and AFP for the detection of HCC.

Materials and Methods

Search strategy

This systematic review and meta-analysis study was carried out; the work has been reported in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Assessing the Methodological Quality of Systematic Reviews (AMSTAR) guidelines [14]. A systematic search was conducted on PubMed, Medline, Web of Science, Scopus, the Cochrane Library, Embase, Google Scholar, and CINAHL from database inception until February 2023 to look for potentially eligible articles. The search strategy used the following combinations of search terms: "des-gamma-carboxy prothrombin" OR "protein induced by vitamin K absence or antagonist II" OR "PIVKA-II" OR "DCP" AND "alpha-fetoprotein" OR "AFP" AND "hepatocellular carcinoma" OR "primary liver cancer" OR "hepatic carcinoma" OR "HCC". All retrieval processes were performed independently by two researchers.

Selection criteria

Relevant articles were screened by title and abstract after removing duplicates. Studies were eligible for inclusion if they addressed the performance evaluation of PIVKA-II and AFP for HCC diagnosis. The remaining studies were then examined in full text to confirm eligibility.

Inclusion criteria for articles were: 1) original articles reporting diagnostic accuracy of PIVKA-II and AFP for HCC in the same patients; 2) studies with sample size ≥ 30; 3) publications reporting sensitivity, specificity, and area under the ROC curve (AUC) outcomes; and 4) studies conducted in adults.

The exclusion criteria included: 1) unavailable full text electronically; 2) non-English publications; 3) comments, letters, editorials, protocols, and guidelines; and 4) studies with insufficient outcome data.

Data extraction

Two independent authors retrieved information from the eligible articles following the inclusion and exclusion criteria, and information were collected on a standardized data sheet that included: 1) study and year of publication; 2) country; 3) sample size of HCCs/controls; 4) cut-off value of PIVKA-II; 5) cut-off value of AFP; 6) etiology of HCC; 7) sensitivity of PIVKA-II/AFP; and 8) specificity of PIVKA-II/AFP.

Study quality assessment

The methodological quality of the included studies was evaluated independently, by two authors, using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) tool, which includes four criteria that judge bias and applicability: "patient selection", "index test", "reference standard", and "flow and timing" [15]. Each is assessed in terms of risk of bias, and the first three domains were also assessed with respect to applicability. Each item is answered with "yes", "no", or "unclear". The answer "yes" means low risk of bias, whereas "no" or "unclear" means the opposite. Any disagreements were resolved by inviting a third reviewer to participate in the discussion. RevMan Version 5.4 (Cochrane Collaboration, Oxford, UK) was used to visualize the quality assessment results.

Statistical analysis

Diagnostic meta-analysis of PIVKA-II and AFP was conducted on the analytical software Meta-disc 1.4 (Universidad Complutense, Barcelona, Spain) and Comprehensive Meta-Analysis version 3 (Biostat Inc., USA) in order to analyze the pooled sensitivity and specificity with 95% confidence intervals (CIs) across studies. A value of $P < 0.05$ was considered as

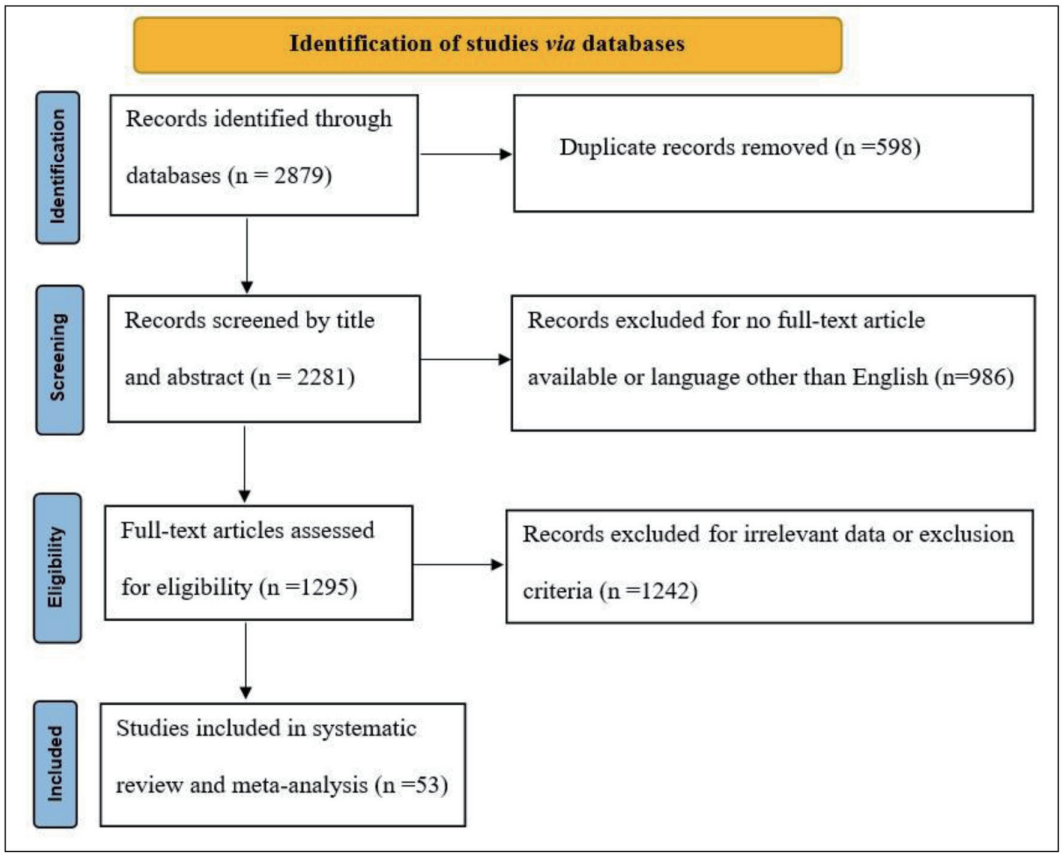

Figure 1. PRISMA flow diagram. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

the level of significance. The Cochrane Chi-squared test was used to evaluate heterogeneity among articles, with P-value < 0.05 indicating the existence of heterogeneity. To estimate the impact of heterogeneity on the meta-analysis, I^2 value was calculated. I^2 values ≥ 50% and P < 0.05 indicated a moderate to high degree of heterogeneity among pooled studies. A fixed-effects design was used when I^2 < 50% and P > 0.05; otherwise, a random-effects model was adopted [16]. The summary receiver operating characteristic (SROC) curve, the positive likelihood ratio (PLR), the negative likelihood ratio (NLR), the diagnostic odds ratio (DOR), and the area under the curve (AUC) were also used based on the sensitivity and specificity of each study to assess the diagnostic performance. Subgroup and meta-regression analyses were performed to identify potential sources of heterogeneity according to the characteristics of the included studies. Finally, Egger's test was conducted to evaluate publication bias. This latter was further assessed by the visual inspection of the symmetry in funnel plots.

Results

Identification of studies

The database search identified 2,879 studies to be screened, of which 1,295 abstracts were identified as potentially eligible and retrieved for full text review. Eligibility criteria were met by 53 articles, which were included to this systematic review and meta-analysis study. The PRISMA flowchart is shown in Figure 1.

Characteristics of included studies

The included articles were published between 1989 and 2022 and distributed among 15 countries. The sample size of the included articles varied from 33 to 550 for HCC cases and from 20 to 604 for controls. The most prevalent type of control was cirrhosis (33 studies). The median/mean age of participants was > 40 years in all studies. Characteristics of included studies are summarized in Table 1 [12, 13, 17-67].

Quality assessment

The quality of the 53 studies was methodologically assessed using QUADAS-2 tool. Patient selection plays such a role in conducting experiments that data used in this meta-analysis are mainly from validated groups. As a whole, the qualities of included studies are satisfying and eligible. With respect to domain patient selection, 8/53 studies were identified to

Table 1. Characteristics of the Studies Included in the Meta-Analysis

Study and year of publication	Country	Sample size of HCCs/ controls	Type of controls	Median or mean age of HCC/ control (years)	Cut-off value of PIVKA-II	Cut-off value of AFP	Etiology of HCC	Sensitivity of PIVKA-II/ AFP	Specificity of PIVKA-II/ AFP
Abd El Gawad et al 2014 [17]	Egypt	40/20	Cirrhosis + healthy controls	59/57	1.2 ng/mL	40.5 ng/mL	Mixed	97.5%/82.5%	90%/85%
Beneduce et al 2008 [18]	Italy	33/31	Healthy controls	61/55	2 ng/mL	20 ng/mL	HCV	39%/48%	100%/100%
Caviglia et al 2020 [19]	Italy	149/200	Cirrhosis	67/61	> 73 mAU/mL	> 9.7 ng/mL	Mixed	68%/72%	84%/66%
Cerban et al 2019 [20]	Romania	101/52	Cirrhosis	60.3/59.4	> 63 mAU/mL	> 18.9 ng/mL	Mixed	81.36%/52.54%	60.61%/93.94%
Chan et al 2022 [21]	China	168/208	Disease controls	62.86/52.18	28.4 ng/mL	20 ng/mL	Mixed	86.9%/51.8%	83.7%/98.1%
Chen et al 2020 [22]	China	110/250	Chronic hepatitis B + cirrhosis + healthy controls	55.62/54.29	51 mAU/mL	5.65 ng/mL	HBV	85%/84.1%	93.3%/70.90%
Choi 2013 [13]	South Korea	90/78	Benign liver disease	59.7/55.6	40 AU/L	10 ng/mL	Mixed	62.2%/78.9%	94.9%/84.6%
Cui et al 2003 [23]	China	120/90	Cirrhosis	59/56	40 mAU/mL	20 ng/mL	Mixed	53.3%/58.3%	85.6%/63.3%
Durazo et al 2008 [24]	USA	144/96	Cirrhosis + chronic hepatitis	54.2/45.85	84 mAU/mL	25 ng/mL	Mixed	87%/69%	85%/87%
Ekmen et al 2020 [25]	Turkey	66/46	Cirrhosis	54.53/54.45	2.63 ng/mL	6.08 ng/mL	Mixed	71%/77%	83%/77%
Ertle et al 2012 [26]	Germany	164/422	Viral hepatitis, cirrhosis, other chronic liver diseases such as NASH, AIH and others	64/48.8	5 ng/mL	10 ng/mL	Mixed	63.4%/54.9%	94.5%/94.5%
Feng et al 2021 [27]	China	168/153	Healthy controls	ND	35.60 mAU/ mL	17.76 ng/mL	Mixed	83.93%/64.29%	91.50%/90.20%
Fujiyama et al 1992 [28]	Japan	200/197	Cirrhosis + chronic hepatitis + hemangioma + liver cysts	60.7/52.6	0.11 AU/mL	150 ng/mL	Mixed	54%/54%	98%/95.9%
Gentile et al 2017 [29]	Italy	56/104	HCV without HCC	70/66	> 36 mAU/mL	> 12 ng/mL	HCV	78.6%/60%	66.3%/77.2%
Grazi et al 1995 [30]	Italy	111/116	Postnecrotic cirrhosis + liver metastases from colorectal cancer + benign liver lesions + tumors not affecting the liver without hepatic metastases, and other diseases	60.9/49.9	0.09 AU/mL	20 ng/dL	Mixed	53.3%/54.9%	88.1%/97.4%

Table 1. Characteristics of the Studies Included in the Meta-Analysis - *(continued)*

Study and year of publication	Country	Sample size of HCCs/ controls	Type of controls	Median or mean age of HCC/ control (years)	Cut-off value of PIVKA-II	Cut-off value of AFP	Etiology of HCC	Sensitivity of PIVKA-II/ AFP	Specificity of PIVKA-II/ AFP
Guan et al 2022 [31]	China	139/345	ND	60.6/56.2	40 mAU/mL	20 ng/mL	Nonalcoholic fatty liver	74.8%/52.5%	91.0%/97.4%
Hadi et al 2022 [32]	Malaysia	40/123	Liver cirrhosis + non-cirrhotic high-risk patients	64.5/56.5	36.7 mAU/mL	14.2 ng/mL	Mixed	90%/75%	82.1%/93.5%
Huang et al 2017 [33]	China	132/450	Viral hepatitis + liver cirrhosis + metastatic hepatic carcinoma + other benign liver diseases + healthy individuals	53.7/47.45	≥ 40 mAU/mL	≥ 20 ng/mL	Mixed	80%/68%	89%/91%
Ismail et al 2017 [34]	Egypt	66/83	Malignant tumors or benign liver lesions	59/46	28 ng/mL	20 ng/mL	Mixed	90.9%/68.2%	97.6%/91.6%
Jang et al 2016 [35]	France	208/193	Cirrhosis	61.02/57.85	> 10 ng/mL	> 20 ng/mL	Mixed	51%/62%	91.2%/90.2%
Ji et al 2016 [36]	China	236/285	Hemangiomas of liver, metastatic hepatic carcinoma and liver cirrhosis + healthy control	51/50.22	40 mAU/mL	20 ng/mL	Mixed	82.63%/67.80%	89.12%/91.23%
King et al 1989 [37]	South Africa	98/120	Hepatic metastases + amoebic hepatic abscesses + chronic hepatic parenchymal disease	46.7/54.77	> 1.5 mU/mL	> 20 ng/mL	Mixed	67.3%/83.7%	84.2%/90.8%
Lee et al 2021 [38]	China	158/62	Chronic hepatitis B	ND	ND	ND	HBV	68.4%/57.6%	98.4%/93.5%
Lim et al 2015 [39]	South Korea	361/276	Cirrhosis	58/55	40 mAU/mL	20 ng/mL	Mixed	62.9%/56.8%	90.8%/82.8%
Liu et al 2022 [40]	China	105/172	HCV-infected patients	60.8/55.8	40 mAU/mL	20 ng/mL	HCV	78.1%/56.2%	89.0%/90.1%
Loglio et al 2020 [41]	Italy	64/148	HBV-infected patients	66/60	> 48 mAU/mL	> 4.2 ng/mL	HBV	64%/56%	91%/94%
Marrero et al 2003 [42]	USA	55/104	Cirrhosis and chronic hepatitis	56.2/51	125 mAU/mL	11 ng/mL	Mixed	89%/77%	95%/79%
Marrero et al 2009 [43]	USA	419/417	Cirrhosis	60.5/55	150 mAU/mL	20 ng/mL	Mixed	74%/59%	70%/90%
Morota et al 2011 [44]	USA	70/156	Cirrhosis + hepatitis + normal	ND	123.9 AU/L	15.3 mg/L	Mixed	84.3%/62.9%	88.1%/92.3%
Nomura et al 1999 [45]	Japan	36/49	Cirrhosis	ND	ND	20 ng/mL	Mixed	27.8%/58.3%	95.9%/75.5%
Park et al 2016 [46]	South Korea	79/77	Cirrhosis	62.33/55.59	> 40 mAU/mL	>10 ng/mL	Mixed	70.89%/68.35%	70.13%/81.82%

Table 1. Characteristics of the Studies Included in the Meta-Analysis - *(continued)*

Study and year of publication	Country	Sample size of HCCs/ controls	Type of controls	Median or mean age of HCC/ control (years)	Cut-off value of PIVKA-II	Cut-off value of AFP	Etiology of HCC	Sensitivity of PIVKA-II/ AFP	Specificity of PIVKA-II/ AFP
Peng et al 2022 [47]	China	148/143	Cirrhosis	55/51	> 199.9 mAU/mL	> 619.3 ng/mL	HBV	78.65%/49.44%	99.30%/98.60%
Pote et al 2014 [48]	France	85/43	Cirrhosis	57.8/54.8	42 mAU/mL	5.5 ng/mL	Mixed	73%/61%	81%/50%
Qi et al 2019 [49]	China	120/89	Chronic liver disease	56/47	33.080 mAu/mL	11.880 ng/mL	Mixed	83.5%/73.6%	71.6%/80.7%
Seo et al 2015 [50]	South Korea	157/879	Chronic hepatitis B	57/45	40 mAU/mL	10 ng/mL	HBV	73.9%/67.5%	89.7%/90.3%
Sharma et al 2010 [12]	India	70/38	Cirrhosis	58.84/47.92	9.2 ng/mL	13.02 ng/mL	Mixed	80%/72.9%	92.1%/65.8%
Shimizu et al 2022 [51]	Japan	56/34	Cirrhosis	62/61	40 mAU/mL	20 ng/mL	Mixed	46.4%/58.9%	97.1%/85.3%
Si et al 2020 [52]	China	266/167	Benign liver disease and healthy individuals	ND	41.74 mAU/ mL	21.8 ng/mL	HBV	81.2%/51.5%	88.5%/89.7%
Song et al 2014 [53]	China	550/604	Malignant disease + chronic liver disease + benign disease + healthy participants	51/41.5	86 mAU/mL	21 ng/mL	Mixed	71.50%/68.00%	86.30%/93.20%
Song et al 2020 [54]	China	88/112	Chronic HBV + cirrhosis	ND	44 mAU/mL	5 ng/mL	Mixed	55.7%/65.9%	94.6%/88.4%
Sterling et al 2009 [55]	Canada	74/298	Healthy participants	54.9/52.1	> 200 ng/mL	20 ng/mL	HCV	56.3%/60.8%	100%/71.1%
Suehiro et al 1993 [56]	Japan	185/90	Cholangiocellular carcinoma + cirrhosis	ND	ND	ND	Mixed	35.1%/65.4%	95.3%/71.8%
Takikawa et al 1992 [57]	Japan	116/253	Cirrhosis	ND	0.1 AU/mL	20 ng/mL	Mixed	52.8%/70.1%	98.8%/75.5%
Tian et al 2022 [58]	China	145/57	Benign liver disease	58.9/48.1	38.91 mAU/ mL	5.6 ng/mL	Mixed	92.4%/88.3%	96.5%/98.2%
Viggiani et al 2016 [59]	Italy	60/60	Benign liver disease	39 - 86/26 - 84	47 mAU/mL	20 mAU/mL	Mixed	60%/55%	90%/55%
Volk et al 2007 [60]	USA	84/169	Cirrhosis	59/53	150 mAU/mL	23 ng/mL	Mixed	86%/69%	93%/91%
Wang et al 2005 [61]	Taiwan	61/66	Chronic hepatitis and cirrhosis	63/54.5	40 mAU/mL	20 ng/mL	Mixed	77%/59%	86.4%/77.3%
Wang et al 2019 [62]	China	176/359	Chronic hepatitis B	53/49	162.22 mAU/mL	145.65 ng/mL	HBV	51.3%/64.8%	93.6%/77.2%
Wang et al 2020 [63]	China	234/396	Chronic hepatitis B	54/48	87.63 mAU/ mL	499.80 ng/mL	HBV	86.80%/52.10%	90.20%/91.40%

Table 1. Characteristics of the Studies Included in the Meta-Analysis - *(continued)*

Study and year of publication	Country	Sample size of HCCs/ controls	Type of controls	Median or mean age of HCC/ control (years)	Cut-off value of PIVKA-II	Cut-off value of AFP	Etiology of HCC	Sensitivity of PIVKA-II/ AFP	Specificity of PIVKA-II/ AFP
Xu et al 2021 [64]	China	308/120	Benign liver disease + cirrhosis	51.4/44.56	40 mAU/mL	25 ng/mL	Mixed	89.0%/86.8%	91.7%/87.6%
Yoon et al 2009 [65]	South Korea	106/100	Non-HCC	54.5/ND	40 mAU/mL	20 ng/mL	Mixed	51.9%/57.5%	97%/88%
Yu et al 2015 [66]	China	134/505	Liver diseases + other cancers + healthy controls	49.6/50.93	200 mAU/mL	195.2 ng/mL	Mixed	64.2%/60.4%	90.8%/89.6%
Zhang and Huang 2022 [67]	China	228/103	Cirrhosis	56/58	25.3 ng/mL	7 ng/mL	Mixed	70.18%/63.16%	82.50%/85.44%

AFP: α-fetoprotein; AIH: autoimmune hepatitis; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HCV: hepatitis C virus; NASH: nonalcoholic steatohepatitis; PIVKA-II: protein induced by vitamin K absence or antagonist-II.

have high risk of bias. However, we revealed a high-risk bias mainly concentrated on the field of index test due to presetting the threshold (20/35 studies). The domains reference standard and flow and timing were partly affected by risk of bias, with 13/53 and 12/53 studies with high risk of bias, respectively. In contrast, there were not too many concerns as for the applicability for the majority of studies included in this meta-analysis. Indeed, high applicability concerns were shown in two studies in patient selection, seven studies in index test, and two studies in reference standard, respectively. Figure 2 shows the details of the quality assessment form.

Data analysis

From forest plots of pooled data (53 studies), we found significant heterogeneity in sensitivity (Chi^2 = 725.78, P = 0.0000, I^2 = 92.8%) and specificity (Chi^2 = 541.73, P = 0.0000, I^2 = 90.4%) outcomes of PIVKA-II (Fig. 3). Similarly, a high heterogeneity was detected in sensitivity (Chi^2 = 341.61, P = 0.0000, I^2 = 84.8%) and specificity (Chi^2 = 664.74, P = 0.0000, I^2 = 92.2%) outcomes of AFP (Fig. 4). Consequently, the random-effect model was used to calculate the pooled estimates.

The pooled sensitivity (95% CI) of PIVKA-II and AFP was 0.71 (0.70 - 0.72) and 0.64 (0.63 - 0.65), respectively, and the pooled specificity (95% CI) was 0.90 (0.89 - 0.90) and 0.87 (0.87 - 0.88), respectively. The forest plots of sensitivity and specificity derived from all the 53 studies are shown in Figure 3 and 4.

The pooled PLR (95% CI) of PIVKA-II and AFP was 7.18 (5.96 - 8.66) and 5.08 (4.20 - 6.15), and NLR (95% CI) was 0.30 (0.27 - 0.35) and 0.42 (0.39 - 0.45), respectively. The DOR (95% CI) of PIVKA-II and AFP was 27.12 (21.14 - 37.79) and 12.94 (10.35 - 16.18), respectively. Finally, the AUC of PIVKA-II and AFP was 0.89 (0.88 - 0.90) and 0.78 (0.77 - 0.79) respectively, suggesting an outstanding diagnostic accuracy of both markers (Table 2).

Figure 5 shows the SROC curves generated from the hierarchical regression model on the overall summary of PIVKA-II and AFP. All the results showed that PIVKA-II was better than AFP in the accuracy of diagnosing HCC.

Investigation for heterogeneity

The forest plots demonstrated that all 53 studies were heterogeneous. As heterogeneity cannot be completely avoided in a meta-analysis, its source and level were further investigated. The threshold effect is the primary source of heterogeneity in a diagnostic test. The Moses' model was weighted by inverse variance, and the Spearman correlation coefficient was used to assess the threshold impact. The findings revealed that the Spearman correlation coefficient for PIVKA-II was 0.284 (P = 0.039) and for AFP was 0.374 (P = 0.006). Thus, a significant threshold effect was found to cause variations in the accuracy estimates among individual studies. In order to further investigate heterogeneity based on the findings from

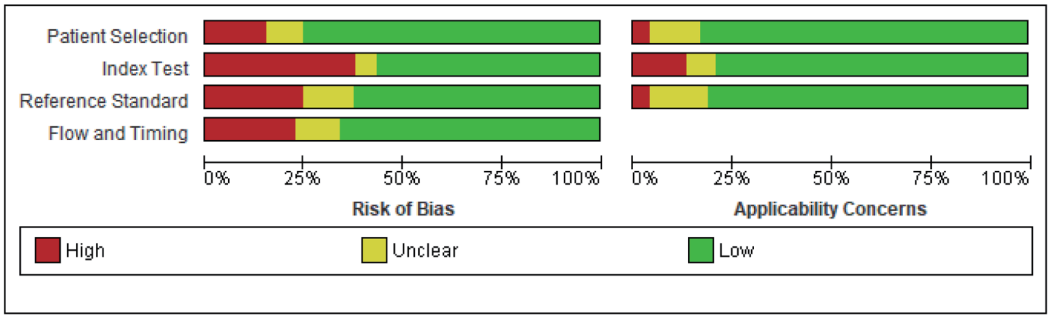

Figure 2. Risk of bias and applicability concerns graph: reviewing authors' judgements about each domain presented as percentages across included studies.

the meta-analysis, regression analysis based on ethnicity, etiology, and sample size was also carried out. This was because it was possible that other factors may have contributed to the variation in accuracy estimates among individual studies. The results demonstrated that heterogeneity was not significantly impacted by changes in ethnicity, etiology, and sample

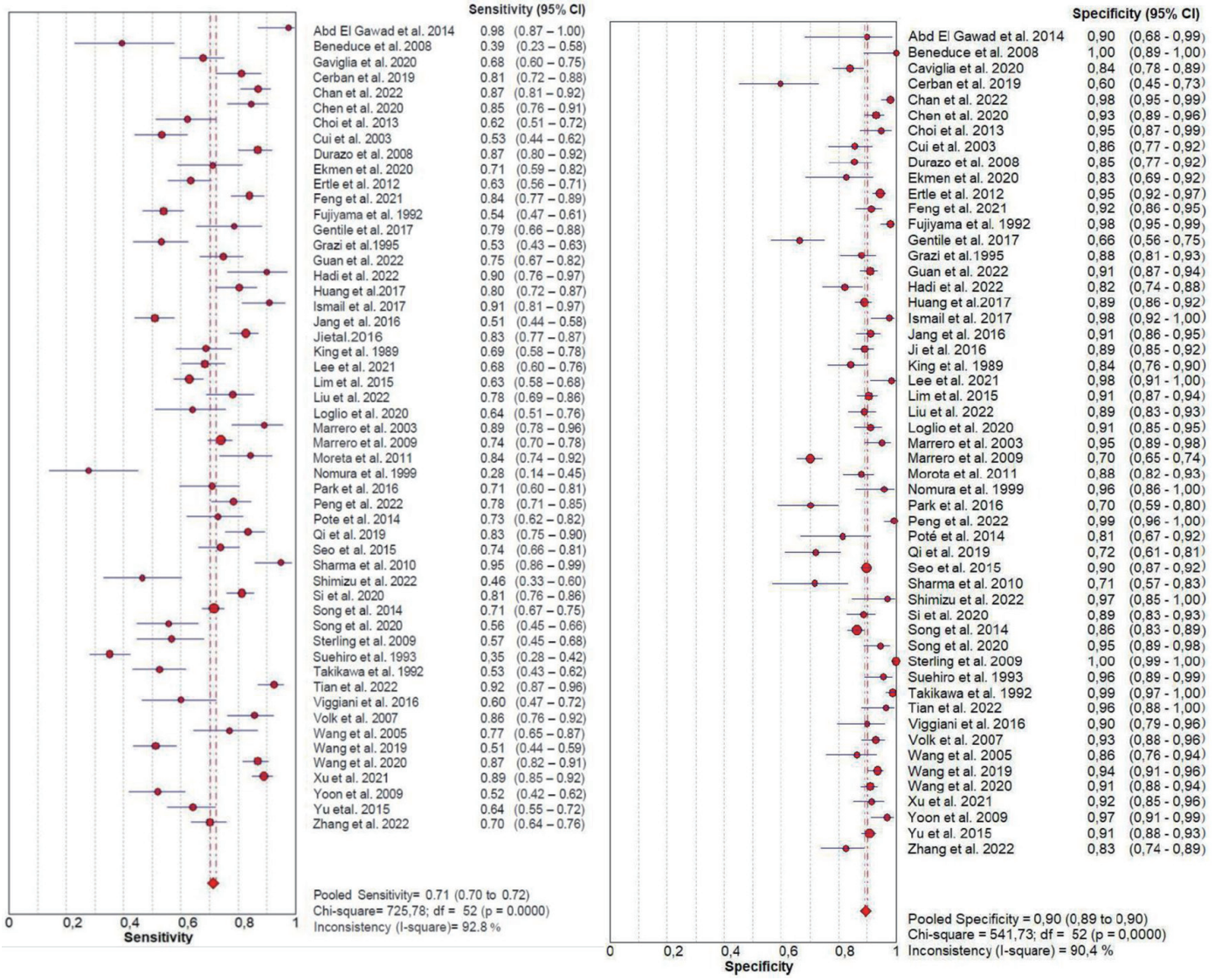

Figure 3. Forest plot for sensitivity and specificity of PIVKA-II. PIVKA-II: protein induced by vitamin K absence or antagonist-II.

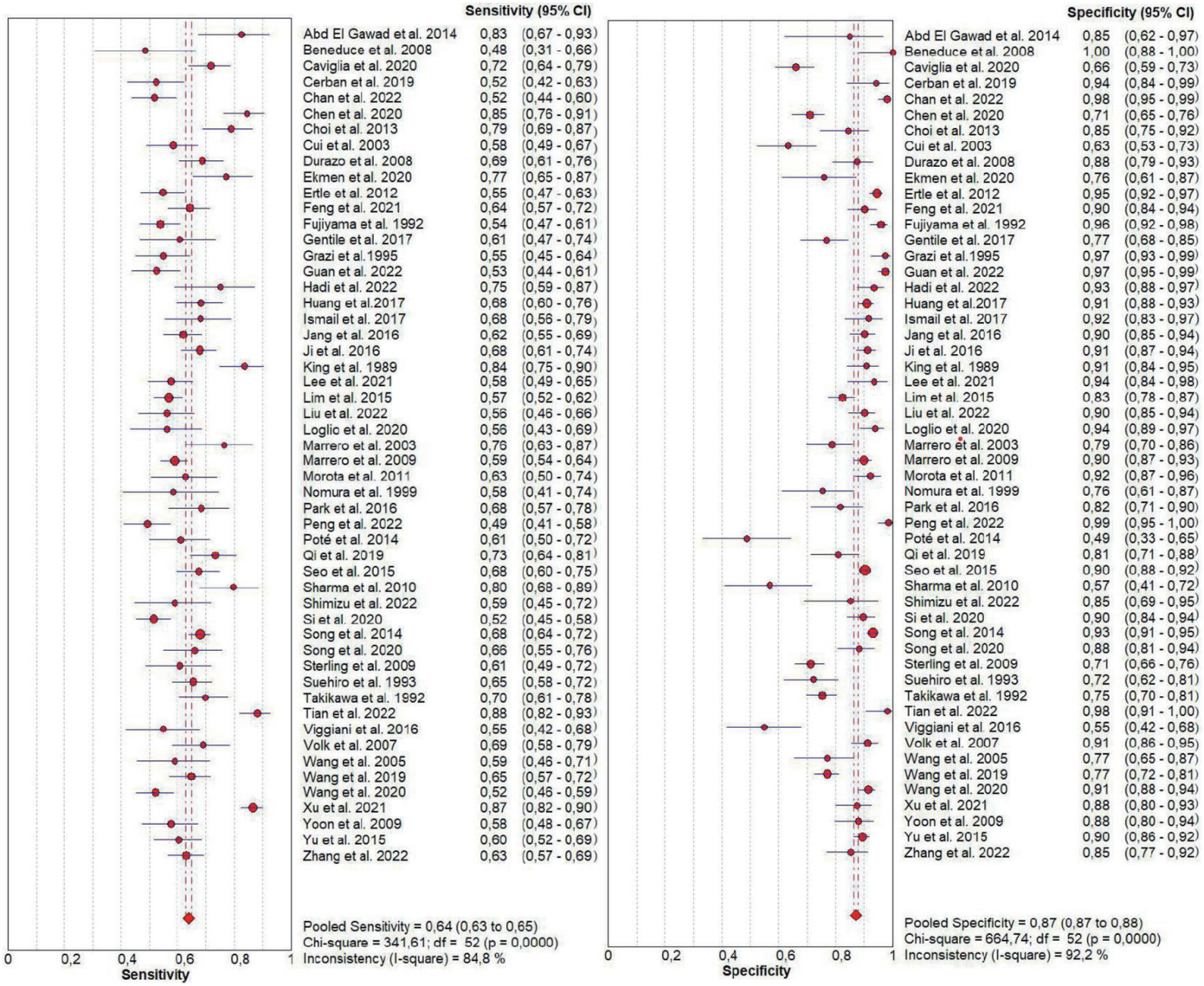

Figure 4. Forest plot for sensitivity and specificity of AFP. AFP: α-fetoprotein.

size ($P < 0.05$) (Table 3).

Publication bias

Funnel plot and Egger's linear regression test were performed to evaluate the publication bias in the 53 studies. An obvious asymmetry was found when reviewing the shape of the funnel plot of the pooled DOR of PIVKA-II for diagnosis of HCC. In addition, Egger's test revealed significant evidence of publication bias ($P = 0.0004$). However, no obvious asymmetry was found when reviewing the shape of the funnel plot of the pooled DOR of AFP for diagnosis of HCC. In addition, Egger's test did not reveal any significant evidence of publication

Table 2. Comparison of Diagnostic Accuracy of PIVKA-II and AFP

Marker	Sensitivity (95% CI)	Specificity (95% CI)	NLR (95% CI)	PLR (95% CI)	DOR (95% CI)	AUC (95% CI)
PIVKA-II	0.71 (0.70 - 0.72)	0.90 (0.89 - 0.90)	0.30 (0.27 - 0.35)	7.18 (5.96 - 8.66)	27.12 (21.14 - 37.79)	0.89 (0.88 - 0.90)
AFP	0.64 (0.63 - 0.65)	0.87 (0.87 - 0.88)	0.42 (0.39 - 0.45)	5.08 (4.20 - 6.15)	12.94 (10.35 - 16.18)	0.78 (0.77 - 0.79)

AFP: α-fetoprotein; AUC: area under the ROC curve; CI: confidence interval; DOR: diagnostic odds ratio; NLR: negative likelihood ratio; PIVKA-II: protein induced by vitamin K absence or antagonist-II; PLR: positive likelihood ratio.

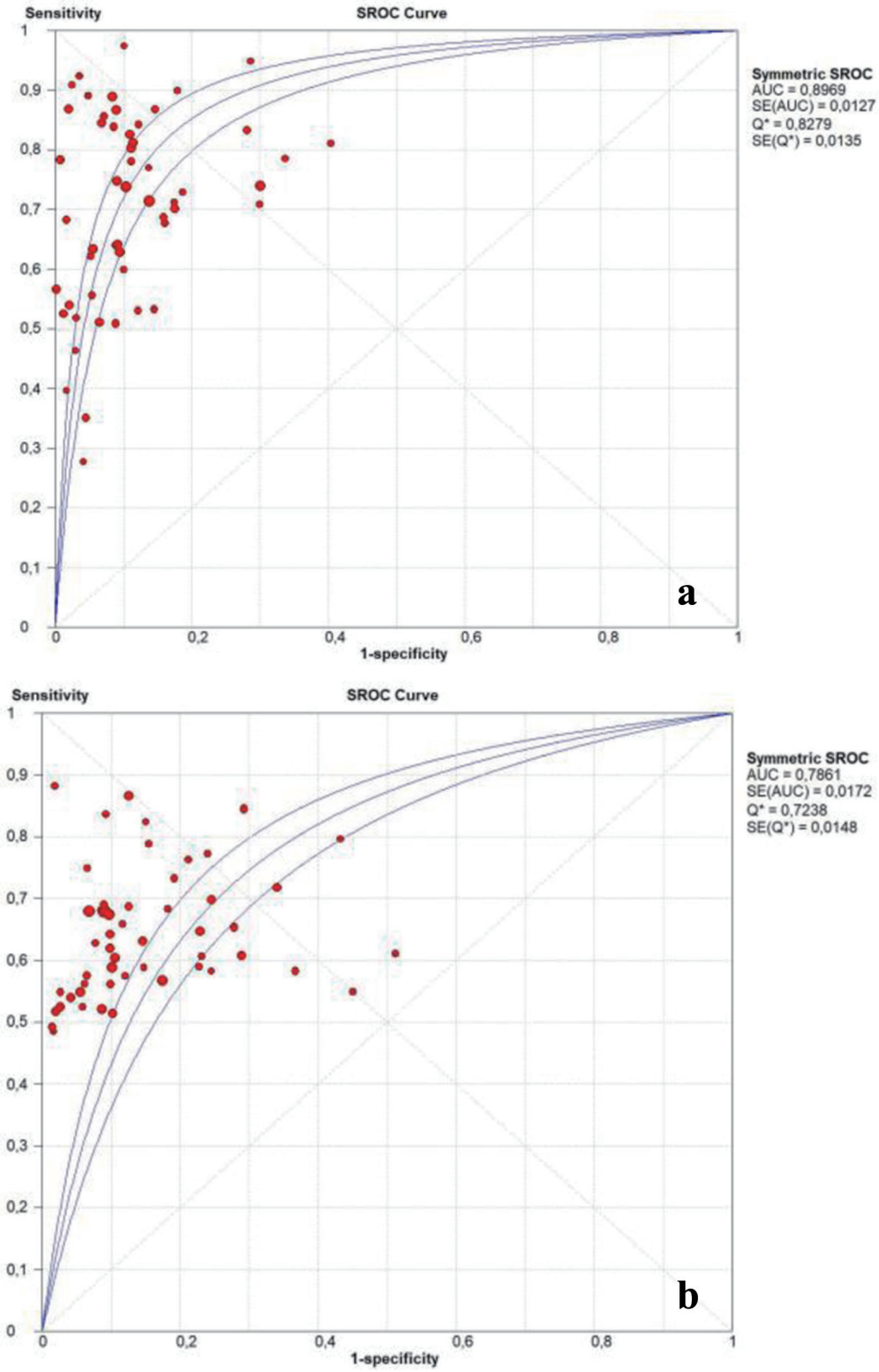

Figure 5. Summary receiver operating characteristic curve of the diagnostic accuracy of PIVKA-II (a) and AFP (b). AFP: α-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II.

Table 3. Meta-Regression Analysis of Potential Sources of Heterogeneity

Factor	PIVKA-II		AFP	
	Coefficient	P value	Coefficient	P value
Ethnicity	0.335	0.105	-0.061	0.673
Etiology	0.185	0.287	-0.084	0.500
Sample size	-0.026	0.930	0.014	0.949

AFP: α-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II.

bias (P = 0.071) (Fig. 6).

Subgroup analysis

The pooled diagnostic accuracy of PIVKA-II or AFP for detection of HCC was analyzed in terms of ethnic group (African, European, Asian, and American patients), etiology (mixed-type HCC, HCV-related, and HBV-related) and sample size of cases (≤ 100 and > 100).

For the subgroup analysis of ethnic group, three studies

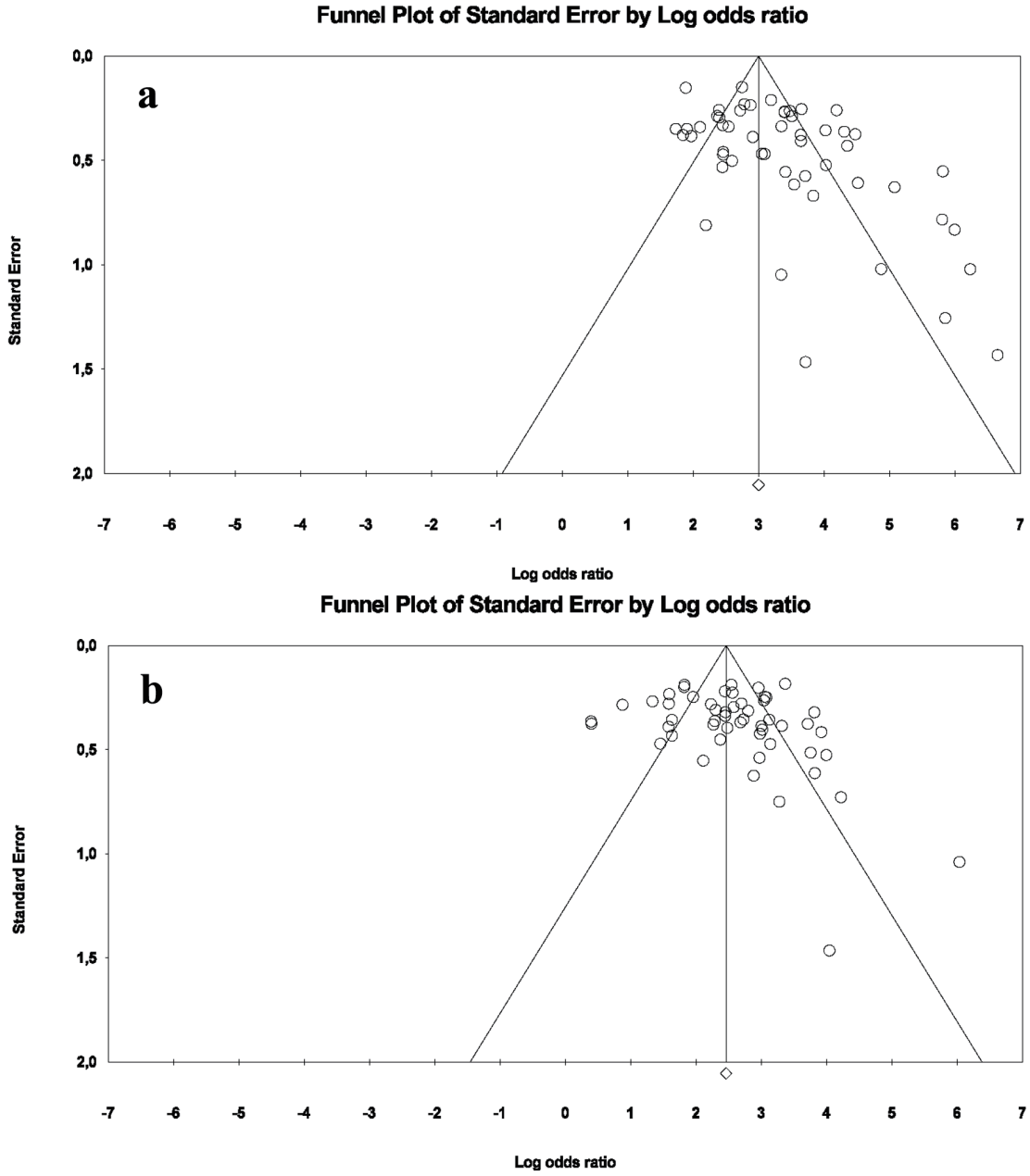

Figure 6. Funnel plot of the pooled DOR of PIVKA-II (a) and AFP (b) for diagnosis of HCC. AFP: α-fetoprotein; DOR: diagnostic odds ratio; HCC: hepatocellular carcinoma; PIVKA-II: protein induced by vitamin K absence or antagonist-II.

Table 4. Subgroup Analysis of the Diagnostic Accuracy of PIVKA-II and AFP

Moderator	Subgroups	PIVKA-II			
		Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	AUC (95% CI)
Ethnicity	Africa	0.817 (0.756 - 0.868)	0.897 (0.849 - 0.933)	10,415 (6,314 - 17,179)	0.968 (0.945 - 0.986)
	Europe	0.634 (0.604 - 0.662)	0.875 (0.857 - 0.892)	12,082 (8,798 - 16,591)	0.812 (0.804 - 0.824)
	Asia	0.716 (0.703 - 0.728)	0.906 (0.899 - 0.913)	30,759 (23,184 - 40,809)	0.910 (0.045 - 0.921)
	America	0.777 (0.747 - 0.804)	0.859 (0.838 - 0.878)	53,251 (15,058 - 188,31)	0.912 (0.903 - 0.923)
Etiology	Mixed	0.706 (0.694 - 0.718)	0.885 (0.887 - 0.893)	24,933 (18,697 - 33,250)	0.901 (0.897 - 0.911)
	HCV	0.675 (0.616 - 0.731)	0.911 (0.885 - 0.932)	31,639 (7,453 - 134,31)	0.845 (0.831 - 0.853)
	HBV	0.749 (0.724 - 0.772)	0.917 (0.905 - 0.927)	40,281 (23,256 - 69,770)	0.912 (0.904 - 0.924)
Sample size	≤ 100	0.711 (0.686 - 0.735)	0.893 (0.879 - 0.907)	27,398 (17,183 - 43,685)	0.903 (0.891 - 0,910)
	> 100	0.714 (0.702 - 0.725)	0.896 (0.889 - 0.902)	27,279 (20,162 - 36,907)	0.890 (0.881 - 0.896)

Moderator	Subgroups	AFP			
		Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)	AUC (95% CI)
Ethnicity	Africa	0.784 (0.721 - 0.839)	0.906 (0.860 - 0.941)	34,544 (19,580 - 60,945)	0.940 (0.934 - 0.946)
	Europe	0.603 (0.574 - 0.633)	0.852 (0.833 - 0.870)	9,145 (4,753 - 17,595)	0.706 (0.697 - 0.714)
	Asia	0.643 (0.629 - 0.655)	0.879 (0.872 - 0.887)	13,858 (10,441 - 17,676)	0.799 (0.784 - 0.808)
	America	0.632 (0.599 - 0.665)	0.848 (0.826 - 0.867)	12,366 (7,213 - 21,202)	0.733 (0.721 - 0.749)
Etiology	Mixed	0.657 (0.645 - 0.669)	0.874 (0.866 - 0.882)	12,967 (9,893 - 16,995)	0.785 (0.778 - 0.796)
	HCV	0.575 (0.513 - 0.635)	0.790 (0.755 - 0.822)	6,865 (3,346 - 14,083)	0.665 (0.650 - 0.670)
	HBV	0.588 (0.561 - 0.615)	0.873 (0.859 - 0.886)	13,718 (9,209 - 20,434)	0.820 (0.809 - 0.831)
Sample size	≤ 100	0.678 (0.652 - 0.702)	0.823 (0.806 - 0.840)	10,350 (6,626 - 16,169)	0.773 (0.764 - 0,779)
	> 100	0.631 (0.619 - 0.643)	0.844 (0.877 - 0.891)	14,678 (11,381 - 19,930)	0.796 (0.789 - 0.802)

AFP: α-fetoprotein; AUC: area under the ROC curve; CI: confidence interval; DOR: diagnostic odds ratio; HBV: hepatitis B virus; HCV: hepatitis C virus; PIVKA-II: protein induced by vitamin K absence or antagonist-II.

were from Africa, 11 from Europe, 33 from Asia, and six from America. Higher diagnostic accuracy values of PIVKA-II were indicated in different ethnic groups compared with AFP. Interestingly, we revealed that the highest diagnostic accuracy values of PIVKA-II and AFP were detected in African patients followed by American, Asian and then European patients (Table 4).

In order to further investigate the impact of HCC etiology, 41 studies dealt with HCC of mixed-etiology, four studies investigated HCV-related, and eight studies examined HBV-related. The performance of both PIVKA-II and AFP were higher when diagnosing HBV-related HCC compared to HCV-related and HCC of mixed-etiology (Table 4).

Twenty-one eligible studies reported the accuracy of PIVKA-II and AFP in diagnosing HCC with a sample size ≤ 100. The remaining studies comprised a sample size > 100. Table 4 presented the subgroup analysis of the diagnostic accuracy of PIVKA-II and AFP when considering the tumor size of HCC. The AUC of PIVKA-II was 0.903 (0.891 - 0.910) and 0.890 (0.881 - 0.896) for detection of HCC with tumor size ≤ 100 and > 100, respectively, while that of AFP was 0.773 (0.764 - 0.779) and 0.796 (0.789 - 0.802).

Discussion

In the last 10 years, the incidence rate of HCC has doubled, adding to the disease's burden. Finding sensitive indicators for early diagnosis and monitoring of recurrence is crucial because this disease has a rapidly penetrating expansion [68]. It was shown that blood indicators for early detection of people at high risk for developing HCC present a chance to lower HCC mortality and lower medical expenses. It seems doubtful that a biochemical marker that is specifically expressed in 100% of HCCs will be discovered given the acknowledged heterogeneity of HCC. Yet, it is likely that using two or three markers in combination will boost the sensitivity of detection. To date, a number of potential biomarkers have been researched in an effort to increase the diagnosis of HCC such as PIVKA-II and AFP [20, 22, 29].

This meta-analysis showed that specificity of PIVKA-II (0.90) was almost comparable to that of AFP (0.87). However, the sensitivity and AUC of PIVKA-II were significantly higher than those of AFP, proving that PIVKA-II is more effective than AFP for detecting HCC. The AUC of PIVKA-II was considerably greater than that of AFP in detecting HCC among patients who were African, American, Asian, and European in subgroup analysis of ethnic groupings. Although AFP worked more effectively in terms of specificity in patients from Africa, PIVKA-II had higher sensitivity and AUC values. Similarly, PIVKA-II outperformed AFP in etiology subgroup analysis for diagnosing HCC with mixed, HBV-, or HCV-related etiologies. Hence, the diagnostic efficacy of PIVKA-II is deserving

of future promotion in clinical practice, according to the findings of the subgroup analysis.

Three systematic review and meta-analysis studies have previously assessed the accuracy of PIVKA-II and/or AFP in HCC diagnosis. Tateishi et al reviewed 17 studies and demonstrated that PIVKA-II (AUC = 0.688) performs better in identifying HCC than AFP (AUC = 0.647) [69]. Li et al performed a systematic review to evaluate the diagnostic effectiveness of PIVKA-II and AFP in detecting HCC among 49 studies. They revealed that the AUC of PIVKA-II and AFP were 0.83 and 0.77, respectively, indicating the superiority of PIVKA- II over AFP [70]. Similarly, Xing et al showed that PIVKA-II is better than AFP in terms of the accuracy for diagnosing HCC in a meta-analysis including 31 studies [71].

These findings are consistent with the results of our study, but our study has some advantages over the above-mentioned meta-analysis in the following aspects. Firstly, we evaluated the diagnostic accuracy of PIVKA-II and AFP among HCC patients, taking studies from various nations into account (15 countries). Secondly, we used eight distinct databases for the literature search and consequently, this meta-analysis is strengthened by its broad inclusion of 53 studies and the large number of people that were examined. Thirdly, we revealed the high methodological quality of the included studies, which showed a low risk of bias.

However, this study is not without limitations. Because this meta-analysis was based on published data, it is possible that publication bias contributed to the non-significant results being less representative. Additionally, it is challenging to conduct a meta-analysis on HCC due to variations in etiology, stage of HCC, and populations. Another drawback was the use of numerous distinct cut-off values. These variations constituted a significant contributor to the inconsistencies in this meta-analysis, making it challenging to compare the findings of various research, and subsequently complicate pooled analysis. Therefore, substantial heterogeneity, which is expected in meta-analysis studies, can change how results can be interpreted [72]. In this context, we demonstrated that the primary cause of heterogeneity in this meta-analysis was the threshold effect, which arises when differences in sensitivities and specificities occur due to different cut-offs values used in different studies. However, our regression analysis failed to attribute the heterogeneity to any one of the clinical characteristics such as ethnicity, etiology, or sample size. As a result, careful consideration must be given to the present work's findings.

The levels of PIVKA-II and AFP, which are used for diagnosing and monitoring HCC, can be influenced by various factors. Age-related genetic mutations are known to increase cancer incidence, but their impact on these markers remains unclear. Regarding sex, males have a higher HCC incidence, possibly due to greater exposure to risk factors, but it is uncertain whether this leads to differences in marker levels. Pregnant women, on the other hand, may exhibit elevated AFP levels. Smoking, a common risk factor for cancer, can indirectly affect these markers by exacerbating liver diseases through oxidative stress. AFP levels can also be elevated by other liver conditions like cirrhosis and hepatitis, as well as various benign and malignant diseases. PIVKA-II levels may increase in conditions such as vitamin K deficiency, coagulation disorders, and liver diseases.

To ensure accurate interpretation of markers like AFP and PIVKA-II, it is crucial to consider the patient's specific condition and comorbidities. This requires a comprehensive assessment of the patient's overall clinical status, which can be facilitated using a scale such as the Charlson Comorbidity Index. Employing such an approach allows for a more precise understanding of how AFP and PIVKA-II levels are influenced by individual patient characteristics.

However, it is important to note that published research articles still need to provide sufficient insight into the factors that may affect the levels of AFP and PIVKA-II. Further research is needed to investigate the effects of age, sex, smoking, liver conditions, vitamin K deficiency, coagulation disorders, certain types of cancer, medication use, and alcohol consumption status on the levels of AFP and PIVKA-II.

In conclusion, our analysis demonstrates that PIVKA-II is a promising biomarker for the detection and monitoring of HCC and it is more accurate than AFP. PIVKA-II has shown a higher accuracy than AFP in detecting: 1) HCC in patients from different races; 2) from both large and small sample size; and also 3) HBV-related, HCV-related or mixed-etiology HCC. To further confirm the effectiveness of PIVKA-II for HCC diagnosis, a prospective cohort study is needed.

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Conflict of Interest

All other authors have no conflict of interest to disclose.

Informed Consent

Not applicable.

Author Contributions

Conceptualization: Nooraldin Merza, Zohaib Ahmed, Dushyant Singh Dahiya, Zohaib Ahmed, Mohamad Nawras, Alsadiq Al-Hillan, and Abdallah Kobeissy. Data curation: Mohamad Nawras, Mohammed Albaaj, Dushyant Singh Dahiya, Yaseen Alastal, Mona Hassan. Formal analysis: Nooraldin Merza. Project administration: Nooraldin Merza. Resources: Dushyant Singh Dahiya and Zohaib Ahmed. Software: Nooraldin Merza. Supervision: Nooraldin Merza, Abdallah Kobeissy. Visualization: Nooraldin Merza and Dushyant Singh Dahiya. The investigation, methodology, validation, writing-original draft, writing-review, and editing: all authors.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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