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Review Article

Diagnostic value of Midkine and AFP in the detection of hepatocellular carcinoma: A systematic review and meta-analysis

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Abstract

Background: Hepatocellular carcinoma (HCC) posed significant health problems and deaths. There are various challenges in the management of HCC, including the late detection or diagnosis. The ongoing diagnostic method in HCC also hinders the detection on the early stages of the disease, thus biomarkers need to be explored further for HCC detection. Serum alpha fetoprotein (AFP) and Midkine (MDK) are two proteins which might be the biomarker of choice in the detection of HCC. This meta-analysis aims to analyze the accuracy of Midkine and AFP in the detection of HCC.

Methods: The systematic review and meta-analysis was conducted by adhering to the Preferred Reporting System for Systematic Review and Meta-Analysis (PRISMA) guidelines. We conduct literature screening and selection followed by quality assessment from various databases such as PubMed, MEDLINE, SpringerLink, ProQuest, EBSCOhost, Cochrane, and EMBASE. The included studies were then extracted and analyzed cumulatively using MedCalc and MetaDTA with forest plot and ROC curve as outcome.

Results: 12 studies were included in this study. The AFP biomarker yields sensitivity value of 62.5% (97.5% CI 0.442 – 0.778) and specificity value of 95% (97.5% CI 0.842 – 0.986), while the Midkine biomarker denotes sensitivity value of 91.6% (97.5% CI 0.83 – 0.961) and specificity value of 82.2% (97.5% CI 0.83 – 0.96).

Conclusions: Both AFP and MDK are proven to be a good diagnostic tool or biomarker in the detection of HCC. The use of both in combination should provide high quality diagnostic marker for HCC suspected patients. Further studies on this should be conducted.

Keywords: AFP; Alpha fetoprotein; Midkine; Hepatocellular carcinoma.

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Hepatocellular carcinoma (HCC) is considered the fifth most prevalent cancer, posing significant health problems and death, as the leading cause of death due to cancer after lung cancer (1, 2). Due to its aggressiveness and heterogeneous in nature, early stage HCC is associated with 5-year survival rates between 40-70% (3). Late detection of HCC often results in no option for definitive therapy. Despite advances of gene-targeted drug therapy, prognosis for treating advanced stage HCC remains clinically uncertain with median progression free survival (PFS) only ranges from 3.1 months to 7.4 months and an objective response rate up to 24% (4). Risk factors triggering the development of HCC may consist of infection of hepatitis B virus, hepatitis C virus, smoking, alcoholism, obesity with fatty liver disease, and other inherited disorders such as Wilson's disease or alpha-1 antitrypsin deficiency (5). Decision to treat HCC depends on the burden and extent of the disease, as well as its etiologies. Surgical resection is one of the most common curative treatment options for HCC; nevertheless, findings of inadequate functional liver reserve following diagnosis often hinders its eligibility. Other options may involve systemic chemotherapy, locoregional radiation therapy, or organ transplantation.

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To understand and guide treatment options, it is imperative to know how HCC is diagnosed and staged. Symptoms related to liver malignancy resemble prodromal stage, such as anorexia, unintended weight loss, fatigue, abdominal pain and jaundice. Physical examination may reveal hepatomegaly and ascites. Ultrasonography, CT scan and MRI are the keystone examinations in the diagnosis of HCC as they encourage the need of liver biopsy for gold standard of diagnosis following specific radiological findings (6). HCC may be hard to detect during the early stage when treatments provide the greatest benefit. Thus, exploring chemical signals involving HCC gene expression is worth the choice.

Serum alpha fetoprotein (AFP) and Midkine (MDK) are two proteins produced by HCC in response to promote the growth of malignant liver cells. AFP is a glycoprotein normally expressed by fetal tissues, which also correlates to liver malignancy in adults. Serum AFP level at above 400 ng/ml is generally considered as diagnostic for HCC. Despite previous studies have identifying AFP as a prognostic factor for survival, the CLIP staging system also utilizes this parameter to be an independent indicator (7). On the other hand, Midkine is a cysteine-rich neurite growth promoting factor 2 (NEGF2) that regulates migration, viability, and activities of non-dormant cells. Expression of MDK protein is firmly discovered during embryogenesis, specifically attributed to neural cell developments. In HCC, MDK has been found to interact with other factors, such as progranulin, inhibitor of NF-kB, negative regulator of Wnt-β-catenin-TGF signalling, and promoter of extracellular matrices degeneration. All of these factors ultimately promote the progression of HCC (8). Based on the presumption that AFP and MDK are bound to the progression of HCC, both proteins are detectable, even in the early stage of malignancy. Analyses of these proteins as diagnostic indicators of HCC were done in numerous previous studies, yet different studies produced various results in terms of its sensitivity and specificity (9-12). This review aimed to provide deeper insights regarding AFP and MDK accuracy in diagnosing HCC based on meta-analysis of multiple studies.

Methods

The systematic review was conducted by adhering to the Preferred Reporting System for Systematic Review and Meta-Analysis (PRISMA).

Article search and screening process: Identification of potential studies involves specific keyword searching in combination with the use of Boolean operators. All search was done in different journals, comprising of PubMed, MEDLINE, SpringerLink, ProQuest, EBSCOhost, Cochrane, and EMBASE. Keywords include “hepatocellular carcinoma, “alpha-fetoproteins”, “Midkine”, and “diagnosis” or “prognosis”. The full search queries used in each database can be seen in table 1. More than 200 records were screened for duplicates and title checks, followed by abstract screening. Studies exploring Midkine and alpha-fetoprotein (AFP) and its diagnostic value, such as sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), or Area Under the Curve (AUC) value. The studies must also be conducted in human subjects. Criteria for excluding records consist of incomplete outcomes, irretrievable full text, and incompatible language. Subsequently, up to 42 records were assessed for eligibility, resulted in only 12 final studies which will be included in the final analysis. We used Mendeley as the reference manager to properly conduct article screening and deduplication. A constructed PRISMA 2020 (Preferred Reporting in Systematic Review and Meta-Analysis) flowchart is shown in figure 1 (13).

Risk of bias analysis: The final included studies were then subjected to evidence grading based on AHRQ (Agency for Healthcare Research and Quality) scale. The quality assessment using AHRQ was conducted to assess selection bias, comparability bias, and bias in outcome. Assessment on sample representativeness, non-respondent selection, ascertainment of exposure, design control for confounders, assessment outcome objectivity, and statistical test was done on the included studies. The tools classify studies into good, fair, or poor quality based on the bias found. Good quality if there is good quality in all aspects, fair if there is only 2 out of 3 aspects of good quality in the selection bias, or poor,if there is a risk of bias in the comparability and outcome.

Data extraction and analysis: The data from each study were extracted, consisting of the study characteristics such as authors, year of publication, study design, study location, sample size, and cut-off value used in the diagnostic analysis of AFP and Midkine marker. On the outcome extraction, the diagnostic value was extracted, such as sensitivity, specificity, PPV, NPV, and AUC to gauge the diagnostic performance in each study. Following data extraction regarding diagnostic accuracy and outcome of serum AFP and Midkine from each study, all results were meta-analyzed and pooled using Forest plots and ROC (receiver operating characteristics) curve (14). The meta-analysis was conducted using the MedCalc software for AUC analysis, while the sensitivity and specificity cumulative analysis was conducted using MetaDTA online software (15, 16). On the analysis, publication bias was also analyzed using Egger’s test.

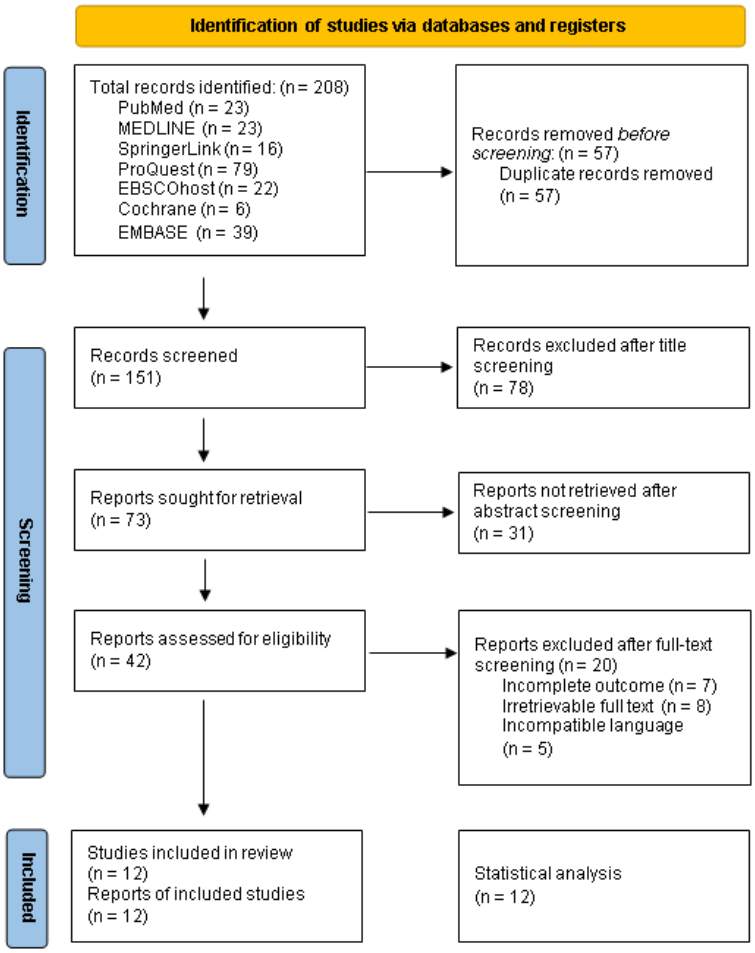


Figure 1. PRISMA 2020 Flowchart for identification of studies via databases and registers

Table 1. Identified records using Boolean-based written keywords in respective search engine

Database	**Search Date:** February 12th 2023 **Keywords**	**Hits**
PubMed	(hepatocellular carcinoma OR HCC OR "carcinoma, hepatocellular"[MeSH Terms] OR hepatocellular carcinoma[Text Word]) AND ("midkine"[MeSH Terms] OR midkine[Text Word]) AND ("alpha-fetoproteins"[MeSH Terms] OR alpha fetoprotein[Text Word] OR AFP) AND (diagnosis OR prognosis)	23
MEDLINE	(hepatocellular carcinoma OR HCC) AND (midkine OR midkine level) AND (alpha-fetoproteins OR alpha fetoprotein OR AFP) AND (diagnosis OR prognosis)	23
SpringerLink	(hepatocellular carcinoma OR HCC) AND (midkine OR midkine level) AND (alpha-fetoproteins OR alpha fetoprotein OR AFP) AND (diagnosis OR prognosis)	16
ProQuest	(hepatocellular carcinoma OR HCC) AND (midkine OR midkine level) AND (alpha-fetoproteins OR alpha fetoprotein OR AFP) AND (diagnosis OR prognosis)	79
EBSCOhost	(hepatocellular carcinoma OR HCC) AND (midkine OR midkine level) AND (alpha-fetoproteins OR alpha fetoprotein OR AFP) AND (diagnosis OR prognosis)	22
Cochrane	(hepatocellular carcinoma OR HCC OR "carcinoma, hepatocellular"[MeSH Terms] OR hepatocellular carcinoma [Text Word]) AND ("midkine"[MeSH Terms] OR midkine[Text Word]) AND ("alpha-fetoproteins"[MeSH Terms] OR alpha fetoprotein[Text Word] OR AFP) AND (diagnosis OR prognosis)	6
EMBASE	(hepatocellular carcinoma OR HCC) AND (midkine OR midkine level) AND (alpha-fetoproteins OR alpha fetoprotein OR AFP) AND (diagnosis OR prognosis)	39

Results

Search Strategy and Results: Systematic searching and thorough selection in seven journal databases have yielded up to 12 studies in which the data will be reviewed and analyzed. Medical subject headings (MeSH) are used as standardized keywords in several databases to increase search specificity (17). There are eight studies where all data are sufficient for analysis. Since the other four does not provide adequate data, they will be included mainly in the discussion section for review. Search results are shown in the table 1.

Study Characteristics and Outcomes: All eight studies are subjected for quality assessment using AHRQ scale. All studies exhibited good quality based on six assessment variables with total score ranging from 7 to 8. Only Omar et al., Osman et al., and Hodeib et al. score "b" in the selection assessment, especially in the non-respondents variable (18-20). Except for the confounder control assessment and the aforementioned variable, all studies score "a" in the rest of the variables. AHRQ grading of each study is shown in the table 2.

Table 2. Quality assessment of selected studies

Study	Selection			Comparability	Outcome		Total quality score	AHRQ standard
	Representativeness of the sample	Non-respondents	Ascertainment of exposure	Design or analysis controlled for confounders	Assessment of outcome	Statistical test		
El-Shayeb et al, 2021	a (*)	a (*)	a (*)	b (*)	a (*)	a (*)	8	Good
Malov et al, 2021	a *)	a (*)	a (*)	b (*)	a (*)	a (*)	8	Good
Omar et al, 2020	a (*)	b	a (*)	b (*)	a (*)	a (*)	7	Good
Omran et al, 2019	a (*)	a (*)	a (*)	b (*)	a (*)	a (*)	8	Good
Osman et al, 2019	a (*)	b	a (*)	b (*)	a (*)	a (*)	7	Good
Mashaly et al, 2018	a (*)	a (*)	a (*)	b (*)	a (*)	a (*)	8	Good
Hodeib et al, 2017	a (*)	b	a (*)	b (*)	a (*)	a (*)	7	Good
Shaheen et al, 2015	a (*)	a (*)	a (*)	b (*)	a (*)	a (*)	8	Good

*Assessment form and complete version of AHRQ grading calculation are located in Appendix 1.
Study is considered:

- Good: 3 or 4 stars in selection domain AND 1 star in comparability domain AND 2 or 3 stars in outcome domain.
- Fair: 2 stars in selection domain AND 1 star in comparability domain AND 2 or 3 stars in outcome domain.
- Poor: 0 or 1 stars in selection domain AND 0 star in comparability domain AND 0 or 1 stars in outcome domain.

(*) Stars are given for each of the study aspects.

As a matter of fact, most of the studies were conducted in the nation of Egypt with only one done in Russia that is of Malov et al. (9). The number of participants ranges from 70 to 244 with that the study done by El-Shayeb et al. (21) that was considered as the largest one. All studies were designed based on cross-sectional type, which ensure applicability in gathering data regarding diagnostic accuracy of serum Midkine and AFP in HCC patients. Cutoff value for serum Midkine and AFP was noted in various studies, yet no study exhibited the exact same value. Study characteristics are showed in the table 3.

Among all studies, only Hodeib et al. did not provide the predictive value outcome of both serum proteins in diagnosing HCC (20). Most of the studies correspond well to the fulfilment of selection criteria in terms of outcome; however, several data inadequacy is sometimes inevitable. Mashaly et al. did not have both serum AFP and Midkine ROC analysis as parts to determine the diagnostic performance but had successfully calculated the accuracy (10). Most of the studies had their data acceptable for study-to-study analysis of diagnostic accuracy and outcomes of each serum protein. Summary of key studies outcome could be seen in the table 4.

Analysis of AFP-related Studies: The accuracy of serum AFP as diagnostic parameter of HCC was found to be various in different studies with the lowest in Omran et al. and the highest in Osman et al. (18, 19). Lowest sensitivity could be found in the Omran et al.'s study., yet identifying, which corresponds to only 29%. Yet, it exhibited the highest value of specificity. Additionally, Omran et al. used the highest cutoff value (400 IU/ml or 484 ng/ml) for serum AFP among all studies (18). Despite the highest diagnostic accuracy of AFP marker in Osman et al.'s study, study with similar cutoff value (El Shayeb et al., 2021) does not provide similar accuracy. However, Osman et al. and El Shayeb et al. exhibited similar AUC value (0.837 vs. 0.83, respectively). The difference is that El Shayeb's study showed lower specificity result of serum AFP as biomarker for HCC (19, 21). Besides, Shaheen et al. have the second lowest sensitivity (sens 40%, spec 96.7%) of serum AFP in detecting HCC, of which also revealed the second lowest accuracy among all studies (accuracy 64.2%, AUC 0.671 [0.546-0.796]). It may disclose potential disparities in terms of methods between studies that have similar cutoff value but different sensitivity, such as Hodeib et al. All eight studies went through Forest plotting. While only four studies (El Shayeb et al., Malov et al., Omar et al., Omran et al.) with complete ROC data and their 95% confidence interval will proceed to AUC analysis (9, 18, 21, 22). In accordance to Forest plot shown in figure 2, all pooled studies denote sensitivity value of 62.5% (97.5% CI 0.442 – 0.778) and specificity value of 95% (97.5% CI 0.842 – 0.986). Additionally, the AUC analysis (figure 3.) showed 0.731 ROC area index (95% CI 0.649 – 0.812, $p<0.001$) with heterogeneity I^2 index of 82.06% (P=0.0008). Egger's test revealed insignificant bias among four studies (P=0.38), yet it did not represent the rest of the studies related to AFP biomarker.

Table 3. Study characteristics

Author; year	Study design	Location	Number of participants	Patients	Controls	Midkine cutoff value (ng/ml)	AFP cutoff value (ng/ml)
El-Shayeb et al. 2021	Cross-sectional study	Egypt	244 participants	Group I: 89 cirrhotic HCV patients without HCC, Group II: 86 cirrhotic HCV patients with HCC (group II)	69 healthy participants	5.1 ng/mL	10 ng/mL
Malov et al. 2021	Cross-sectional study	Russia	110 participants	55 cirrhotic patients with a verified diagnosis of HCC	55 cirrhotic patients without HCC	0.8 ng/mL	20 ng/mL
Omar et al. 2020	Cross-sectional study	Egypt	90 participants	Group I: 40 HCV patients with liver cirrhosis, Group II: 40 HCV cirrhotic patients with hepatocellular carcinoma	10 healthy participants	1.33 ng/mL	41.3 ng/mL

Author; year	Study design	Location	Number of participants	Patients	Controls	Midkine cutoff value (ng/ml)	AFP cutoff value (ng/ml)
Omran et al. 2019	Cross-sectional study	Egypt	196 patients	104 patients with HCC	52 patients with liver cirrhosis and 40 patients with liver fibrosis	1.0 ng/mL	400 IU/L
Osman et al. 2019	Cross-sectional study	Egypt	80 patients	40 HCC patients	24 liver cirrhosis patients and 16 healthy participants	0.34 ng/mL	8 IU/L
Mashaly et al. 2018	Cross-sectional study	Egypt	90 patients	44 patients with HCC	31 patients with cirrhosis and 15 healthy controls	1.683 ng/mL	200 ng/mL
Hodeib et al. 2017	Cross-sectional study	Egypt	70 participants	35 patients presented with HCC on top of cirrhosis.	35 healthy participants	0.65 ng/mL	80 ng/mL
Shaheen et al. 2015	Cross-sectional study	Egypt	100 participants	40 HCC patients	30 liver cirrhosis patients, 30 healthy participants	0.387 ng/mL	88.5 ng/mL

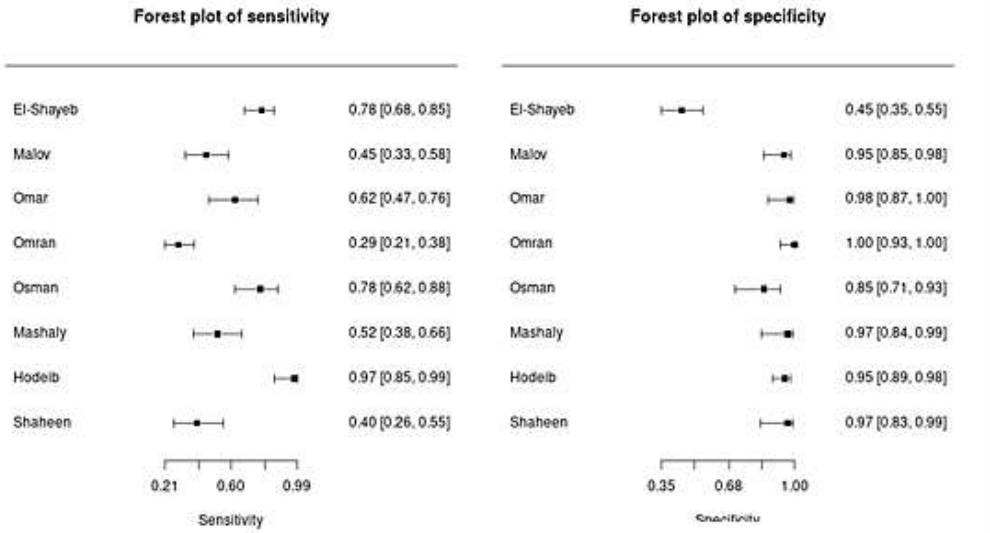
* Abbreviations: HCV: hepatitis C virus; HCC: hepatocellular carcinoma; AFP: alpha-fetoprotein; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve; CI: confidence interval.

Table 4. Key study outcomes

Author; year of publication	Test marker	Study outcomes					
		Sensitivity [95%CI]	Specificity [95% CI]	PPV [95%CI]	NPV [95%CI]	AUC [95% CI]	Accuracy [95% CI]
El-Shayeb et al. 2021	Midkine	100%	90%	89%	100%	0.95 (0.95–0.99)	94%
	AFP	78%	45%	61.5%	71.2%	0.83 (0.73–0.89)	65.14%
Malov et al. 2021	Midkine	85.5%	63.6%	70.1%	81.4%	0.795 (67.4–89.0)	N/A
	AFP	45.5%	94.5%	89.3%	63.4%	0.630 (0.57-0.70)	N/A
Omar et al. 2020	Midkine	87.5%	82.5%	83.3%	86.8%	0.921 (0.87-0.97)	85.0%
	AFP	62.5%	97.5%	96.15%	72.22%	0.79 (0.69 – 0.9)	80%
Omran et al. 2019	Midkine	76%	71%	84%	60%	0.81 (0.71–0.90)	74%
	AFP	29%	100%	100%	41%	0.69 (0.59–0.77)	53%
Osman et al. 2019	Midkine	90%	70%	75%	87.5%	0.812	80%
	AFP	77.5%	85%	83.8%	79.1%	0.837	81.25%

Mashaly et al. 2018	Midkine	81.82%	83.87%	87.8%	76.47%	N/A	82.67%
	AFP	52.27%	96.77%	95.83%	58.82%	N/A	70.67%
Hodeib et al. 2017	Midkine	98.4%	96.2%	N/A	N/A	0.99	N/A
	AFP	97.0%	95.0%	N/A	N/A	0.97	N/A
Shaheen et al. 2015	Midkine	92.5%	83.3%	88%	89.2%	0.941 (0.890–0.992)	88.5%
	AFP	40%	96.7%	94.1%	54.7%	0.671 (0.546–0.796)	64.2%

*Significant results. Abbreviations: AFP: alpha-fetoprotein; PPV: positive predictive value; NPV: negative predictive value; AUC: area under the curve; CI: confidence interval



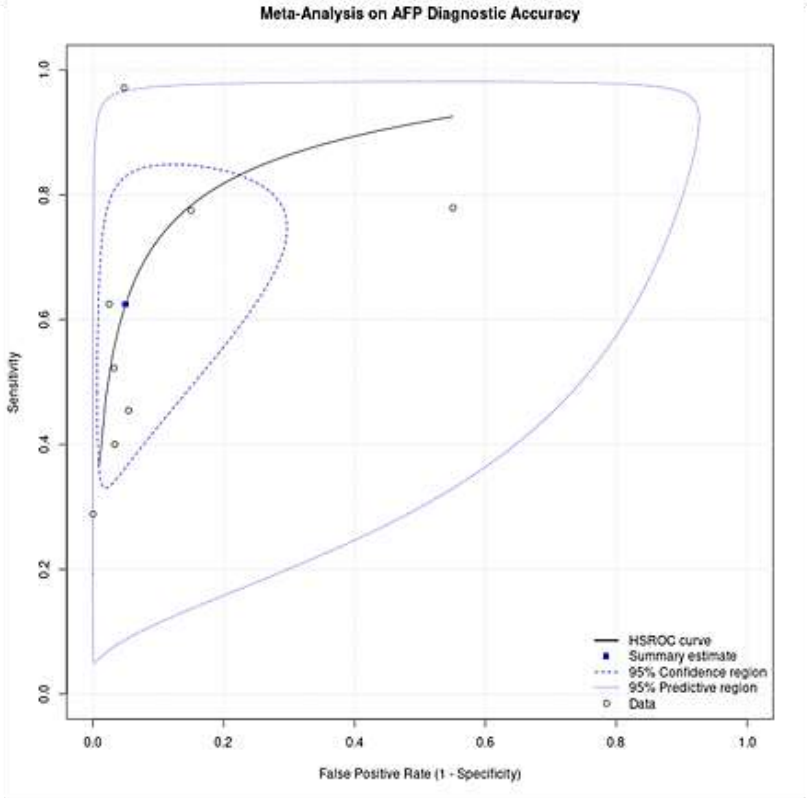


Figure 2. Forest plot analysis of AFP-related studies

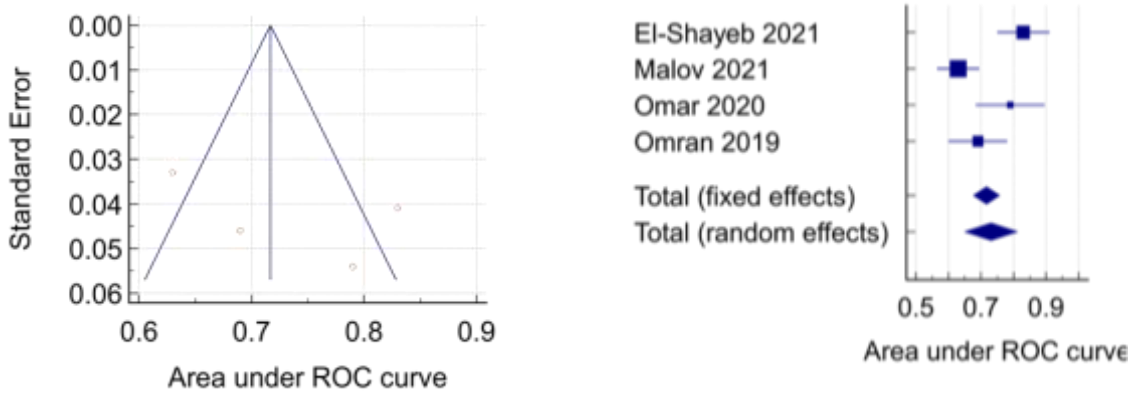
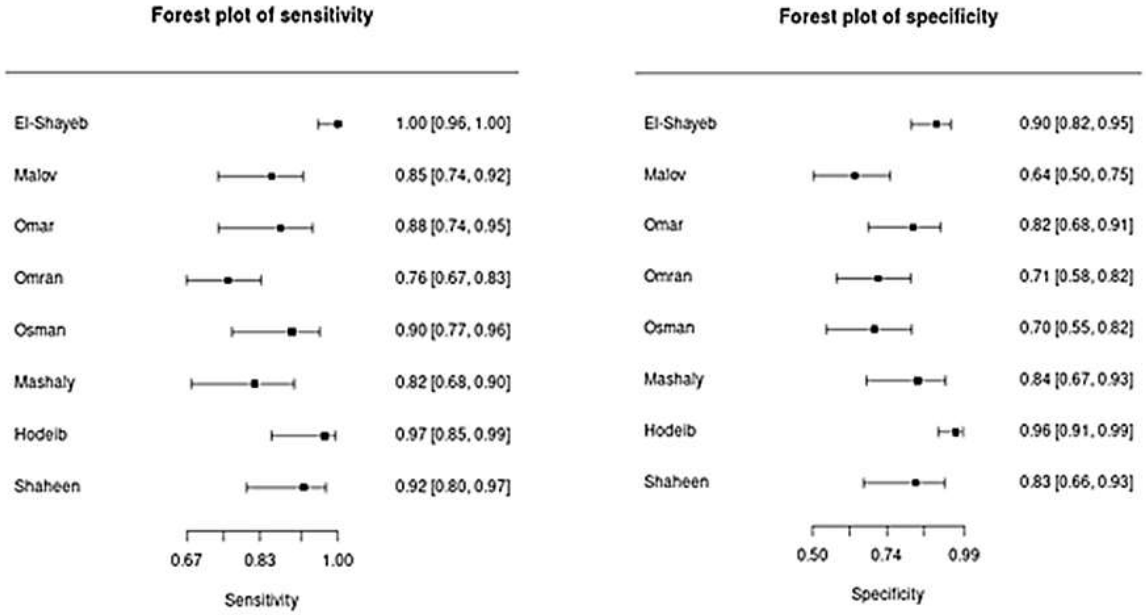


Figure 3. Area under curve analysis of AFP-related studies

Analysis of MDK-related Studies: Highest sensitivity of Midkine protein as biomarker in detecting HCC is from the El Shayeb et al.'s study (Sens 100%, Spec 90%), while the highest specificity was found in the Hodeib et al.'s study (Sens 98.4%, Spec 96.2%). Hodeib et al.'s study displayed Midkine with higher AUC value than the El Shayeb et al.'s study (0.99 vs. 0.95, respectively). Higher cutoff value was also seen in the El Shayeb et al.'s study than the Hodeib et al.'s study despite similarity in sensitivity and specificity (20, 21).

On the other hand, Midkine protein is the least sensitive in the Omran et al.'s study (Sens 76%, Spec 71%) with corresponding AUC value of 0.81 (95% CI 0.71 – 0.9) and 74% accuracy. The lowest specificity of the protein was, hence, discovered in the Malov et al.'s study (Sens 85.5%, Spec 63.6%) with unknown accuracy (9). Only El Shayeb et al. managed to show in the study that the Midkine serum concentration of 5.1 ng/ml has an established accuracy to screen HCC up to more than 90%. Furthermore, all eight pooled studies exhibit sensitivity value of 91.6% (97.5% CI 0.83 – 0.961) and specificity value of 82.2% (97.5% CI 0.83 – 0.96). The forest plot analysis is shown in the figure 4. There are five studies (El Shayeb et al., Malov et al., Omar et al., Omran et al., and Shaheen et al.) with complete data, that underwent AUC analysis (9, 18, 21-23). The analysis (under random effect) revealed 0.903 ROC area index with 95% confidence interval between 0.854 to 0.951 ($p<0.001$). Heterogeneity test denotes significant inconsistent results (I^2 = 74.6%, $p<0.0034$) among the five studies (figure 5). Quantitatively, Egger's test resulted in significant bias (P= 0.0343) in the five studies, but were not conformed to the Begg's test (P=0.0707).



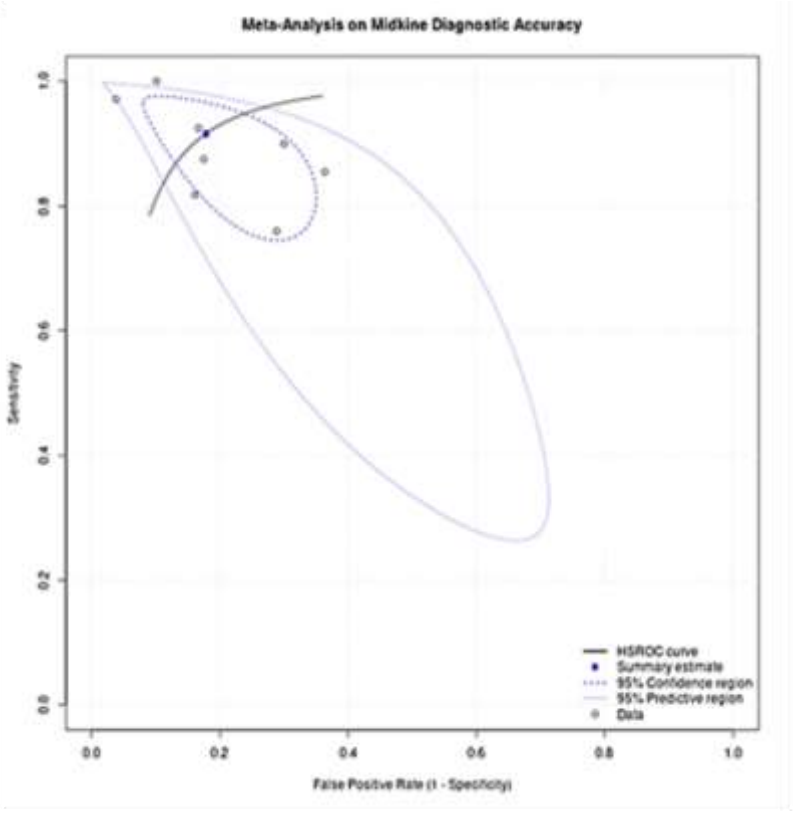


Figure 4. Forest plot analysis of AFP-related studies

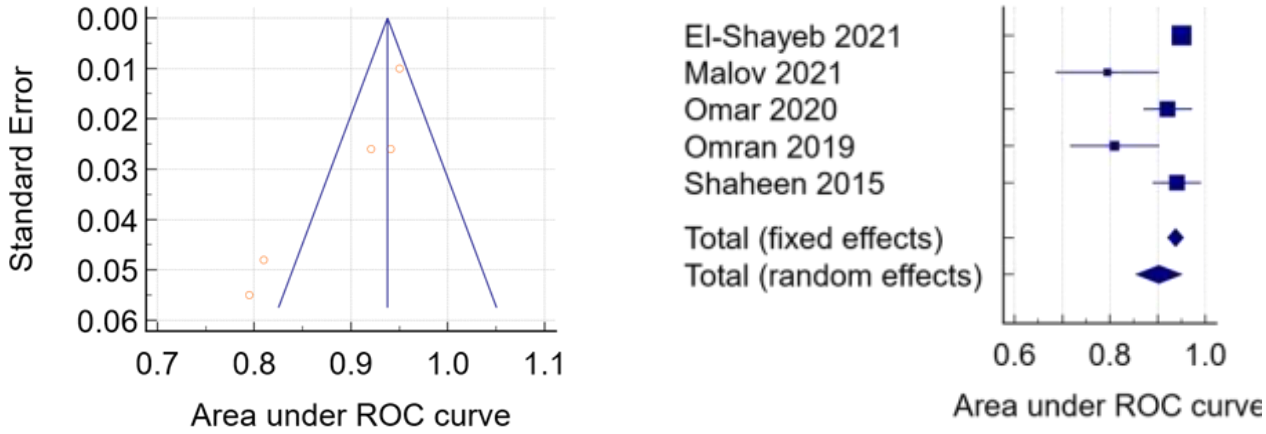


Figure 5. Area under curve analysis of MDK-related studies

Discussion

Our meta-analysis shows the considerable high performance of both MDK and AFP in the diagnosis of HCC. The AFP and Midkine biomarkers prove to have tremendous diagnostic value in the detection of HCC. The Midkine (MDK) yields better sensitivity value, which might be suitable for initial detection and screening for HCC, while AFP yields better specificity value in determining the more accurate diagnosis of HCC. Both markers can be used conjunctively to complement each other.

Diagnostic Accuracy of AFP and MDK Protein: In the Omran et al.'s study, AFP biomarker has the lowest accuracy in detecting HCC due to the fact that it only exhibited 29% sensitivity (but 100% specificity). Omran et

al.'s study aims to propose an ideal diagnostic model using candidate marker in addition to AFP to detect HCC, thus the study may potentially underestimate the diagnostic value of sole AFP biomarker. High cutoff AFP value (400 IU/ml or 484 ng/ml) may result in high false negative findings in the samples, therefore explaining its 29% sensitivity yield of AFP biomarker (18). Additionally, both Osman et al. and El Shayeb et al.'s study has used Zhu et al.'s study as their guide. This is why both studies may have similar cutoff AFP value (8 IU/ml or 9.86 ng/ml, Osman et al; 10 ng/ml, El Shayeb et al). Since there are differences in the number of participants involved in either Osman et al.'s or El Shayeb's study, it may explain the disparity of AFP accuracy in the studies (19, 21). As a result, cutoff value of AFP biomarker yield an important aspect in determining the result of diagnostic accuracy, as well as sensitivity and specificity. This could be found in the study published by Shaheen et al., where it analyzed the diagnostic parameter of different AFP cutoff concentration (23). MDK protein could be used as a biomarker with lower false positive rate in differentiating HCC from non-HCC cirrhotic liver. This statement conforms to the findings by Hodeib et al. and El Shayeb et al (20, 21). Nevertheless, the low specificity of MDK protein found in Malov et al.'s study correlates with its unique purpose of conducting the research. Malov et al. aims to search the most effective serum tumor biomarkers for early diagnosis of HCC by using various aggregate indicators, whereas other studies aim to compare the effectiveness of MDK toward another marker (9). This may, however, confer potential bias. Lowest sensitivity of MDK protein was found in the Omran et al. study, yet identifying HCC with AUC value of 0.81 reinforce previous studies in predicting HCC (18, 24).

The results also described higher specificity value of AFP than that of MDK protein, hence, it likely be used in conjunction with MDK protein to detect HCC. In addition to results described by Zheng et al, 95.12% of AFP negative HCC showed enhanced expression of MDK protein, that significantly increase the detection rate of HCC (25). On the contrary, MDK protein revealed higher sensitivity than that of AFP, which may serve as initial screening of an early stage HCC in patients with or without cirrhosis. Both AFP and MDK protein are acceptable parameters used to find the existence of HCC based on AUC analysis (0.903 vs. 0.731). AUC value above 0.9 in MDK protein is considered as excellent diagnostic parameter that correlates with previous studies published by Vongsuvanh et al. As AFP may produce false negative result, the use of MDK protein as complementary biomarker increases the diagnostic yield in AFP-negative HCC (11).

Limitations and Recommendations: This study has several limitations. First, different cut-off value for AFP and MDK protein among studies could result in different accuracy. This is reflected from the significantly heterogeneous output of AUC calculation (I^2 AFP = 82.06%; I^2 MDK = 74.6%) among studies. Second, restricted publication bias could be found in MDK-related studies involved in the forest plot analysis. This is caused by the contradictory results of Begg's test and Egger's test in the MDK-related studies. This may emerge from the effect of reference bias in the beginning of the study that AFP is suboptimal in detecting HCC, which therefore aimed to analyze MDK as subsequent novel biomarker in alternative to or conjunction with AFP. Lastly, most of the studies in the analysis tend to overestimate the accuracy of MDK protein compared to that of AFP. This could be explained by the fact that the average accuracy and AUC value of MDK protein is higher than that of AFP among studies. Future studies are needed to elaborate objective value of serum AFP and MDK as diagnostic parameters of HCC, given that the aims of the study must not compare only two of those biomarkers.

The AFP and Midkine biomarkers prove to have tremendous diagnostic value in the detection of HCC. The Midkine (MDK) yields better sensitivity value, which might be suitable for initial detection and screening for HCC, while AFP yields better specificity value in determining the more accurate diagnosis of HCC. Thus, the two biomarkers can be used in conjunction to provide optimal diagnostic value for HCC detection. Further studies still should be conducted to complement this finding, particularly, the combination of both biomarkers in HCC detection.

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Ethics Approval: Ethics are not relevant because the study is a meta-analysis. The study has been registered with PROSPERO.

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Conflict of Interests: The authors declare that there is no conflicts of interest.

Authors' contribution: ML and DD contributed to the concept and design of this study. DD and SSS contributed to literature searching and eligible study screening. ML, DD, and SSS contributed to the data extraction and analysis.

ML, DD, and SS contributed to the manuscript preparation. DD, SSS, and CP contributed reviewed the final version.

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