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Viewpoint

Diagnostic role of microRNA-125b for hepatocellular carcinoma

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It is estimated that there was 841 000 new cases of liver cancer and 782 000 associated deaths worldwide in 2018, ranking as the sixth most common cancer and the fourth leading cause of cancer-related deaths [1]. With approximately 90% of total cases, hepatocellular carcinoma (HCC) is the most frequent type of primary liver cancer, and is a major public global health challenge at present [1]. The majority of HCC patients are usually at advanced stages when diagnosed, which misses the optimal treatment and prognosis is poor. Alpha-fetoprotein (AFP) is the most widely applied diagnostic serum biomarker to detect HCC at present; however, the diagnostic accuracy of AFP is unsatisfactory, with sensitivity of 53% and specificity of 90% for early stage HCC [2]. Recently, plenty of studies reported that microRNA-125b (miR-125b) might function as potential diagnostic biomarker in HCC [3–8]. miR-125 family, consisting of miR-125a, miR-125b-1, and miR-125b-2, is closely associated with differentiation, proliferation, invasion, and metastasis of cancer cells. However, the diagnostic accuracy of miR-125b remains inconsistent.

In order to evaluate the diagnostic accuracy of miR-125b for HCC, we performed a meta-analysis following the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) statement in this viewpoint. Firstly, we conducted a literature search in the including databases: PubMed, Web of Science, Embase, and Medline from January 1, 2000 to December 20, 2018. The search terms were as follows: ("miR-125b" OR "microRNA-125b") AND ("hepatocellular carcinoma" OR "hepatocellular cancer" OR "HCC" OR "liver cancer") AND ("diagnosis" OR "diagnostic" OR "ROC curve" OR "sensitivity" OR "specificity"). Consequently, we identified 13 studies composing 1254 HCC cases and 1031 controls in the screened 6 publications [3–8] after removing duplicates, and screened full text concerning the diagnostic role of miR-125b through database searching.

The main characteristics and quality assessment of the included studies [3–8] were summarized in Table 1. The publication years of these included studies ranged from 2016 to 2018. Among the 6 studies, four studies [3,4,6,8] were conducted in China; the other two [5,7] were from Egypt. The sample type was serum or plasma. The detected method of miR-125b was quantitative real-time polymerase chain reaction (qRT-PCR). The control types comprised healthy control (HC), liver cirrhosis (LC), chronic hepatitis B (CHB), and chronic hepatitis C (CHC).

As mentioned above, the sensitivity and specificity of the widely applied biomarker AFP were 0.53 and 0.90, respectively; we calculated the pooled results of sensitivity, specificity to assess the diagnostic efficiency of miR125b for HCC. As shown in Fig. 1(A) and (B), the pooled sensitivity and specificity of miR-125b were 0.81 (95% CI: 0.74–0.87) and 0.84 (95% CI: 0.76–0.89), respectively. As shown in Fig. 2, the introduction of miR-125b changed the post-test probability of HCC. We evaluated the post-test probabilities assuming that the pre-test probabilities of patients with HCC were 25%, 50%, and 75%, respectively. As shown in Fig. 2, an abnormal test result for miR-125b increased the probability to 63%, 83%, and 94%, respectively, whereas a normal test result for miR-125b reduced the probability to 7%, 18%, and 40%, respectively. The above pooled results indicated that miR-125b had moderate-to-high diagnostic efficiency for HCC.

The diagnostic value of miR-125b was reported in a wide range of cancer types, such as breast cancer [9] and non-small cell lung cancer [10], especially HCC [3–8]. Our current meta-analysis indicated that miR-125b is a potential biomarker of HCC.

As a novel potential diagnostic biomarker for HCC, miR-125b has several conspicuous merits. First, miR-125b is an appropriate diagnostic biomarker in term of stability. Second, miR-125b is a reproducible, objective, and non-invasive biomarker, which can be easily detected in blood or body fluids. Last but not least, miR-125b has moderate-to-high sensitivity and specificity for diagnosis of HCC.

However, there were still several limitations to draw the conclusion. First, miR-125b was reported as a novel biomarker in HCC diagnosis in recent years; thus, the pooled results are based on only 6 studies with a relatively small sample size. Second, we only included articles published in English, which might omit the studies published in other languages and result in ethnicity bias. Finally, it was hard to diagnose HCC in early stage by applying just a single biomarker; therefore, it is necessary to combine miR-125b with other biomarkers to improve the diagnostic efficacy.

In summary, this viewpoint provides evidence that miR-125b could serve as a potential diagnostic biomarker for HCC. Due to the limitations, further better-designed and independent studies are of great need to confirm the diagnostic role of miR-125b for HCC.

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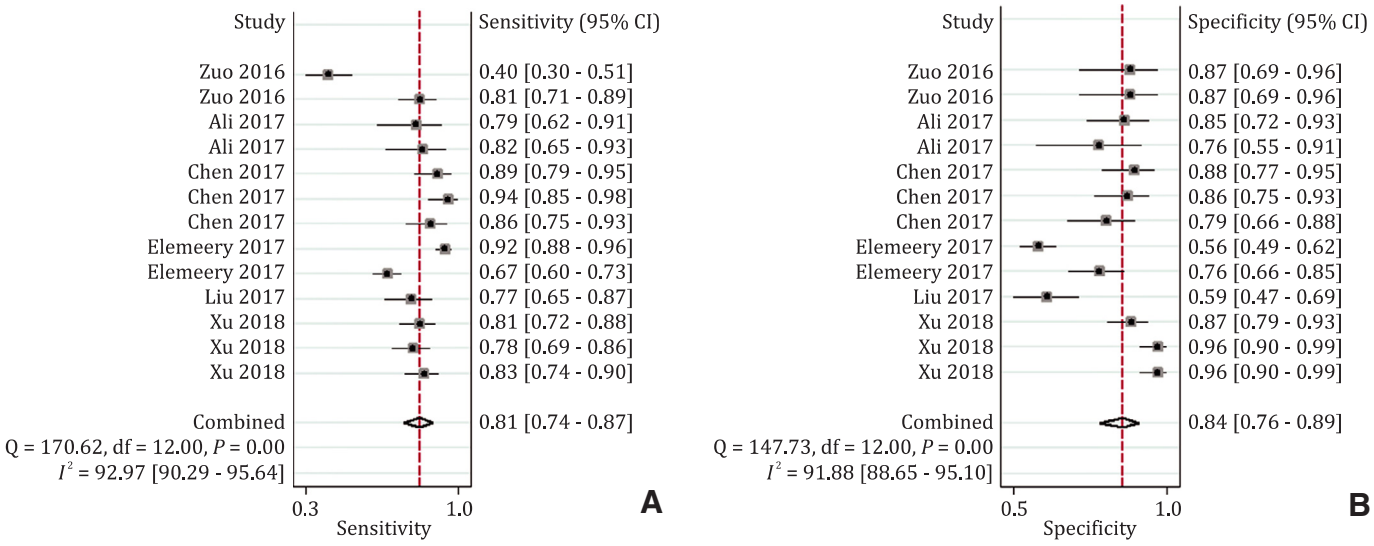

Fig. 1. Forest plots of sensitivity (**A**) and specificity (**B**) of miR-125b for diagnosis of HCC.

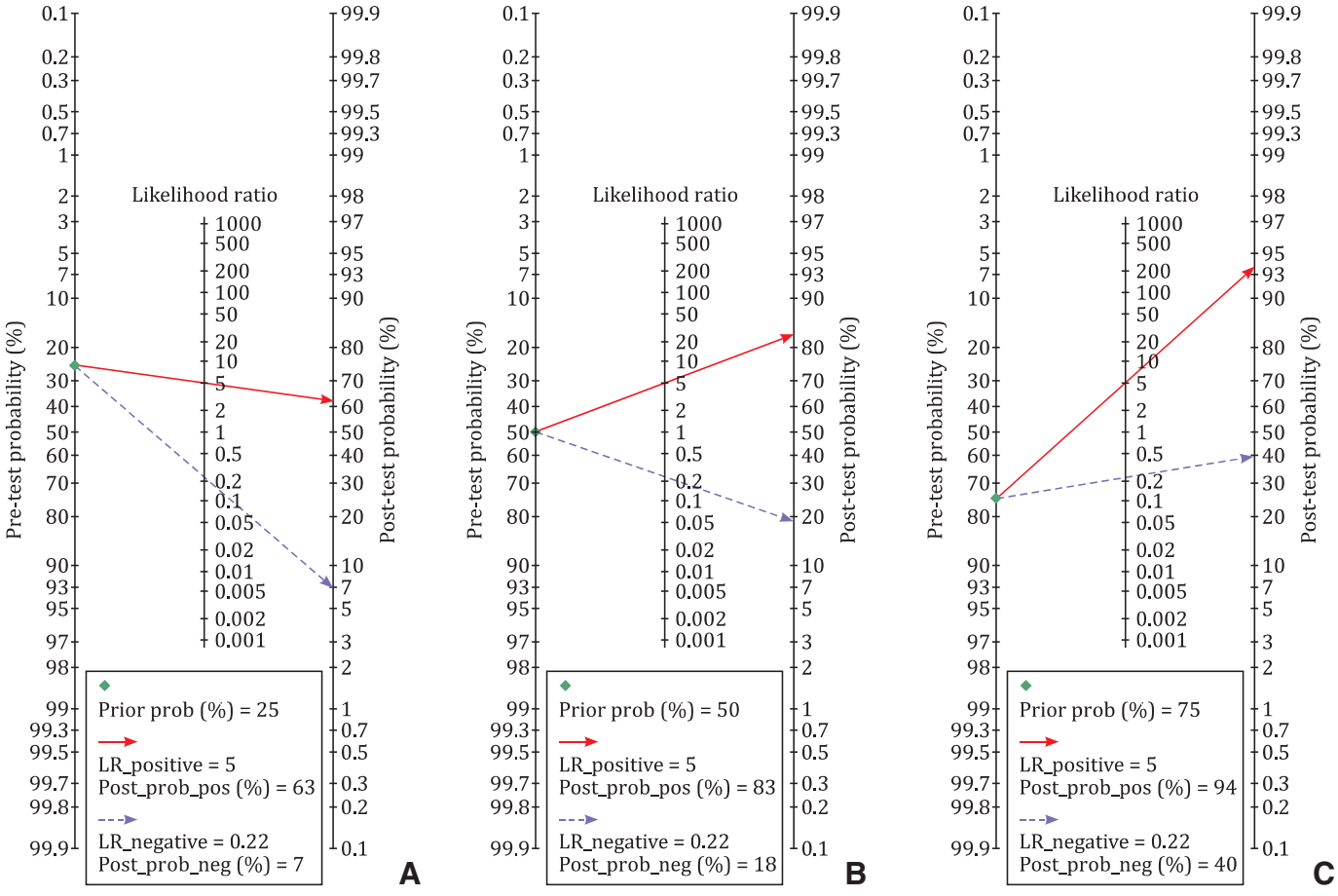

Fig. 2. Fagan nomogram analysis for miR-125b showing post-test probability of HCC after abnormal test result (upper line) and normal test result (lower line).

Table 1
Summary of main characteristics and quality assessment of included studies.

Studies	Year	Country	Sample	Detected methods	Control types	HCC/ controls	Expression level	Cutoff value	AUC	Sensitivity	Specificity	tp	fp	fn	tn
Xu et al. [3]	2018	China	Serum	qRT-PCR	HC	100/100	Down	Optimal	0.94	83%	96%	83	4	17	96
					LC	100/100	Down	Optimal	0.91	78%	96%	78	4	22	96
					CHB	100/100	Down	Optimal	0.80	81%	87%	81	13	19	87
Liu et al. [4]	2017	China	Serum	qRT-PCR	HC	66/82	Up	Optimal	0.69	77%	59%	51	34	15	48
Elemeery et al. [5]	2017	Egypt	Serum	qRT-PCR	HC	224/84	Down	NA	0.70	67%	76%	149	20	75	64
					CHC	224/250	Down	NA	0.77	92%	56%	207	111	17	139
Chen et al. [6]	2017	China	Plasma	qRT-PCR	HC	64/56	Down	NA	0.90	86%	79%	55	12	9	44
					CHB	64/63	Down	NA	0.96	94%	86%	60	9	4	54
					LC	64/59	Down	NA	0.96	89%	88%	57	7	7	52
Ali et al. [7]	2017	Egypt	Serum	qRT-PCR	HC	34/25	Down	Optimal	0.72	82%	76%	28	6	6	19
					CHC	34/52	Up	Optimal	0.83	79%	85%	27	8	7	44
Zuo et al. [8]	2016	China	Serum	qRT-PCR	HC	90/30	Down	Optimal	0.82	81%	87%	73	4	17	26
					CHB	90/30	Down	Optimal	0.63	40%	87%	36	4	54	26

AUC: area under the curve; tp: true-positive; fp: false-positive; fn: false-negative; tn: true-negative; qRT-PCR: quantitative real-time polymerase chain reaction; HC: healthy control; LC: liver cirrhosis; NA: not available; CHB: chronic hepatitis B; CHC: chronic hepatitis C.

Contributors

CJX proposed the study. LF, BQW and JLYQ conducted study design, literature search, data extraction, statistical analysis, and manuscript drafting. HQL and ZX assisted with literature search, data extraction, quality assessment. BQW and JLYQ were responsible for drafting and revising of the manuscript. LF, BQW and JLYQ contribute to this paper equally. CJX is the guarantor.

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Ethical approval

Not needed.

Competing interest

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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