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Serum non-coding RNAs for diagnosis and stage of liver fibrosis

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Abstract

Background: All chronic liver diseases could lead to liver fibrosis. Accurate diagnosis and stage of fibrosis were important for the medical determination, management, and therapy. Liver biopsy was considered to be the gold criteria of fibrosis diagnosis. However, liver biopsy was an invasive method with some drawbacks. Non-invasive tests for liver fibrosis included radiologic method and serum-based test. Radiologic examination was influenced by obesity, cost, and availability. Serum-based test was widely used in the screening and diagnostic of liver fibrosis. However, the accuracy was still needed to be improved.

Methods: Recent studies showed serum non-coding RNAs: microRNA, long non-coding RNA(lncRNA), and circular RNA(circRNA), which have the potentiality to be non-invasive markers for liver fibrosis. The recent progress was summarized in this review.

Results: These studies showed serum non-coding RNAs exerted a good diagnostic performance for liver fibrosis. A panel that included several non-coding RNAs could increase the accuracy of single marker.

Conclusions: Serum microRNAs, lncRNAs, and circRNAs could be potential non-invasive markers for diagnosis and stage of liver fibrosis. More high-quality clinical study is needed for further research.

KEYWORDS
circRNA, diagnosis, liver fibrosis, lncRNA, microRNA, stage

1 | INTRODUCTION

Although the liver has regeneration capacity, chronic liver injury would lead to liver fibrosis.[1] Advanced fibrosis would result in liver-related mortality: liver failure, and hepatocellular carcinoma.[2] The diagnosis of early liver fibrosis and accurate fibrosis stage was important for the screening, diagnosis, and treatment of liver fibrosis. Liver biopsy was the gold method to examine fibrosis. However, it has several implications: inconvenience for doctors and patients, invasive method which could cause pain and bleeding, and indeterminacy due to that specimen was only a very small part of the liver.[3] Non-invasive tests for fibrosis were developed, which include radiologic and serum-based test. Radiologic examinations include ultrasonography, magnetic resonance imaging, and elastography; however, they also have some implications: obesity impact, inconvenience, and high cost.[4] Serum-based methods include serum algorithm

model based on indirect markers such as liver function markers and serum direct markers which were correlated with fibrosis.[4] Recent studies have shown that serum non-coding RNAs such as microRNA, long non-coding RNA(lncRNA), and circular RNA(circRNA) played important roles in the diagnosis and stage of liver fibrosis.[5–7] The recent progress were summarized in this review. It may be that the microRNAs, lncRNAs, and circRNAs which were released from the liver could enter into circulating vessels and subsequently be detected for the diagnosis and stage of liver fibrosis (Figure 1).

2 | MICRORNA

MicroRNAs were a class of about 22nt regulatory non-coding RNAs which were produced in virtually all cells in the body.[8,9] MicroRNAs could repress the expression of its target genes through binding to the 3' UTR of complementary mRNAs.[10,11] Research also showed microRNAs played important roles in HBV and HCV-related liver injury and fibrosis.[12,13] The role of serum microRNAs for the diagnosis and stage of liver fibrosis was summarized in this part (Table 1).

2.1 | MicroRNA21

It has been shown that microRNA21 played an important role in liver fibrosis.[14,15] Research by Wu et al showed the expression of circulating microRNA21 in serum was significantly correlated with liver fibrosis stages of CHB patients in China, which was according to METAVIR score system through liver biopsy.[16] Twenty-eight patients with CHB were enrolled and further analysis showed microRNA21 exhibited an inferior predictive performance to stage liver fibrosis as compared to the FIB4 and APRI.[16] The AUC for microRNA21 to differentiate patients with mild fibrosis (F1 and F2) from those with severe fibrosis (F3 and F4) was 0.64.[16] That is to say serum microRNA21 was correlated with fibrosis stages, but the diagnostic performance is not good enough to distinguish fibrosis stages of CHB patients.[16] It was still unknown that whether serum microRNA21 could discriminate early liver fibrosis from healthy controls or not.[17] Another research by Migita et al enrolled 46 type 1 autoimmune hepatitis (AIH) patients who underwent liver biopsy, 40 patients with chronic hepatitis C virus (CHC), and 13 healthy controls in America.[17] Results showed the expression of serum microRNA21 was significantly elevated in

AIH patients than CHC patients and healthy controls.[17] The serum microRNA21 was reversely correlated with liver fibrosis stages of AIH.[17] However, the diagnostic performance of microRNA21 for liver fibrosis in AIH patients was not exerted. Research by Bao et al enrolled 123 CHB patients who underwent liver biopsy and 20 healthy controls. Results showed that the expression of microRNA21 in serum was much higher in CHB patients than healthy controls.[18] The expression of serum microRNA21 was also reversely correlated with fibrosis stages of CHB patients, which was consistent with that in AIH patients.[18] The AUC for serum microRNA21 to distinguish the patients with mild fibrosis (F0–F2) from those with severe fibrosis (F3–F4) was 0.7589.[18] Taken all these researches, it is concluded that serum microRNA21 could be a potential marker for the diagnosis of early fibrosis and staging fibrosis in AIH and CHB patients.

2.2 | MicroRNA122

MicroRNA122 which was an abundant microRNA in the liver accounted for about 70% of all hepatic microRNAs.[19,20] MicroRNA122 had a strong association with HBV and HCV replication and regulated several metabolic processes including oxidation, synthesis fatty acid, and cholesterol biosynthesis.[21–24] Research by Omran et al enrolled 40 Egyptian CHC patients who underwent liver biopsy and 20 healthy controls.[25] The results showed the expression of serum microRNA122 was much higher in CHC patients than that of healthy controls.[25] Further analysis showed the AUC of microRNA122 to differentiate CHC patients with early fibrosis from healthy controls was 1.[25] The sensitivity and specificity was 100% and 100%, respectively.[25] These results indicated serum microRNA122 could be a potential non-invasive marker for early fibrosis diagnosis in CHC patients. However, the research showed serum microRNA122 could not distinguish mild fibrosis (F1, F2) from severe fibrosis (F3, F4) in CHC patients.[25] Research by Bihrer et al enrolled 68 therapy-naive German CHC patients who underwent liver biopsy and 19 healthy controls and the results were accordant with the research by Omran et al.[26] The expression of serum microRNA122 was elevated in CHC patients than healthy controls and serum microRNA122 has no correlation with liver fibrosis stages in CHC patients.[26] Similar results were gained in another research by Nakamura et al.[27] The research by Nakamura et al also enrolled 91 Japanese CHB patients who
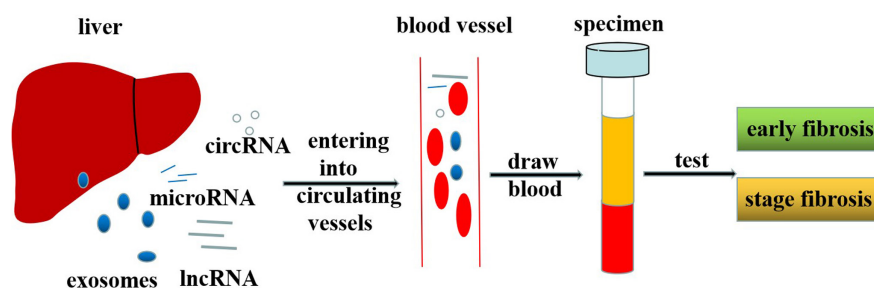

FIGURE 1 MicroRNAs, lncRNAs, circRNAs and exosomes which were released from liver enter into circulating vessels. The blood which contain these molecules are drawed from patients. Then the blood specimen are tested for diagnose of early fibrosis or stage fibrosis in patients with liver diseases.

TABLE 1 Serum microRNAs for diagnosis and stage of liver fibrosis

Number	MicroRNA	Diseases	Country	Fibrosis diagnostic method	Expression/source	Cohort	AUC for fibrosis	AUC for early fibrosis	AUC for late fibrosis	AUC for stage fibrosis or late fibrosis	Reference
1	microRNA21	CHB	China	Liver biopsy	Up/serum	28	NT	NT	NT	0.64	16
		AIH	America	Liver biopsy	Up/serum	46	NT	NT	NT	NT	17
		CHB	China	Liver biopsy	Up/serum	123	NT	NT	NT	0.7589	18
2	MicroRNA122	CHC	Egypt	Liver biopsy	Up/serum	40	NT	1.0	NT	Can not	25
		CHC	German	Liver biopsy	Up/serum	68	NT	NT	NT	Can not	26
		CHB	Japan	Liver biopsy	Up/serum	91	NT	NT	NT	0.668	27
		MAFLD	Egypt	Fibro-scan	Up/serum	120	NT	NT	NT	NT	28
3	let-7a-5p	CHC	Japan	Liver biopsy	Up/serum	84	NT	NT	NT	0.892	30
		schistosomiasis infected patients	Australia	Ultrasound	NT/serum	163	NT	NT	NT	0.6598	31
4	let-7d-5p	schistosomiasis infected patients	Australia	Ultrasound	NT/serum	163	NT	NT	NT	0.6270	31
5	microRNA214	Biliary atresia	Japan	Liver biopsy	NT/serum	28	NT	NT	NT	0.805	33
6	microRNA155	NT(liver cirrhosis)	China	Liver biopsy	NT/plasma exsosomes	94	NT	NT	0.971	NT	40
		CHC	Egypt	Liver biopsy	NT/serum	145	NT	NT	NT	Can not	41
7	MicroRNA29a	NT	Germany	NT	Down/serum	67	NT	NT	0.838	NT	46
		CHC,CHB	France	NT	Down in severe fibrosis /serum	72,83	NT	NT	NT	NT	47
8	MicroRNA-1373g-3p	CHC	China	Liver biopsy	Up in moderate to severe fibrosis compared to mild fibrosis/serum	61	NT	NT	NT	0.790	49
		CHC	China	Liver biopsy	Up in moderate to severe fibrosis compared to mild fibrosis/serum	112	NT	NT	NT	0.841-0.933	50
9	MicroRNA34a	CHC	China	Liver biopsy	Up/serum	41	NT	0.8274	0.8904	NT	54
10	MicroRNA17	CHB	China	Liver biopsy	Up/serum	200	NT	0.685	0.9169	NT	58
11	MicroRNA20a	CHC	America	Liver biopsy	Up/serum	44	0.704	NT	NT	NT	60
12	MicroRNA138	CHC	Egypt	Liver biopsy	Up/serum	71	NT	0.866	0.924	NT	63
13	microRNA150-5p	schistosomiasis infected patients	Australia	Ultrasonography	Down in severe fibrosis compared to mild fibrosis/serum	163	NT	NT	NT	0.6838	31

(Continues)

TABLE 1 (Continued)

Number	MicroRNA	Diseases	Country	Fibrosis diagnostic method	Expression/source	Cohort	AUC for fibrosis	AUC for early fibrosis	AUC for late fibrosis	AUC for stage fibrosis or late fibrosis	Reference
14	microRNA146a-5p	schistosomiasis infected patients	Australia	Ultrasonography	Down in severe fibrosis compared to mild fibrosis/serum	163	NT	NT	NT	0.6575	31
		schistosomiasis infected patients	Australia	Ultrasound	Down/serum exosomes	104	0.6315	NT	NT	NT	64
15	microRNA532-5p	schistosomiasis infected patients	Australia	Ultrasound	Down/serum exosomes	104	0.6884	NT	NT	NT	64
16	MicroRNA29b	CHB	China	Liver biopsy	Down in severe fibrosis compared to mild fibrosis/serum	123	NT	NT	NT	0.7237	18
17	MicroRNA29c	CHB	China	Liver biopsy	Down in severe fibrosis compared to mild fibrosis/serum	123	NT	NT	NT	0.8121	18
18	MicroRNA143	CHB	China	Liver biopsy	Down in severe fibrosis compared to mild fibrosis/serum	123	NT	NT	NT	0.8123	18
19	MicroRNA223	CHB	China	Liver biopsy	Down in severe fibrosis compared to mild fibrosis/serum	123	NT	NT	NT	0.7806	18
20	MicroRNA374	CHB	China	Liver biopsy	Down in severe fibrosis compared to mild fibrosis/serum	123	NT	NT	NT	0.7282	18

Abbreviations: CHB, chronic HBV hepatitis; CHC, chronic HCV hepatitis; MAFLD, metabolic-associated fatty liver disease; NT, Not mentioned.

received liver biopsy and 23 healthy controls.[27] Results showed the expression of serum microRNA122 was much higher in CHB patients than that of healthy controls.[27] Further results showed the serum microRNA122 was down-regulated in CHB patients with severe fibrosis (F3, F4) compared with CHB patients with mild or moderate fibrosis (F1 or F2).[27] ROC analysis showed the AUC of serum microRNA122 to predict severe fibrosis in CHB patients was 0.668.[27] That is to say serum microRNA122 could differentiate mild or moderate fibrosis from healthy controls and also distinguish differentiate mild or moderate fibrosis from severe fibrosis in CHB patients. However, it is hard for serum microRNA122 to distinguish healthy people from CHB patients with severe fibrosis.[27] Research by Hegazy et al enrolled 120 Egyptian patients with metabolic-associated fatty liver disease (MAFLD), who underwent Fibro-scan examination to stage liver fibrosis.[28] Results showed serum microRNA122 was up-regulated in MAFLD patients with fibrosis than controls.[28] However, the expression of serum microRNA122 decreased gradually from patients with mild fibrosis (F1) to patients with severe fibrosis (F4).[28] The expression pattern of serum microRNA122 was similar to that in CHB patients.[28] In conclusion, serum microRNA122 could be a potential non-invasive marker for early fibrosis diagnosis and could be used to distinguish fibrosis stages among patients with liver fibrosis.

2.3 | Let-7

It has been reported that several let-7 family numbers were correlated with the progression of liver fibrosis in HCV-infected patients.[29] Research by Matsuura et al enrolled 84 Japanese CHC patients who underwent liver biopsy.[30] Results showed serum let-7a-5p expression was significantly lower in patients with severe fibrosis(F4) than in those with mild and moderate fibrosis (F1–F3).[30] ROC analysis showed the AUC of serum let-7a-5p to differentiate CHC patients with liver cirrhosis from those with fibrosis was 0.892.[30] The sensitivity and specificity were 92% and 80%, respectively.[30] These results indicated serum let-7a-5p could be a potential marker to distinguish CHC patients with severe fibrosis from those with mild and moderate fibrosis.[30] Another research by Cai et al enrolled 163 schistosomiasis japonica patients with liver fibrosis.[31] The liver fibrosis was staged by ultrasound methods. Results showed the expression of serum let-7a-5p and let-7d-5p were negatively correlated with fibrosis stages.[31] The expressions of let-7a-5p and let-7d-5p were significantly higher in patients with mild fibrosis (Grade0 and 1) than in those with moderate or severe fibrosis (Grade2 and 3).[31] ROC analysis showed the AUC of let-7a-5p and let-7d-5p to distinguish schistosomiasis japonica patients with mild fibrosis (Grade0 and 1) from those with severe fibrosis (Grade2 and 3) were 0.6598 and 0.6270, respectively.[31] In conclusion, these results indicated that let-7 (let-7a-5p and let-7d-5p) could serve as a potential marker to differentiate severe fibrosis from mild fibrosis in CHC and schistosomiasis japonica-infected patients.

2.4 | MicroRNA214

MicroRNA array analysis showed microRNA214 was up-regulated during hepatic stellate cell (HSC) activation.[32] MicroRNA214 could promote HSC activation and liver fibrosis through inhibiting suppressors-of-fused homolog (Sufu) expression.[32] The expression of microRNA214 was higher in patients with liver cirrhosis than in those without cirrhosis.[32] Research by Yoneyama et al enrolled 54 Japanese Biliary atresia (BA) patients with different fibrosis by liver biopsy, among whom the serum of 28 BA patients was also collected.[33] Results showed the expression of microRNA214 was significantly higher in BA patients with severe fibrosis (F3–F4) than in those with mild fibrosis (F0–F2).[33] ROC analysis showed the AUC of serum microRNA214 to distinguish BA patients with severe fibrosis from those with mild fibrosis was 0.805 (95%CI:0.591–0.921).[33] The sensitivity and specificity were 58.8% and 90.9%,respectively.[33] These results showed serum microRNA214 could be a potential marker to distinguish BA patients with severe liver fibrosis from those with mild liver fibrosis.

2.5 | MicroRNA155

It has been shown that microRNA155 was closely related to hepatic cancer and hepatitis.[34–36] Several studies also show that microRNA155 plays a promoting role in renal, cardiac, and liver fibrosis.[37–39] Research by Niu et al enrolled 94 patients with cirrhosis and 50 healthy volunteers.[40] The expression of microRNA155 in exosomes from the plasma of patients and healthy controls were detected by quantitative real-time polymerase chain reaction (qPCR) method.[40] Results showed the expression of microRNA155 in exosomes was higher in patients with liver cirrhosis than that of healthy controls.[40] ROC analysis showed the AUC of microRNA155 to distinguish liver cirrhosis from healthy controls was 0.971.[40] The sensitivity and specificity were 93.62% and 94%, respectively.[40] Another research by Shaker et al enrolled 145 Egyptian CHC patients who underwent liver biopsy.[41] Results showed the expression of microRNA155 was not significantly different among CHC patients with different fibrosis stages.[41] These results showed microRNA155 may be a potential marker for the diagnosis of liver cirrhosis. However, it is hard for serum microRNA155 to stage liver fibrosis in CHC patients. It also needs further research to verify its potential use for the diagnosis of early liver fibrosis.

2.6 | MicroRNA29

Several studies have shown that microRNA29 plays an important role in liver fibrosis and cardiac fibrosis, lung fibrosis, systemic sclerosis, and keloid.[42,43] MicroRNA29 played a protective role in liver injury and fibrosis.[44,45] Research by Roderburg et al showed microRNA29 was down-regulated in fibrotic liver tissues in mice and humans.[46] Sixty-seven German patients with chronic liver diseases at different stages and 17 healthy volunteers were enrolled in this study.[46]

Results showed the expression of microRNA29a in serum was much lower in patients with liver fibrosis than that of healthy controls.[46] Further analysis showed the serum microRNA29a expression was higher in patients with Child A stage than that of patients with Child B and C stages.[46] There is a significantly positive correlation between the expression of serum microRNA29a and MELD-score.[46] ROC analysis showed the AUC of serum microRNA29a to distinguish patients with liver fibrosis and healthy people was 0.838.[46] Another research by Appourchaux et al enrolled 83 CHB and 72 CHC patients in France.[47] Results showed that the expression of serum microRNA29a was much lower in patients with severe fibrosis (F3, F4) than those with early or mild fibrosis (F0, F1, F2).[47] These results showed serum microRNA29 could be a potential non-invasive marker for the diagnostic and stage of liver fibrosis and cirrhosis.

2.7 | MicroRNA-1373g-3p

MicroRNA-1273g-3p was a member of microRNA-1273 family which was newly discovered in 2011.[48] Research by Niu et al showed up-regulation of microRNA-1273 could increase the expression of smooth muscle actin alpha (a-SMA), alpha1 chains of type I collagen (Col1A1), and reduce the apoptosis of HSC.[49] Sixty-one Chinese CHC patients who underwent biopsy and 20 healthy volunteers were enrolled in this study.[49] The expression of microRNA-1273g-3p in serum of patients and healthy controls was detected by the qPCR method.[49] Results showed the expression of serum microRNA-1273g-3p was much higher in CHC patients with moderate to severe fibrosis (F2–F4) than that in those with mild fibrosis (F < 2).[49] ROC analysis showed the AUC of serum microRNA-1273g-3p to predict moderate to severe fibrosis among CHC patients with fibrosis was 0.790 (95% CI:0.675–0.904).[49] Another research by Nan et al enrolled 112 Chinese CHC patients who underwent biopsy.[50] The expression of serum microRNA-1273g-3p was positively correlated with fibrosis stages of CHC patients. ROC analysis showed the AUC of serum microRNA-1273g-3p to predict the early or mild fibrosis (F = 1) among CHC patients with fibrosis was 0.841 (95% CI:0.761–0.921).[50] The sensitivity and specificity were 85% and 69%, respectively.[50] Further analysis showed the AUC for serum microRNA-1273g-3p to distinguish CHC patients with severe fibrosis (F4) from patients with mild to moderate fibrosis was 0.933 (95% CI:0.874–0.993).[50] The sensitivity and specificity were 80% and 95%, respectively.[50] These results indicated serum microRNA-1273g-3p could be a potential marker to stage liver fibrosis in CHC patients. It still needs further research to confirm the capacity of serum microRNA-1273g-3p to diagnose early liver fibrosis.

2.8 | MicroRNA34a

Several studies have shown that microRNA34a plays a promoting role in liver fibrosis through activation of HSC cells and inducing hepatocytes apoptosis.[51–53] Research by Li et al enrolled 41 Chinese CHC patients and 18 healthy volunteers.[54] The expression of microRNA34a was detected by the qPCR method.[54] Results showed the expression of serum microRNA34a was higher in CHC patients than that of healthy controls.[54] There is no significant difference between CHC patients with no fibrosis (F0) and healthy controls.[54] The expression of serum microRNA34a in CHC patients with mild fibrosis (F1, F2) was significantly higher than that of healthy participants.[54] The expression of serum microRNA34a in CHC patients with severe fibrosis (F3, F4) was significantly different from that in healthy controls, CHC patients with no fibrosis(F0), and CHC patients with mild fibrosis (F1, F2).[54] ROC analysis showed the AUC of serum microRNA34a to differentiate CHC patients with mild fibrosis from healthy controls was 0.8274 (95% CI:0.681–0.973).[54] The sensitivity and specificity were 71.4% and 83.3%, respectively.[54] The AUC of serum microRNA34a to distinguish CHC patients with severe fibrosis (F3, F4) from healthy controls was 0.8904 (95% CI:0.789–0.992).[54] The sensitivity and specificity were 77.8% and 88.3%, respectively.[54] These results showed serum microRNA34a could be a potential marker to diagnose early or mild fibrosis and severe fibrosis in CHC patients. However, it is needed to confirm the proficiency of serum microRNA34a in a big cohort. It is still unknown whether serum micro34a could stage liver fibrosis or not.

2.9 | MicroRNA17

Several studies have shown that microRNA17 played a promoting role in renal fibrosis, cystic fibrosis, and liver fibrosis.[55–57] Research by Li et al enrolled 200 Chinese CHB patients with liver fibrosis who underwent liver biopsy and 50 healthy participants.[58] The CHB patients were staged into four different stages::S0-1 (mild fibrosis), S2 (pronounced fibrosis), S3 (advanced fibrosis), and S4 (cirrhosis).[58] The expression of serum microRNA17 was detected in the serum of patients and controls by qPCR.[58] Results showed the expression of serum microRNA17 was much higher in patients with liver fibrosis than that of healthy controls.[58] However, the expression of serum microRNA17 decreased gradually from mild fibrosis (S0–S1) to cirrhosis (S4).[58] ROC analysis showed the AUC of serum microRNA17 to distinguish CHB patients with mild fibrosis (S0-S1) from healthy controls was 0.685 (95% CI: 0.5813–0.7894).[58] The AUC of serum microRNA17 to differentiate CHB patients with S2 fibrosis from healthy controls was 0.6716 (95% CI: 0.5622–0.781).[58] The AUC of microRNA17 to differentiate CHB patients with S3 fibrosis and S4 fibrosis from healthy controls was 0.7932 and 0.9169, respectively.[58] These results indicated serum microRNA17 could be a potential non-invasive marker for the diagnosis of early and severe fibrosis in CHB patients. However, the potential of microRNA17 to stage liver fibrosis should be further researched.

2.10 | MicroRNA20a

It has been reported that microRNA20a played an important role in liver fibrosis through PTEN/PI3K/Akt pathway.[59] To further research the role of microRNA20a in liver diseases, 44 HCV-infected

patients, 20 non-HCV patients with liver fibrosis diagnosed by liver biopsy, and 22 healthy volunteers in America were enrolled in the study by Shrivastava et al.[60] MicroRNA20a was highly expressed in the serum of HCV-infected patients with fibrosis as compared with non-HCV-related patients with fibrosis and healthy volunteers.[60] The expression of serum microRNA20a gradually increased from early fibrosis (F0–F2) to late fibrosis stage (F3–F4) in HCV-infected patients.[60] ROC analysis showed microRNA20a had an AUC of 0.704 (95%CI: 0.571–0.836) with a sensitivity of 61.4% and specificity of 81.8% in discriminating HCV-infected patients with fibrosis from healthy controls.[60] The AUC of serum microRNA20a to differentiate non-HCV-related patients with fibrosis from HCV-infected patients with fibrosis was 0.679 (95%CI: 0.542–0.817).[60] These results showed serum microRNA20a could be a potential marker for the diagnosis of early fibrosis and staging liver fibrosis in HCV-infected patients. However, it is still needed to confirm the result in a big cohort.

2.11 | MicroRNA138

Studies have shown that microRNA138 played an inhibitory role in lung fibrosis through YAP-Twist axis and regulating ZEB2.[61,62] To further research the potential of serum microRNA138 as a non-invasive marker for fibrosis, 36 Egyptian CHC patients with early fibrosis (F1, F2), 35 Egyptian CHC patients with late fibrosis (F3, F4), and 40 healthy participants were enrolled in the study by Ahwany et al.[63] The fibrosis stage was divided by liver biopsy according to the Metavir scoring system.[63] The expression of serum microRNA138 in CHC patients and healthy controls was detected by the qPCR method.[63] Results showed serum microRNA138 was highly expressed in CHC patients with fibrosis as compared with that of healthy controls.[63] The expression of microRNA138 was higher in CHC patients with late fibrosis than that of CHC patients with early fibrosis.[63] ROC analysis showed the AUC of serum microRNA138 to differentiate CHC patients with early fibrosis from healthy controls was 0.866 (95%CI: 0.756–0.941), with 89.3% sensitivity and 71.4% specificity.[63] Serum microRNA138 could gain an AUC of 0.924 for discriminating CHC patients with late fibrosis from healthy controls.[63] These results indicated serum microRNA138 could be a potential non-invasive marker for the diagnosis of early and late fibrosis in CHC patients.[63] However, it still needs further research to study whether serum microRNA138 could stage liver fibrosis in CHC patients and other liver diseases or not.

2.12 | Other microRNAs

The expression of many serum microRNAs was dis-regulated during the liver fibrosis process in many liver diseases. Research by Cai et al enrolled 163 Australian patients with schistosomiasis and the fibrosis grade in patients was divided through ultrasonography.[31] Results showed the expression of serum microRNA150-5p and microRNA146a-5p was significantly correlated with fibrosis grade.[31]

The expression of serum microRNA150-5p and microRNA146a-5p was lower in patients with severe fibrosis (grade 2 and 3) than that of patients with mild fibrosis (grade 0 and 1).[31] ROC analysis showed the AUC of serum microRNA150-5p and microRNA146a-5p to distinguish patients with mild fibrosis from those with severe fibrosis was 0.6838 and 0.6575, respectively.[31] The AUC of serum microRNA150-5p and microRNA146a-5p together to differentiate patients with mild fibrosis from those with severe fibrosis could be 0.6950.[31] These results indicated that serum microRNA150-5p and microRNA146a-5p could be potential non-invasive markers to separate schistosomiasis-infected patients with mild fibrosis from those with severe fibrosis. Another research by Cai et al enrolled 104 Australian patients with schistosomiasis and the expression of microRNAs in serum exosomes of patients was detected by the qPCR method.[64] Results showed microRNA146a-5p and microRNA532-5p in exosomes were significantly correlated with fibrosis grades.[64] The expression of microRNA146a-5p and microRNA532-5p was lower in patients with no fibrosis (grade: 0) than that of patients with fibrosis (grade: 1–3).[64] ROC analysis showed the AUC of exosomal microRNA146a-5p and microRNA532-5p to distinguish patients with no fibrosis and patients with fibrosis was 0.6315 and 0.6884, respectively.[64] The AUC of combing exosomal microRNA146a-5p and microRNA532-5p to predict patients with fibrosis could be 0.6962.[64] These results showed that exosomal microRNA146a-5p and microRNA532-5p could be a potential non-invasive marker to predict liver fibrosis in patients with schistosomiasis. Research by Bao et al enrolled 123 Chinese treatment-naive CHB patients who underwent biopsy.[18] Results showed the expression of serum microRNA29a, 29b, 29c, 143, 223, 21, and 374 was lower in CHB patients with late liver fibrosis (S3–S4) than that of those with early liver fibrosis (S1-S2).[18] ROC analysis showed the AUC of microRNA29a, 29b, 29c, 143, 223, 21 and 374 to differentiate CHB patients with early fibrosis from those with late fibrosis was 0.8030, 0.7237, 0.8121, 0.8123, 0.7806, 0.7589, and 0.7282, respectively.[18] The AUC of the panel of microRNA29a, microRNA143, microRNA223, and platelet count(PLT) to distinguish CHB patients with early fibrosis from those with late fibrosis could be 0.936 which was superior to aspartate aminotransferase to platelet patio index (APRI) and fibrosis 4 score (FIB-4).[18] These results showed serum microRNAs could be potential markers for fibrosis stage in CHB patients. Research by Appourchaux et al enrolled 102 French CHB patients and 178 CHC patients who underwent biopsy.[47] Results showed the expression of microRNA29a, 92a, and 122 were significantly down-regulated and microRNA146a and 222 were significantly up-regulated in CHB patients with late fibrosis (F3–F4) than those with mild fibrosis (F1–F2).[47] However, the expression of these microRNAs was not significantly different between CHC patients with mild and late fibrosis.[47] ROC analysis showed the AUC of the panel of serum microRNA122, micrRNA222, platelet count, and alkaline phosphatase(ALP) to distinguish the CHB patients with late fibrosis from those with early fibrosis was 0.86 which was superior to APRI and FIB-4.[47] These results showed a combination of serum microRNAs and baseline predictors could be non-invasive markers for fibrosis stage in CHB

patients. Research by Shaker et al enrolled 145 Egyptian HCV-infected patients who underwent biopsy.[41] Results showed serum microRNA122 was significantly down-regulated and serum microRNA203a and microRNA223 were significantly up-regulated in patients with moderate to severe fibrosis (Fγ2) as compared with patients with no to mild fibrosis (F0–F1).[41] The expression of serum microRNA126, 129, 203a, 223 was higher in patients with fibrosis(Fγ3) and cirrhosis (F = 4) than in those with fibrosis F0–F2 and F0–F3, respectively.[41] ROC analysis showed the AUC of the panel of microRNA129, microRNA223, aminotransferase aspartate(AST), and platelet count to predict patients with fibrosis Fγ2, Fγ3, and F = 4 among CHC patients could be 0.785, 0.91, and 0.96, respectively, which were superior to APRI and FIB-4.[41] These results showed the model of serum microRNAs and other related liver markers could be a potential non-invasive marker for fibrosis stage in CHC patients.

3 | LNCRNAs

Long non-coding RNAs (lncRNAs) are a class of more than 200nt non-coding RNA.[65] LncRNAs could serve as ceRNA to regulate the roles of microRNA to participate the physiological and pathological progress.[65] LncRNA plays an important role in the development and progression of many diseases such as cancer, diabetes, cardiovascular diseases, and so on.[65,66] The role of lncRNAs on liver diseases has been researched.[65,66] The role of serum lncRNAs on the diagnosis of liver fibrosis was summarized (Table 2).

3.1 | LincRNA-p21

Long intergenic non-coding RNA-p21 (lincRNA-p21) was about 3 kb long and located approximately 15kb upstream of cycle regulator gene p21/Cdkn1a.[67] Research demonstrated that lincRNA-p21 could regulate cell proliferation, cycle, apoptosis, DNA damage response, metabolism, and reprogramming.[67–70] Research by Yu et al showed that the level of lincRNA-p21 was lower in the serum of CHB patients than in healthy controls.[71] The study enrolled 417 therapy-naive patients with CHB and 363 healthy controls, most of them were Chinese people.[71] All CHB patients underwent liver biopsy to divide into different fibrosis stages (F0 = no fibrosis, F6 = cirrhosis) according to the Ishak scoring system.[71] The serum level of lincRNA-p21 was negatively correlated with fibrosis stages.[71] Further receiver operating characteristic curve (ROC) analysis showed serum lincRNA-p21 could distinguish CHB patients with fibrosis from healthy people, the area under the ROC curve (AUC) was 0.854 (95% confidence interval [CI]: 0.805–0.894) with 100% sensitivity and 70% specificity, when the cutoff value was 3.65.[71] ROC analysis showed lincRNA-p21 could differentiate CHB patients with low fibrosis scores (F0–F1 stage) from healthy controls and the AUC was 0.760 (95% CI: 0.682–0.826).[71] The AUC of serum lincRNA-p21 to differentiate CHB patients with medium fibrosis (F2–F4 stages) from healthy controls was 0.856 (95% CI: 0.801–0.901) with 100% sensitivity and 73.3% specificity.[71] The AUC of serum lincRNA-p21

TABLE 2 Serum lncRNAs and circRNAs for diagnosis and stage of liver fibrosis

Number	LncRNA or CircRNAs	Diseases	Country	Fibrosis diagnostic method	Expression/source	Cohort	AUC for fibrosis	AUC for early fibrosis	AUC for late fibrosis	AUC for stage fibrosis	Reference
1	lincRNA-p21	CHB	China	Liver biopsy	Down/serum	417	0.854	0.760	0.935	0.875-0.954	71
2	Scarna10	Liver fibrosis	China	Liver biopsy	Up/serum	38	NT	NT	NT	NT	74
3	MEG3	CHB	China	Liver biopsy	Down/serum	100	0.8844	0.5237	0.9395	0.7861-0.8281	85
4	GAS5	CHB	China	Liver biopsy	Down/serum	518	0.993	NT	NT	NT	96
		NAFLD	Korea	Liver biopsy	Up/plasma	51	NT	NT	NT	NT	97
5	RABGAP1L-DT-206	NAFLD	Egypt	Transient elastography	Up/serum	100	0.844	NT	NT	0.944	98
6	H19	Biliary atresia	China	surgery	Up/exosomes	16	NT	NT	NT	NT	108
7	MALAT1	CHB	China	Liver biopsy	Up/serum	151	0.901	NT	NT	NT	112
8	TGFB2-OT1	NAFLD	Italy	Liver biopsy	Up/serum	63 and 50	NT	NT	NT	0.786-0.797	113
9	CircMTO1	CHB	China	Liver biopsy	Down/serum	360	0.914	0.847	0.962	0.762-0.880	115

Abbreviations: CHB, chronic HBV hepatitis; CHC, chronic HCV hepatitis; NAFLD, Nonalcoholic fatty liver disease; NT, not mentioned.

to differentiate CHB patients with high fibrosis (F5–F6 stages) from healthy controls was 0.935 (95% CI: 0.882–0.969) with 100% sensitivity and 77.5% specificity.[71] LincRNA-p21 could also discriminate CHB patients with different fibrosis scores.[71] The AUC of lincRNA-p21 to differentiate CHB patients with medium fibrosis scores from patients with low fibrosis scores was 0.875 (95% CI: 0.800–0.930) with 70.9% sensitivity and 92.3% specificity.[71] The AUC of serum lincRNA-p21 was 0.954 (95% CI: 0.859–0.993) with 81.4% sensitivity and 96.1% specificity in distinguishing CHB patients with high fibrosis scores from those with medium scores.[71] These results were very meaningful and they indicated serum lincRNA-p21 could be a potential non-invasive marker for the early diagnosis of liver fibrosis. They also indicated that lincRNA-p21 could be used as a potential marker to stage fibrosis in CHB patients. LincRNA-p21 showed better sensitivity in differentiating CHB patients with different fibrosis scores from healthy people than that in staging liver fibrosis in CHB patients. The specificity of lincRNA-p21 was better in staging liver fibrosis in CHB patients than that in differentiating CHB patients with liver fibrosis from healthy people. Serum lincRNA-p21 had no significant correlation with HBV replication and liver function.[71] But serum lincRNA-p21 was negatively correlated with fibrosis markers:α-smooth muscle actin(α-SMA) and Collagen Type I Alpha 1 Chain (Col1A1).[71] These results further showed lincRNA-p21 could be a potential marker for liver fibrosis. A previous study demonstrated lincRNA-p21 could inhibit hepatic stellate cell (HSC) activation.[72] All these researches demonstrated that lincRNA-p21 played an important role in fibrosis. However, another research showed the expression of serum lincRNA-p21 was higher in patients with CHB, HBV cirrhosis, CHC, or alcoholic liver disease than that of healthy controls.[73] The result was inconsistent with the former research by Yu et al. The reason may be due to the difference of cohort size, sample storage condition and time, case selection, and so on. Further research is needed to confirm that lincRNA-p21 could be a marker for liver fibrosis by enrolling more cases and standardizing sample storage condition and time.

3.2 | Scarna10

Scarna10 was a 300 nt long lncRNA and up-regulated in mouse fibrosis livers according to microarray analysis.[74] Further experiments showed the expression of scarna10 was up-regulated in fibrosis mouse models treated with CCl_4 or bile duct ligation (BDL).[74] The expression of scarna10 was higher in human livers with fibrosis than in healthy controls, gradually rose from patients with no fibrosis (F0) to those with severe fibrosis (F4) and was positively correlated with Col1A1, not ALT, AST, or α-SMA.[74] The serum scarna10 in 38 patients with fibrosis was higher than that of 35 healthy people.[74] The expression of scarna10 in the serum of 45 humans with cirrhosis was higher than that of humans with fibrosis.[74] These results indicated scarna10 could be a potential non-invasive marker for liver fibrosis. However, the diagnostic performance of scarna10 for liver fibrosis has not been researched. It is also needed to explore the potential application value of scarna10 in different types of liver diseases.

3.3 | MEG3

Maternally expressed gene 3 (MEG3) was a 1.6 kb long lncRNA.[75] MEG3 was expressed in many tissues and could act as a tumor suppressor.[75] Its loss of expression has been observed in different types of cancer such as liver cancer, lung cancer, gastric cancer, and so on.[76–78] Research showed MEG3 played an important role in fibrosis diseases, such as liver fibrosis, pulmonary fibrosis, renal fibrosis, and cardiac fibrosis.[79–82] MEG3 played an inhibitory role in the activation of HSC and the expression of MEG3 decreased both in vivo and in vitro during fibrosis progression.[83,84] These results indicated that MEG3 might be a potential marker for liver fibrosis. Research by Chen et al showed serum MEG3 expression was lower in CHB patients than that in healthy controls.[85] 100 Chinese CHB patients and 80 healthy controls were enrolled in the study.[85] CHB patients were divided into mild fibrosis (F0–F1), middle-level fibrosis (F2–F4), and high-level fibrosis (F5–F6) through liver biopsy examination based on ISHAK method (F0 = no fibrosis, F6 = cirrhosis).[85] Results showed serum MEG3 expression was negatively correlated with the fibrosis degree.[85] The AUC of serum MEG3 to distinguish CHB patients with fibrosis from healthy people was 0.8844 and cutoff was 5.112.[85] The AUC of serum MEG3 to differentiate CHB patients with low-level fibrosis from healthy people was 0.5237 and cutoff value was 2.988.[85] The AUC of serum MEG3 to differentiate CHB patients with middle and high-level fibrosis from healthy control were 0.7085 and 0.9395, respectively.[85] These results indicated that serum MEG3 exerted better diagnostic performance in differentiating CHB patients with middle and high-level fibrosis from healthy controls than that in distinguishing CHB patients with low-level fibrosis from healthy participants. The diagnostic performance of serum MEG3 was not good enough to differentiate CHB patients with low-level fibrosis from healthy controls. The reason may be that patients with no fibrosis (F0) accounted for almost 50% of the patients with mild fibrosis (F0, F1). The AUC of serum MEG3 to distinguish CHB patients with medium fibrosis from those with mild fibrosis was 0.8281.[85] The AUC of serum MEG3 to differentiate CHB patients with high fibrosis from those with medium fibrosis was 0.7861.[85] These results indicated serum MEG3 could be used to distinguish fibrosis stages. Further experiments showed serum MEG3 was negatively correlated with α-SMA and Col1A1.[85] However, serum MEG3 has no significant correlation with HBV DNA, ALT, bilirubin, or albumin level.[85] Another study enrolled 12 CHB patients with mild fibrosis (F < 2), 13 patients with moderate to severe fibrosis (2 < F < 4), and 25 healthy people and the fibrosis stages of patients were based on the 4 factors (FIB-4).[86] The expression of serum MEG3 was lower in patients with liver fibrosis than in healthy controls.[86] The serum MEG3 expression was lower in patients with moderate to severe fibrosis than that in patients with mild fibrosis.[86] These results were consistent with the research by Chen et al. All the above research indicated serum MEG3 could be a potential marker for diagnosis and stage of liver fibrosis in CHB patients.

3.4 | GAS5

Growth arrest-specific transcript 5 (GAS5) could act as a tumor suppressor and is often lowly expressed in different types of cancer.[87,88] Research has shown that GAS5 played an inhibitory role in organ fibrosis such as liver fibrosis, renal fibrosis, cardiac fibrosis, oral submucous fibrosis, and so on and the expression of GAS5 was down-regulated in fibrosis tissues.[89–92] Previous studies have demonstrated that the expression of GAS5 was reduced in mouse and human fibrosis livers and activated HSC, and could inhibit liver fibrosis.[89,93,94] The study by Guo et al enrolled 518 CHB patients who underwent liver biopsy and 420 healthy controls in China and the results showed the expression of serum GAS5 was lower in CHB patients than in healthy controls.[95] ROC analysis showed the serum GAS5 could differentiate CHB patients with fibrosis from healthy people with an AUC of 0.993 (95% confidence interval [CI]: 0.972 to 0.992).[95] The cutoff value was 2.88, which was ΔCt(Ct target-Ct reference).[95] The sensitivity and specificity were 93.1% and 100%, respectively.[95] Serum GAS5 exerted good diagnostic performance to distinguish CHB patients with fibrosis from healthy people. The expression of serum GAS5 gradually decreased from CHB patients with mild fibrosis (F0–F1) to medium fibrosis (F2–F4) and severe fibrosis (F5–F6).[95] These results indicated GAS5 could be used to stage liver fibrosis. Further analysis showed the expression of serum GAS5 decreased in a HAI score-dependent manner.[95] The expression of serum GAS5 was lower in CHB patients with elevated ALT than that of normal ALT.[95] The expression of serum GAS5 was not significantly different between hepatitis B virus e antigen (HBeAg) positive and negative CHB patients.[95] These results indicated the expression of serum GAS5 might be correlated with neco-inflammation and liver damage of liver fibrosis. Another study enrolled 51 patients with nonalcoholic fatty liver disease (NAFLD) who underwent liver biopsy in Korea.[96] The results showed that plasma GAS5 expression was higher in patients with advanced fibrosis than in those without.[96] However, the expression of plasma GAS5 was lower in patients with cirrhosis than in those with fibrosis.[96] The result disagreed with the research by Guo et al. This may be due to the different amount of enrolled cases, patients from different countries, and different etiology. In conclusion, serum GAS5 was a potential marker for liver fibrosis in CHB patients.

3.5 | RABGAP1L-DT-206

It is less known about the role of lncRNA-RABGAP1L-DT-206 in liver fibrosis. Research by Albadawy et al showed the expression of serum RABGAP1L-DT-206 was dysregulated in NASH/NAFLD patients.[97] A total of 200 participants in Egypt were enrolled in this study.[97] There were 100 healthy controls, 60 NASH/NAFLD patients without advanced fibrosis, and 40 patients with advanced fibrosis.[97] The fibrosis staging was based on transient elastography (Fibroscan).[97] Research showed the serum lncRNA-RABGAP1L-DT-206 expression

was higher in NASH/NAFLD patients than that of healthy controls.[97] ROC analysis showed the AUC of serum RABGAP1L-DT-206 to differentiate NASH patients with fibrosis from healthy controls was 0.844 (95% confidence interval [CI]: 0.82–0.905).[97] The cutoff value which was ΔCt(Ct target-Ct reference) was 4.8.[97] The sensitivity and specificity were 81% and 83%, respectively.[97] Further analysis showed the AUC of serum RABGAP1L-DT-206 to distinguish NASH/NAFLD patients with advanced fibrosis (F3–F4) from those with mild fibrosis (F0–F2) was 0.944 (95% confidence interval [CI]: 0.869–1), when the cutoff value was 3.4.[97] The sensitivity and specificity were 100% and 79%, respectively.[97] The RABGAP1L-DT-206 may influence liver inflammation through a stimulator of interferon genes (STING) signaling pathway.[97] These results indicated serum RABGAP1L-DT-206 could be a potential non-invasive marker for the diagnosis and stage of liver fibrosis in NASH/NAFLD patients.

3.6 | H19

LncRNA H19 was a long non-coding RNA with 2.3 kb length.[98] Research has demonstrated that H19 played an important role in liver fibrosis, lung fibrosis, renal fibrosis, cardiac fibrosis, and oral submucous fibrosis.[99–103] Several researches further demonstrated H19 played a promoting role in liver fibrosis and the expression of H19 increased in fibrotic liver tissues.[99,104,105] Research by Xiao et al showed the expression of H19 was higher in liver tissues and serum exosomes of biliary atresia (BA) patients who underwent liver surgery than in healthy controls in China.[106] The exosomes were extracted from serum of 8 BA patients with mild fibrosis (F1, F2), 8 BA patients with severe fibrosis (F3, F4), and age-matched controls.[106] Results showed that the expression of H19 in serum exosomes was higher in BA patients than in healthy controls.[106] The expression of H19 was higher in BA patients with severe fibrosis than those with mild fibrosis.[106] These results showed that H19 could be a potential marker for the diagnosis of liver fibrosis in BA patients. However, the diagnostic performance of H19 in liver fibrosis among patients with BA and other liver diseases needed to be further researched.

3.7 | MALAT1

It has been shown that metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) played an important and promoting role in liver fibrosis.[107–109] 151 CHB patients with liver fibrosis who underwent liver biopsy in China were enrolled in the research by Wang et al.[110] Results showed the expression of serum MALAT1 was significantly higher in CHB patients with liver fibrosis than that of healthy controls.[110] ROC analysis showed the AUC of serum MALAT1 to differentiate CHB patients with fibrosis from healthy controls was 0.901 (95% confidence interval [CI]: 0.869–1).[110] The cutoff value which was ΔCt(Ct target-Ct reference) was 2.81.[110] The sensitivity and specificity were 0.781 and 0.968, respectively.[110] These results showed serum MALAT1 could be a

potential marker for the diagnosis of liver fibrosis in CHB patients. Further results showed the serum MALAT1 expression gradually increased with the fibrosis stage.[110] This indicated serum MALAT1 could help to stage liver fibrosis. However, the diagnostic performance of serum MALAT1 to stage liver fibrosis was not exerted. Further analysis showed the expression of serum MALAT1 was negatively correlated with inflammation factors: tumor necrosis factorα (TNFα), interleukin-6 (IL-6), and C-reactive protein (CRP). Serum MALAT1 expression was positively correlated with markers of fibrosis: hyaluronic acid (HA), precollagen III (PCIII), collagen IV (C-IV), and laminin (LN). These results indicated MALAT1 might exert its role by influencing inflammation and fibrosis of liver. In a word, MALAT1 could be a potential non-invasive marker to diagnose liver fibrosis in CHB patients.

3.8 | TGFB2-OT1

Seventy-one NAFLD patients diagnosed by liver biopsy and 28 controls in Italy were enrolled in a study by Mauro et al.[111] Microarray analysis showed the expression of lncRNA TGFB2-OT1 was up-regulated in patients with severe liver fibrosis (F3–F4) versus those with mild fibrosis.[111] The up-regulated expression of TGFB2-OT1 was further validated in an independent internal cohort which included 63 NAFLD patients and 25 controls, and an external cohort including 50 NAFLD patients.[111] Further analysis showed serum TGFB2-OT1 expression was positively correlated with FIB-4, liver stiffness measurements, Kleiner lobular inflammation, and fibrosis scores.[111] ROC analysis showed the AUC of serum TGFB2-OT1 in internal and external cohort for distinguishing NAFLD patients with severe fibrosis (F3–F4) from those with mild fibrosis were 0.797 (95%CI: 0.697–0.981) and 0.786 (95%CI: 0.623–0.950), respectively.[111] The sensitivity was 65% and 62.5%, respectively.[111] The specificity was 81.3% and 94.4%, respectively.[111] Serum TGFB2-OT1 gained a similar diagnostic performance in different cohorts. The AUC for serum TGFB2-OT1 plus FIB-4, and TGFB2-OT1 plus Fibroscan to differentiate CHB patients with severe fibrosis (F3–F4) from those with mild fibrosis could be 0.891 and 0.892, respectively. These results indicated serum lncRNA TGFB2-OT1 could be a potential non-invasive marker for liver fibrosis staging in NAFLD patients.

4 | CIRCRNAs

4.1 | CircMTO1

CircMTO1 (hsa_circ_0007874) was a circular RNA (circRNA) which was derived from the mitochondrial tRNA translation optimization 1 (MTO1) gene.[112] CircMTO1 was down-regulated in hepatocellular carcinoma (HCC) tissues and played an inhibitory role in HCC progression.[112] To research serum circRNAs as markers for liver fibrosis, research by Zheng et al enrolled 360 Chinese treatment-naive CHB patients who underwent liver biopsy and 360 healthy controls.[113] The expression of serum circMTO1 was detected by the qPCR method.[113] Results showed serum circMTO1 was significantly down-regulated in CHB patients as compared with healthy controls.[109] The expression of serum circMTO1 was significantly negatively correlated with fibrosis markers of Col1A1 and α-SMA.[113] The CHB patients were divided into three groups: mild fibrosis (F0–F1), moderate fibrosis (F2–F4), and severe fibrosis (F5–F6).[113] The expression of serum circMTO1 was gradually down-regulated from CHB patients with mild fibrosis to those with severe fibrosis.[113] The expression of serum circMTO1 was also gradually down-regulated in CHB patients with histological activity index (HAI) score increasing.[113] The ROC analysis showed the AUC of serum circMTO1 to discriminate CHB patients from healthy people, CHB patients with mild fibrosis from healthy people, CHB patients with moderate fibrosis from healthy people, CHB patients with severe fibrosis from healthy people, CHB patients with moderate fibrosis from CHB patients with mild fibrosis, CHB patients with high fibrosis from CHB patients with mild fibrosis and CHB patients with high fibrosis from CHB patients with moderate fibrosis was 0.914, 0.847, 0.934, 0.962, 0.774, 0.880, and 0.762.[113] Further analysis showed serum circMTO1 was not correlated with viral replication and liver function.[113] These results showed serum circMTO1 could be a non-invasive marker for diagnosis of early or mild fibrosis and fibrosis stage in CHB patients.

5 | CONCLUSION

These researches have shown that serum microRNAs, lncRNAs, and circRNAs could be potential non-invasive markers for early fibrosis diagnosis or staging fibrosis. However, there were still no multiple-center clinical trial in most research. It still needs further research to study the clinical practice of serum non-coding RNAs in big cohorts. Single serum microRNA, lncRNA, or circRNA may not be good enough for clinical practice. A panel which included several non-coding RNAs or combination with other serum markers such as APBI, FIB-4 could increase the accuracy of serum markers to predict liver fibrosis or stage fibrosis. More high-quality researches are needed to promote the clinical application of the serum non-coding RNAs in patients with liver fibrosis.

CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest.

DATA AVAILABILITY STATEMENT
All the data in this review were cited from the references. No new data were generated.

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