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Circulating MicroRNA Signatures for Distinguishing Early From Advanced Hepatic Fibrosis: A Review of the Evidence

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Abstract

The stage of hepatic fibrosis governs prognosis and management in chronic liver disease, yet the methods used to establish it are imperfect. Biopsy is invasive and subject to sampling error, and serum indices and elastography leave many patients with intermediate disease unclassified. Circulating microRNAs have been proposed as an additional non-invasive marker because they are stable in blood, measurable by standard molecular methods and linked to hepatocyte injury and to the activation of hepatic stellate cells. This narrative review examines the published evidence that microRNA signatures can separate early from advanced fibrosis. It describes how microRNAs enter and persist in the circulation, the candidates most often reported in chronic viral hepatitis and fatty liver disease, and the reasons why findings differ between studies. Those reasons are mainly methodological: an imperfect histological reference, pre-analytical variation such as haemolysis, the lack of an agreed normalisation strategy, comparisons of extreme groups, and panels that were never tested outside the data in which they were found. The review concludes that several microRNAs differ on average between stages, but that no signature has yet been shown to resolve the cases that existing tests leave indeterminate.

Keywords: *Circulating microRNA, Hepatic fibrosis, Non-invasive biomarkers, miR-122, Diagnostic accuracy, Chronic liver disease*

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1. Introduction

Chronic liver disease of almost any cause, whether viral hepatitis, metabolic steatohepatitis, alcohol or autoimmunity, converges on one process: the replacement of working parenchyma by scar. Activated hepatic stellate cells lay down collagen in response to sustained injury, and over years the deposits link portal tracts and central veins until the lobular architecture is lost (Bataller and Brenner, 2005; Friedman, 2008). How far that process has gone matters more to the patient than how inflamed the liver happens to be on a given day. Stage sets the urgency of antiviral or lifestyle treatment, the need for surveillance for varices and hepatocellular carcinoma, and the outlook.

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The practical difficulty lies in the middle of the range. Cirrhosis can usually be recognised, and a healthy liver can usually be confirmed, with tools already in routine use. Separating early fibrosis, confined to the portal tracts, from advanced fibrosis with bridging septa is harder. Biopsy, the historical reference, samples a minute fraction of the organ and carries a small but real risk. Serum indices built from routine tests, and elastography, leave a grey zone of indeterminate results (EASL and ALEH, 2015).

Circulating microRNAs entered this field with a strong prior in their favour. They are short non-coding RNAs that regulate gene expression after transcription (Bartel, 2004), some are close to tissue-specific, and they survive in serum and plasma in a form that ordinary quantitative PCR can measure (Mitchell et al., 2008). More than a decade of studies has since proposed single microRNAs and multi-marker panels as discriminators of fibrosis stage. This review asks what that body of work shows, why its results so often disagree, and what a signature would have to demonstrate before it could sit beside the tests clinicians already use.

2. Scope and Approach

This is a narrative review of the published literature. It draws on the foundational papers on extracellular microRNA, on widely cited studies of circulating microRNAs in chronic hepatitis and fatty liver disease, on the methodological literature concerning microRNA quantification, and on the guidelines and reporting standards that govern diagnostic accuracy research. No formal search protocol was followed and no pooled estimates are offered; the studies named are those that shaped the debate and do not amount to a census. The emphasis falls on the quality of evidence, because the central difficulty in this field is less a shortage of candidate markers than a shortage of candidates tested in a way that permits a firm conclusion.

3. Biological Basis for a Blood Signal

Two questions precede any discussion of accuracy: how liver microRNAs come to be present in blood at all, and which of them have a credible connection with scarring.

3.1. How microRNAs reach the circulation and persist there

Naked RNA added to plasma is degraded within minutes, yet endogenous microRNAs withstand prolonged storage and repeated freezing and thawing (Mitchell et al., 2008). The explanation is that they travel protected. Arroyo et al. (2011) showed that a large share of plasma microRNA is bound to Argonaute2 protein outside any vesicle, while a smaller share is enclosed in exosomes and other membrane particles. The distinction has practical weight. Hepatocyte-derived miR-122 was found in that work mainly in the protein-bound fraction, so a method that enriches vesicles will see a different profile from one that extracts whole plasma. Passive release from dying cells and regulated export from living ones both contribute, and no assay in routine use can tell the two apart.

3.2. MicroRNAs within the fibrogenic process

Three groups of microRNA recur in the fibrosis literature. The first reflects hepatocyte injury. miR-122 is by far the most abundant microRNA in hepatocytes and is scarcely expressed elsewhere (Lagos-Quintana et al., 2002); in rodent models of toxic liver injury its plasma concentration rises earlier and more steeply than the aminotransferases (Wang et al., 2009). The second group takes part in matrix regulation. Members of the miR-29 family repress collagen transcripts, are suppressed by transforming growth factor β in stellate cells, and are reduced in fibrotic liver in both mice and humans (Roderburg et al., 2011). The third comprises microRNAs whose hepatic expression tracks progression without a settled mechanism, such as the miR-199 and miR-200 families described in chronic hepatitis C by Murakami et al. (2011).

This grouping already hints at a problem. A marker of hepatocyte death reports activity, and activity and stage are correlated but distinct. A person with quiescent cirrhosis may release little miR-122, since few hepatocytes remain and few are dying, while one with an acute flare on a background of minimal scarring may release a great deal. A signature that separates early from advanced disease in a cohort where the two travel together can fail when they come apart.

4. The Reference Standard and Its Limits

Every accuracy estimate for a fibrosis marker is an estimate of agreement with histology, and histology is an imperfect witness. Staging systems such as METAVIR for viral hepatitis (Bedossa and Poynard, 1996) and the NASH Clinical Research Network system for fatty liver disease (Kleiner et al., 2005) assign ordinal categories from F0 to F4 on the basis of architecture, not the quantity of collagen. The categories are not equally spaced, and the boundary of greatest clinical interest, between F2 and F3, rests on a pathologist's judgement of whether septa bridge.

Sampling adds a second layer of error. When biopsies were taken from both lobes at laparoscopy in chronic hepatitis C, the two cores were assigned different stages in a substantial minority of patients (Regev et al., 2002), and modelling of virtual biopsies from resected livers showed that the reliability of staging depends heavily on the length of the core (Bedossa et al., 2003). A blood test cannot agree perfectly with a reference that does not agree with itself. The apparent ceiling on performance is therefore lower than unity, and a marker judged mediocre against biopsy might be nearer the truth than the biopsy was. That possibility cannot be examined without outcome data, which few microRNA studies possess.

A new marker also arrives in a field that is no longer empty. The aspartate aminotransferase to platelet ratio index (Wai et al., 2003) and FIB-4 (Sterling et al., 2006) cost nothing beyond routine blood tests, and transient elastography gives a liver stiffness reading at the bedside in minutes (Sandrin et al., 2003). Guidelines recommend combining them and reserving biopsy for discordant or indeterminate results (EASL and ALEH, 2015). The relevant question for a microRNA signature is therefore whether it resolves the cases those tests leave open, not whether it does better than chance.

5. Candidate Signatures Across Aetiologies

Table 1 summarises the microRNAs most often put forward, the tissue they are thought to come from and the main reservation attached to each. The paragraphs that follow take the two disease areas in which most of the work has been done.

Table 1: Circulating microRNAs most often discussed as markers of hepatic fibrosis stage			
MicroRNA	Likely source and role	Reported behaviour with advancing disease	Main reservation
miR-122	Hepatocytes; abundant and nearly liver-specific	Rises in serum with histological severity (Cermelli et al., 2011)	Follows necroinflammation more than scar
miR-34a	Hepatocytes; linked to cell stress and apoptosis	Rises with severity in hepatitis C and fatty liver (Cermelli et al., 2011)	Expressed in many tissues
miR-29a	Stellate cells; represses collagen transcripts	Lower in serum in advanced fibrosis (Roderburg et al., 2011)	Modest differences; depends on platform
miR-192, miR-375	Liver, gut and pancreatic islets	Higher in steatohepatitis than in simple steatosis (Pirola et al., 2015)	Affected by metabolic comorbidity
miR-199 and miR-200 families	Liver tissue; cell of origin uncertain	Hepatic expression rises with stage (Murakami et al., 2011)	Evidence mainly from tissue, not blood
miR-16, miR-451	Red cells and platelets	Often used as a reference signal	Altered by haemolysis (Kirschner et al., 2011)

5.1. Chronic viral hepatitis

An early and much cited study by Cermelli et al. (2011) measured a small set of microRNAs in the serum of people with chronic hepatitis C and found miR-122 and miR-34a raised in proportion to histological

severity, with similar findings in a separate group with fatty liver disease. [Roderburg et al. \(2011\)](#) reported the opposite direction for miR-29a, whose serum level was lower in advanced fibrosis than in early disease or in controls. Together these papers set the template for the field: a marker of injury that rises, a regulator of matrix that falls, and the suggestion that a ratio or panel might do better than either alone.

Later work complicated the picture. Serum miR-122 follows aminotransferase activity closely, so its relation to stage weakens once inflammation is taken into account, and it would be expected to decline again in end-stage cirrhosis as hepatocyte mass shrinks. Antiviral treatment alters the profile long before any scar could regress. None of this invalidates the markers. It does mean that a threshold derived in untreated hepatitis C cannot be carried over to a treated patient, or to another virus, without fresh evidence.

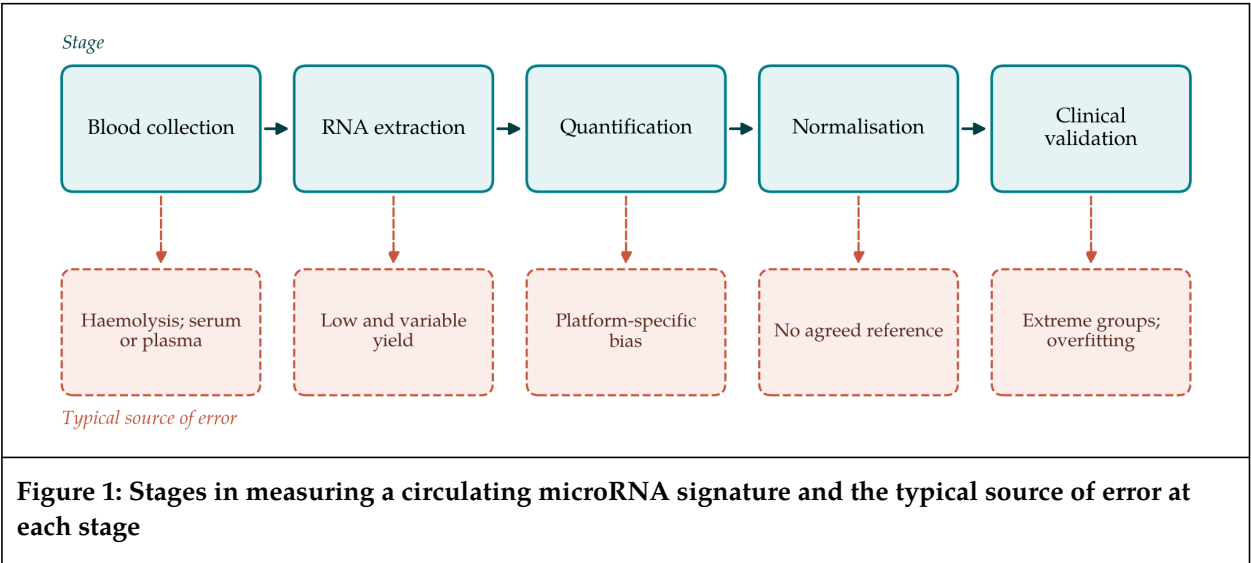
5.2. Non-alcoholic fatty liver disease

In fatty liver disease the first task is to separate simple steatosis from steatohepatitis, and the second to stage fibrosis within steatohepatitis. [Pirola et al. \(2015\)](#) profiled serum microRNAs and found miR-122, miR-192 and miR-375 higher in steatohepatitis than in simple steatosis, with miR-122 also related to fibrosis. The work is notable for linking the serum signal to expression in liver tissue, which few studies attempt. Its limits are equally instructive: miR-192 and miR-375 are not specific to the liver, both being expressed in gut and pancreatic islets, and the metabolic conditions common in this population, type 2 diabetes and obesity among them, alter circulating microRNA on their own account.

Across both disease areas the same pattern recurs. Individual studies report good separation of early from advanced fibrosis, the panels proposed differ from one study to the next, and the microRNA common to most of them, miR-122, is the one most plainly tied to injury and least plainly tied to scarring. Independent replication of a complete panel, with its original cut-offs, in a different population is uncommon.

6. Why Results Disagree: Measurement Before Biology

Much of the inconsistency can be traced to how the measurement is made. Figure 1 sets out the stages between venepuncture and a reported result, with the characteristic source of error at each.



The specimen comes first. Serum and plasma give different profiles because clotting releases platelet contents, and red cells are rich in miR-16 and miR-451, so that even slight haemolysis shifts the measured level of those and other microRNAs ([Kirschner et al., 2011](#)). [Pritchard et al. \(2012\)](#) showed that many microRNAs proposed as circulating disease markers are highly expressed in blood cells and vary with cell counts. That finding bears directly on liver disease, in which thrombocytopenia and hypersplenism

worsen with stage: a platelet-derived microRNA could fall in advanced fibrosis for reasons unconnected with hepatic RNA.

Extraction and quantification follow. Plasma contains little RNA, yields are too low to check by spectrophotometry, and recovery varies between kits and between runs. Quantitative PCR, microarray hybridisation and small-RNA sequencing each have their own biases, and the MIQE guidelines, which set out what must be reported for a PCR experiment to be interpretable, are followed unevenly ([Bustin et al., 2009](#)). Normalisation is the least settled step of all. There is no accepted housekeeping microRNA in plasma. Some groups normalise to miR-16, which is sensitive to haemolysis; some to a spiked-in synthetic sequence, which corrects for extraction but not for biological input; some to the mean of all detected microRNAs, a strategy that works in profiling experiments but is unavailable when only a handful of targets are measured ([Mestdagh et al., 2009](#)). Two laboratories can therefore measure the same sample faithfully and report opposite fold changes.

7. Judging Diagnostic Claims

Beyond the bench, the design of many studies limits what can be inferred. A common pattern compares patients with biopsy-proven cirrhosis against healthy volunteers or against patients with minimal disease. Such contrasts of extreme groups inflate discrimination, because the people a clinician actually struggles to classify, those at F2 or F3, are absent. Diagnostic accuracy should be estimated in a consecutive series of the people in whom the test would be used, with the index test read blind to the reference, and reported in the form set out by STARD ([Bossuyt et al., 2015](#)).

Panel discovery raises the further hazard of overfitting. When hundreds of microRNAs are screened in a few dozen patients, some combination will separate any two groups by chance, and a signature selected and evaluated in the same data will look better than it is. [Ransohoff \(2004\)](#) set out the remedy for molecular markers generally: lock the assay and the decision rule, then test them in an independent sample that played no part in their selection. Internal cross-validation is a partial substitute at best. In the fibrosis literature, a locked panel tested externally with its original thresholds remains the exception.

A signature must also add something. The comparison that matters is against FIB-4 and elastography in the same patients, and specifically within their indeterminate zone. A panel that reproduces what a platelet count and an aminotransferase already convey, at many times the cost and with a turnaround of days, will not change practice however good its area under the curve.

8. Gaps and Future Work

Several lines of work would move the question forward. Pre-analytical handling needs to be standardised and reported: tube type, time to centrifugation, a check for haemolysis, and storage conditions. Absolute quantification against synthetic standards, for instance by digital PCR, would remove the dependence on a reference gene and make results portable between laboratories. Markers of matrix turnover, of which the miR-29 family is the best characterised, deserve more attention than markers of hepatocyte injury, since they lie closer to the process being staged.

Study design matters as much as chemistry. Prospective cohorts with paired biopsy and elastography, adequate numbers at intermediate stages, and follow-up to clinical outcomes would allow a signature to be judged against what finally counts: decompensation, cancer and death. The shift in clinical emphasis from viral hepatitis towards metabolic liver disease also means that validation must now include people with obesity and diabetes, in whom both the existing tests and microRNA profiles behave differently. Whether vesicle-enriched fractions give a more liver-specific signal than whole plasma is an open and tractable question.

9. Conclusion

Circulating microRNAs are stable, measurable and biologically connected to liver injury and fibrogenesis, and several, notably miR-122, miR-34a and miR-29a, differ on average between people with early and advanced fibrosis. What the published evidence does not yet establish is a signature that distinguishes

those stages reliably in the patients for whom existing non-invasive tests are indeterminate, reproduced across laboratories and aetiologies with fixed thresholds. The obstacles are mostly methodological and therefore soluble: an imperfect reference standard, uncontrolled pre-analytical variation, unsettled normalisation and study designs prone to optimism. Until they are addressed, microRNA signatures are best regarded as promising research tools and not as substitutes for the staging methods currently recommended.

Conflict of interest

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