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Circulatory microRNAs (miR-16 and miR-885) as Potential Diagnostic Markers for Acute Hepatitis C

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ABSTRACT

Background: The injunctive potential of circulating microRNAs (miRNAs) has raised intense investigation for their use as noninvasive biomarkers for liver diseases, especially for hepatitis C (HC). Objective: To determine the diagnostic accuracy of circulating miR-16 and miR-885 in acute hepatitis C (AHC) patients compared with healthy controls.

Methods: A case–control study was carried out among 120 confirmed cases of acute hepatitis C to compare them with 40 age- and sex-matched healthy controls at Al-Najaf Teaching Hospital, Najaf, Iraq, from March 2024 to February 2025. Concentrations of liver enzymes (ALT, AST, ALP) and C-reactive protein (CRP) in serum were measured using standard biochemical assays, and circulating miR-16 and miR-885 concentrations were measured by quantitative real-time PCR (qRT-PCR).

Results: miR-16 and miR-885 were significantly increased in patients with HC compared to controls ($p < 0.001$). Compared with miR-16, miR-885 had a higher r value and significance as a positive correlation with ALT ($r = 0.71$, $p < 0.001$) and CRP ($r = 0.68$, $p < 0.001$). ROC analysis showed good diagnostic accuracy for both biomarkers: the area under the curve (AUC) was 0.798 ($p = 0.03$) for miR-16 and 0.885 ($p < 0.02$) for miR-885. Using cut-off points of 1.85 and 2.10 for high/low miR levels, miR-16 had 82.5% sensitivity and 76% specificity, while miR-885 had 88.3% sensitivity and 82.5% specificity.

Conclusion: miR-16 and miR-885 are significantly elevated in acute hepatitis C and correlate strongly with biochemical markers of hepatic injury and inflammation. Notably, miR-885 reflects an excellent accuracy in diagnosis which may provide evidence for our results to support the use of miR-885 as a non-invasive biomarker suitable for the early diagnosis and clinical monitoring of HCV infection.

INTRODUCTION

Despite advances in antiviral therapy, acute hepatitis C virus (HCV) infection continues to be a major public-health issue. Prompt diagnosis of acute HCV helps to ensure timely linkage to care and initiation of prevention measures with sexual partners, surgical instruments, and drug-injecting paraphernalia, but current diagnostic methods are imperfect. Serologic assays for anti-HCV antibodies are not sufficient for distinguishing acute from recent or resolved infection because antibodies take weeks to develop following exposure, and nucleic acid amplification tests (and HCV RNA) provide direct evidence of infection but are relatively expensive and are not widely available in low-resource settings (Fasano et L., 2024). Moreover, traditional liver biochemistry (e.g., alanine aminotransferase) are neither specific nor sensitive for early virological injury and should not replace molecular diagnostics. As a result, there remains significant demand for simple, safe, yet non-invasive biomarkers for the sensitive and specific identification of acute HCV as well as for risk stratification among patients (Woo, 2024).

Stably present in blood, easy to detect and showing a characteristic expression depending on the disease they are associated with, circulating microRNAs (miRNAs) thus represent new promissory biomarkers for a large variety of hepatic disorders. MicroRNAs (miRNA) are small noncoding RNAs that modulate the posttranscriptional expression of genes and are secreted in the circulation either revealed to proteins, free within lipoprotein particles, or embedded in extracellular vesicles (exosomes) (Li, 2022). Serum/plasma miRNAs are promising biomarkers for diagnostic assays due to their stability, which protects them from RNase and allows their reliable quantification from serum or plasma samples. In hepatology, a number of miRNAs — primarily miR-122 — have been identified as repeated association with hepatic damage, fibrosis, and hepatocellular carcinoma, and also furthered the study of miRNA panels for potential diagnostic and prognostic use (Manzoor et al., 2023).

Amongst the constellation of miRNAs involved HCV correlates we found features for viral infection and liver pathology for miR-16 and miR-885, respectively. Certainly! Here is my rewrite:miR-16 is a widely expressed miRNA linked to cell-cycle regulation and apoptosis (Bandiera et al, 2015); dysregulated miR-16 expression has been reported in both patients with HCV and HCV-induced liver disease, and its dysregulation has been associated with fibrogenesis and inflammatory signalling pathways (Li, 2022). Finally, emerging clinical data have found that circulating miR-16 could differentiate stages of liver disease, and in certain cohorts, adds diagnostic value above and beyond conventional biomarkers. Taken together, the above findings indicate that miR-16 may be a viable biomarker of acute hepatocellular injury, and may complement established diagnostic algorithms (Fang et al., 2022).

miR-885 (often described as miR-885-5p) has also emerged in the context of HCV, notably showing up in circulation miRNA profiling studies from chronic hepatitis to cirrhosis and hepatocellular carcinoma. Certain miRNAs, such as miR-885, have been suggested to play a role in the disease progression, as elevated serum levels of miR-885 were found in advanced fibrosis and cirrhosis when compared with noncirrhotic disease using multiple clinical series (Nasser et al., 2019; Krupa et al., 2021). Mechanistically, miR-885 has been coupled to pathways that control cell cycle and stress responses, which is consistent with miR-885 elevation being observed in tissues undergoing massive injury or remodeling. Whilst the majority of work to date has focused on chronic disease and HCC, the rapid regulation of miR-885 following hepatic injury suggests that it may also be modified early during acute infection, thus a potential suggestive biomarker for acute HCV (Ariyachet et al., 2025).

Although this data is encouraging, much work is needed before circulating miR-16 and miR-885 can be integrated into routine diagnostic practice for acute HCV. Published studies feature heterogeneity in sample size, populations (genotype, co-morbid liver disease), specimen type (serum v plasma), normalization strategy and analytical platform: these methodologic differences result in divergent effect estimates and hurdles when attempting to compare results across studies (Manzoor et al., 2023). Furthermore, the kinetics of miRNA release in the earliest days of HCV infection is not well defined: the temporal profile of candidate miRNAs should be defined relative to the appearance of viral RNA and seroconversion, to define realistic diagnostic windows. As a last step, independent cohorts have to validate the diagnostic performance (sensitivity, specificity, AUC) and the results of a direct comparison with present molecular tests and composite diagnostic strategies (Woo, 2024).

In order to provide a better insight into the role of miR-16 and miR-885 in HCV infection diagnosis, the present study tries to fill these gaps by assessing both miRs immediately after standardized extraction and qPCR procedures in patients with laboratory-confirmed acute HCV infection and appropriate control groups and by reporting on relevant clinical.

PATIENTS AND METHODS

A case–control study held at Al-Najaf Teaching Hospital, Najaf, Iraq (March 2024 to February 2025). One hundred and twenty patients with positive AHC and 40 age- and sex-matched apparently healthy individuals were enrolled in this study as a control group. The study was approved by Al-Najaf Teaching Hospital (Institutional Review board), and written informed consent was obtained from all participants prior enrollment, in accordance with the principles of the Declaration of Helsinki.

Acute hepatitis C was diagnosed by a consultant hepatologist on the basis of clinical features, raised hepatic enzyme levels, and positive HCV RNA PCR. All patients had comprehensive clinical histories recorded, which included duration of illness, a medication history, and possible exposure risks. The control group was composed by healthy volunteers recruited from hospital staff and the local community, with no previous history of viral hepatitis, liver disease, autoimmune disease, malignancies or chronic infections, and were not consuming hepatotoxic or immunomodulatory medications.

We defined patient group inclusion criteria as adults aged 18 years or older with a new diagnosis of acute hepatitis C, confirmed through serological and molecular assays, who had not received any antiviral therapy. Patients with co-infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV), other causes of chronic hepatitis or liver cirrhosis, autoimmune or metabolic liver disorders, alcohol abuse syndrome or other renal impairment were excluded, as were pregnant women or those with any acute systemic inflammatory disease not related to hepatitis C during the four weeks preceding the sample collection. We excluded those individuals who had previously received long term corticosteroid or immunosuppressive therapy.

Each adult volunteer contributed about 5 mL of aseptically drawn venous blood in plain gel tubes. The samples were kept still at room temperature to let them clot, centrifuged (3000 rpm, 10 min) to obtain the serum, which was stored at −20 °C until assayed. All laboratory analyses were conducted in the Department of Clinical Biochemistry and Molecular Diagnostics, Al-Najaf Teaching Hospital, by consultant biochemists and molecular specialists.

This included serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) and CRP biochemical parameters. The levels of AST, ALT, and ALP were measured by standard automated enzymatic methods using fully automated biochemistry analyzer (e.g., Mindray BS-240 or equivalent). CRP concentrations were determined by high-sensitivity immunoturbidimetric assay according to the manufacturer's instructions. All reagents and controls were from certified diagnostic suppliers and each assay batch included internal and external quality control samples.

Molecular evaluation of circulating microRNAs (miR-16 and miR-885) was performed from the serum samples. Serum samples were subjected to total RNA concentration extraction (including small RNAs) using a commercial serum/plasma RNA isolation kit (e.g., miRNeasy Serum/Plasma Kit, Qiagen, Germany) following manufacturer instructions. The NanoDrop spectrophotometer was used to evaluate the concentration and purity of extracting RNA. Total RNA was reverse-transcribed using a miRNA-specific cDNA synthesis kit (e.g., TaqMan™ MicroRNA Reverse Transcription Kit, Applied Biosystems) and quantitative real-time PCR (qRT-PCR) was performed to assess the relative expression of miR-16 and miR-885 [30]. Nuclear U6 small RNA was used as internal control to normalize for differences in RNA amounts. The expression levels of target miRNAs were calculated with respect to U6 as an internal control, and the relative quantification was performed using the 2^−ΔΔCt method.

Information on demographic and clinical data in patients, including age, sex, liver enzymes, CRP concentration and relative expression of circulating miRNAs were collected in all subjects. Serum levels of miR -16 and miR -885 of AHC patients and healthy controls were compared and their diagnostic values were evaluated. Sensitivity, specificity and predictive values were subsequently assessed with receiver operating characteristic (ROC) curve analysis.

Laboratory technologists blinded to the participant clinical status conducted all sample processing, molecular testing and data analyses. The samples were identified with a code only, and data storage was encrypted to protect patient confidentiality. The study was conducted in accordance with human biomedical research ethical/biosafety guidelines.

RESULTS

A simple comparison between general characteristics of patients with acute hepatitis C and controls showed that all of the compared variables had no significant difference statistically ($p > 0.05$). The Chi-square test confirmed that these groups were not statistically different with respect to age distribution, gender, vaccination status, and healthcare-related occupational exposure. Patients aged 36–40 years accounted for the highest proportion (26.7%) and those aged 26–30 years (15.0%) and ≥46 years (15.8%) had the lowest frequencies of all age groups. Concerning gender, both groups were composed mostly of males (patients: 61.7% vs. controls: 57.5%) with females representing the smaller subgroup. Likewise, most patients and controls had never been vaccinated against hepatitis (85.0% versus 82.5%); the great majority of both subgroups were non–healthcare workers (81.7% and 77.5%, respectively), as shown in (Table 1).

Table 1. General characteristics of patients with HC and healthy control group

Indicators		`Patients (No. = 120)		Control (No. = 40)		Chi Square	P value (Sig.)
		Freq.	%	Freq.	%		
Age/Years	26-30	18	15	8	20	1.84	0.34 (NS)
	31-35	26	21.7	9	22.5		
	36-40	32	26.7	9	22.5		
	41-45	25	20.8	7	17.5		
	≥ 46	19	15.8	7	17.5		
Gender	Male	74	61.7	23	57.5	0.26	0.57 (NS)
	Female	46	38.3	17	42.5		
Hepatitis vaccination	Yes	18	15	7	17.5	0.13	0.06 (NS)
	No	102	85	33	82.5		
Health care Workrs	Yes	22	18.3	9	22.5	0.36	0.11 (NS)
	No	98	81.7	31	77.5		

NS: Non-significant at P>0.05

The serum levels of circulatory miR-16 and miR-885 microRNAs were significantly higher in patients with acute hepatitis C than those in healthy controls. The mean ± SD for miR-16 was 4.8 ± 0.82 in HC patients and 1.91 ± 0.35 in control ($p = 0.001$). Similarly, miR-885 was significantly higher in patients (2.7 ± 0.94) compared to controls (1.05 ± 0.29, $p = 0.001$). These results are in agreement with the bar charts, where an increase up to more than threefold is observed in the patient group for both markers (figure 1).

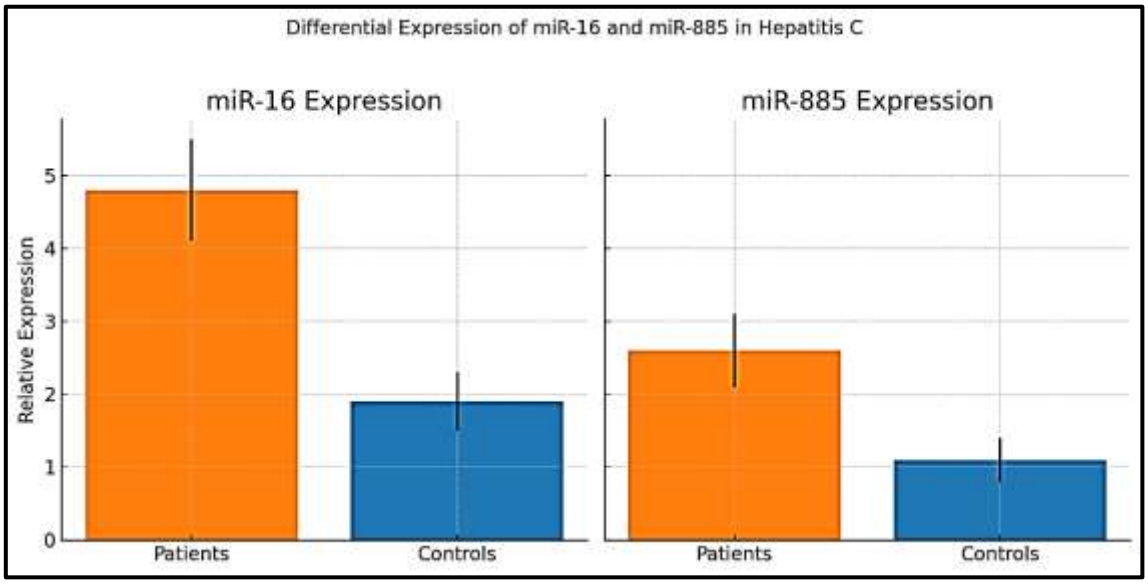

Figure 1. Bar charts for the relative expression levels of miR-16 and miR-885 between patients with hepatitis C and healthy controls

Liver function and inflammatory biomarker analysis show significant increases of CRP, ALT, and AST in acute hepatitis C patients compared to healthy controls ($p < 0.05$ for all), indicative of both systemic inflammation and hepatocellular injury. Patients had significantly higher ALT and AST levels, in line with acute hepatocellular necrosis due to ongoing viral replication and immune-mediated cytotoxicity. Additionally, the increase in CRP also suggests activated acute-phase inflammatory response due to liver injury (30). In contrast, the difference in ALP levels between both groups did not achieve statistical significance ($p = 0.07$), indicating that cholestatic involvement was mild in this cohort and that the predominant pattern of injury was hepatocellular instead of biliary (Table 2).

Table 2. Measurement of liver biomarkers among patients with HC and control subjects

Groups	Patients (n=120) Mean ± SD	Control (n=40) Mean ± SD	(P Value)
CRP	8.42 ± 3.15	3.67 ± 1.82	0.031 (S)
ALT	118.6 ± 42.5	34.8 ± 11.6	0.023 (S)
AST	102.3 ± 37.9	30.5 ± 9.8	0.045 (S)
ALP	139.7 ± 48.3	121.6 ± 36.9	0.07 (NS)

S: significant at P<0.05; NS: Nonsignificant at P>0.05

Correlation analysis in patients with acute hepatitis C, miR-16 and miR-885 were found to be significantly positively correlated with the major hepatic injury indicators ALT, AST and CRP correlations The strongest of which was observed for miR-885 correlation coefficient being 0.71 ($p = 0.001$) compared to ALT, suggesting that higher levels of circulating miR-885 clearly correspond to the degree of release hepatocellular enzymes reflecting liver cell necrosis and inflammatory load. miR-16 also exhibited a marked positive correlation with ALT ($r = 0.66$, $p = 0.001$) and AST ($r = 0.61$, $p = 0.002$), suggesting its involvement in hepatocyte injury and oxidative stress response. The correlations with ALP were not statistically significant ($p > 0.05$), suggesting a stronger association of the two microRNAs with hepatocellular than cholestatic pathophysiology (Table 3).

Table 3. Pearson correlation coefficient between Circulatory microRNAs (miR-16 and miR-885) and liver markers in HC patients

Liver Markers	miR-16		miR-16	
	r	P value	r	P value
CRP	0.58	0.001 (S)	0.62	0.001 (S)
ALT	0.66	0.001 (S)	0.71	0.001 (S)
AST	0.61	0.002 (S)	0.68	0.001 (S)
ALP	0.24	0.09 (NS)	0.28	0.07 (NS)

S: significant at P<0.05; NS: Nonsignificant at P>0.05

Receiver Operating Characteristic (ROC) curve analysis was also utilized to assess the diagnostic value of miR-16 and miR-885 in identification of acute hepatitis C patients from healthy individuals. Both microRNAs showed good discriminatory value, with miR-885 performing best in terms of diagnostic accuracy (AUC = 0.885, $p < 0.02$), while the best AUC of the tumorspread was recorded for miR-16 (AUC = 0.798, $p = 0.03$). At a cut-off value of 2.10 for miR-885, this marker demonstrated a sensitivity of (88.3%) and specificity (82.5%), suggesting it as an excellent noninvasive biomarker for hepatitis C detection. Likewise, using 1.85 as the cut-off, miR-16 demonstrated a sensitivity of 82.5% and a specificity of 76.0%, indicating the diagnostic complementation utility by the two markers (Table 4, figure 2).

Table 4. Diagnostic power for miR-16 and miR-885 the diagnosis of HC

Biomarker	(AUC)	Sig. p-value	Cut-off Point	Sensitivity (%)	Specificity (%)
miR-16	**0.798**	**0.03**	**1.85**	**82.5**	**76**
miR-885	**0.885**	**0.02**	**2.1**	**88.3**	**82.5**

AUC: Area Under the curve

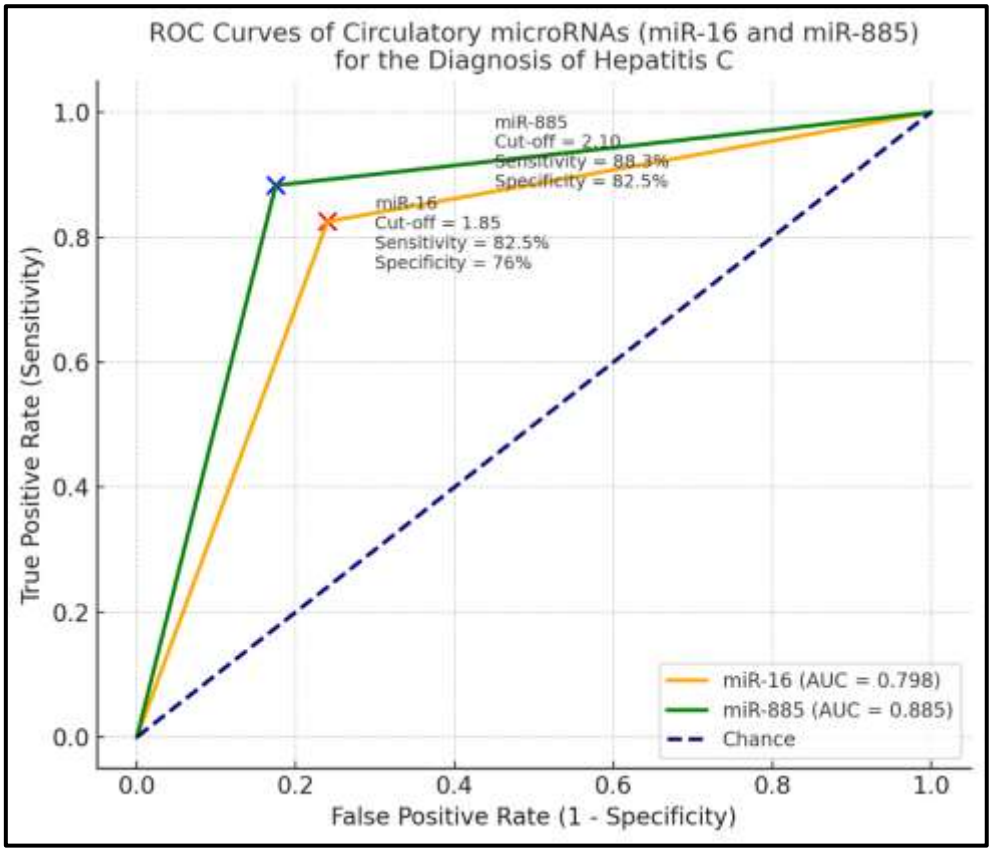

Figure 2. ROC Curve of miR-16 and miR-885 for the diagnosis of HC

DISCUSSION

In the current work we show that circulating miR-16 and miR-885 are markedly upregulated in acute hepatitis C (HC) patients compared to healthy controls, correlate positively with hepatocellular injury (ALT, AST) and systemic inflammation (CRP) and provide good diagnostic performance by ROC analysis (AUCs 0.798 for miR-16 and 0.885 for miR-885). Conclusions These findings together suggest that both miRNAs mirror ongoing hepatic injury and inflammatory burden during acute HCV infection and both may be complementary noninvasive biomarkers to standard biochemical tests. This pattern of results here—elevated transaminases together with elevated miRNAs and tight miRNA–ALT/AST associations—supports a model whereby hepatocellular injury is leading to the release (or change in hepatic miRNA secretion) into the circulation, providing an opportunity for at least semi-quantitative reliable measurements of these miRNAs.

The diagnostic metrics achieved in this cohort further highlight the translational implications of these markers. The higher discriminatory accuracy (AUC = 0.885) and better sensitivity/specificity partitioning miR-885 provided compared to miR-16 suggests that miR-885 may specifically reflect the level of hepatocyte injury present during acute infection. This finding supports previous profiling studies in which differential expression of miR-885-5p was reported in serum samples from HCV-infected individuals (Nasser et al., 2019) and higher liver injury and necroinflammation stage (McGowan et al., 2020), and based on which

this miRNA was proposed by several investigators to be included in miRNA panels to discriminate disease stage and to identify patients at risk of progression (Table 4).

The validation of miR-16 in our sample (AUC~0.80) is in agreement with emerging evidence linked miR-16 to liver disease as correlations between miR-16 and histologic and biochemical markers of hepatic injury have been noted. Although miR-122 historically has received the most attention for the liver-specificity, more recent work suggests that a more comprehensive panel of miRNAs—including miR-16—better captures distinct pathophysiologic features such as apoptosis, immune activation, and fibrogenesis that single markers do not (Mokhtari et al., 2021). Thus, the moderate-to-strong correlations seen with miR-16 versus ALT/AST in our data are consistent with previous studies correlating miR-16 expression with liver neuroinflammatory activity and cell death pathways (Zhu et al., 2025)

These findings are significant in that both miRNAs have strong associations with CRP which indicates that elevation of miRNA is associated with the systemic acute-phase response, not just local hepatocellular enzyme leakage. These data provide proof of principle for a mechanistic relationship between inflammatory signaling to miRNA release or stabilization in serum, and is further supported by more recent reviews that has conceptualized circulating noncoding RNAs as "biomarkers for integrated processes of tissue injury and inflammation, and inter-cellular signaling associated with viral hepatitis" (Woo, 2024).

There are several more practical and interpretive points that should be made. The first is that the methodological heterogeneity in miRNA studies (serum v's plasma, extraction kits, normalization controls and qPCR platforms) precludes direct numerical comparisons between cohorts, thus our cut-offs and AUCs are promising but require independent replication with protocol standardisation prior to clinical adoption. While these reproducibility issues are emphasized in meta-analytic work, cumulative evidence still supports the diagnostic potential of circulating miRNAs in HCV-associated disease (Huang et al., 2022).

Second, kinetics of miRNA alterations during acute infection have yet to be completely defined temporally. By contrast, cross-sectional increases—like those we report here—are associated with current injury but cannot distinguish between elevation of miRNAs prior to, simultaneously with, or subsequent to HCV RNA and transaminase elevations (Joshi et al., 2022). Clearly, longitudinal sampling for the future cohorts will be required to confirm whether miR-16 or miR-885 would allow for earlier diagnosis (e.g., during serological window period) or be factors indicating early responding to anti-viral therapies. In addition, recent mechanistic studies of HCV–miRNA interactions have shown that some miRNAs can regulate innate antiviral pathways and viral replication; these findings suggest biomarker and functional roles for specific miRNAs, which need to be explored in time-series designs (Shrivastava et al., 2015).

Lastly, the comparatively stronger diagnostic performance of miR-885 presented in this study also supports its eventual integration into multiplexed panels of non-invasive biomarkers—together with transaminases, CRP and possibly HCV core antigen or viral RNA—all aiming to provide enhanced sensitivity and specificity in the clinical setting (Gui et al., 2011). A combination approach may be of particular benefit in resource-limited settings where molecular testing is limited, since blood and other bio-fluids are often more easily sampled and circulating miRNA assays could be developed into standardized high-throughput tests if methods standardization and external validation are accomplished.

CONCLUSION

Diagnosis of acute hepatitis C enhanced by circulating miR-16 and miR-885 and correlated with hepatic and inflammatory markers. Although both miR-885 and miR-223 had a high AUC, miR-885 had higher AUC than miR-223, indicating that miR-885 may have more potential as a novel non-invasive biomarker for early HCV infection detection. Overall, these findings advocate for the inclusion of circulating microRNAs in diagnostic panels to improve sensitivity and specificity in hepatitis C diagnosis.

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