



ORIGINAL RESEARCH ARTICLE

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# Role of liver biopsy versus non-invasive biomarkers for diagnosis of significant fibrosis and cirrhosis: a web-based survey

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## Abstract

**Background:** Liver biopsy is the standard reference for staging hepatic fibrosis. Non-invasive methods for assessment of hepatic fibrosis and cirrhosis are becoming increasingly popular.

**Objective:** We aimed at exploring the change in practice regarding the use of liver biopsy and non-invasive methods for staging hepatic fibrosis and cirrhosis among hepatologists.

**Methods:** We performed a survey-based study that recruited hepatologists from various Egyptian institutions. Physicians were deemed eligible if they had a degree in internal medicine with hepatology as a subspecialty. We utilized an online-based survey that assessed the acceptability and reliability of liver biopsy, serum biomarkers, and radiological tools for evaluating liver fibrosis and cirrhosis.

**Results:** A total of 573 responses were retrieved (response rate = 80.3%). Out of them, 58% were having more than 15 years of experience as a hepatologist.

Liver biopsy is still considered the gold standard for assessment of hepatic fibrosis and cirrhosis by 61% of participants. Liver biopsy was accepted by 44% of their patients. 84% reported the need for a more practical alternative to liver biopsy to assess disease progression or response to treatment. 78.34% of participants know serum biomarkers, 84.08% reported that they were acceptable by their patients, 37.79% thought they are reliable. 95.4% were familiar with radiological methods of non-invasive assessment of hepatic fibrosis, 89.1% reported that radiological methods were acceptable by their patients, 62% think that they are reliable and 78% reported they were applicable in clinical practice. Sixty-five percent think that combining non-invasive methods is better than using a single method. Forty percent of participants thought that radiological methods are easier to use for assessment of hepatic fibrosis followed by a combination of non-invasive methods, serum biomarkers, and liver biopsy respectively.

**Conclusion:** In conclusion, liver biopsy is still considered the most reliable method for evaluation and staging of liver cirrhosis by hepatologists in Egyptian institutions, despite the modest acceptance by the patients. Nonetheless, non-invasive methods are gaining acceptance by Egyptian physicians and patients, and most of them consider these methods as reliable and applicable tools for predicting the course of liver cirrhosis.

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**Keywords:** Non-invasive tools, Liver biopsy, Cirrhosis, Acceptability, Reliability, Egypt

## Introduction

Liver cirrhosis is the end stage of various chronic liver diseases that has the cardinal features of extensive hepatic fibrosis, scarring, and regenerative nodules; which, in return, lead to irreversible deformity of physiological hepatic architecture [1]. Liver cirrhosis is a serious, relatively prevalent, cause of global morbidity and mortality; recent estimates demonstrated that liver cirrhosis accounted for nearly 2.5% of the total global deaths in 2017—around 1.3 million deaths—, ranking it as the 11th leading attribute of global mortality [2–4]. The distribution of liver cirrhosis shows notable ethnic and socioeconomic variations, with the highest prevalence reported among low-income African countries [4]. Liver cirrhosis is a major cause of disability and represents a global economic burden as well. Several hepatic disorders can lead to the development of liver cirrhosis such as chronic viral hepatitis, alcoholism, and non-alcoholic steatohepatitis [5].

Early recognition and monitoring of liver cirrhosis are the cornerstones for optimal treatment outcomes and reducing the risk of complications in cirrhotic patients [6, 7]. To date, liver biopsy is the gold standard procedure for diagnostic and prognostic evaluation of liver cirrhosis, previous reports showed that liver biopsy finding is the most consistent, independent, predictor of outcomes of chronic liver diseases [8, 9]. Nonetheless, the invasive and painful nature of liver biopsy is a major disadvantage that can result in various post-procedure complications; other disadvantages of liver biopsy include its high cost and the possibility of sampling errors during specimen retrieval and handling [10]. Thus, the use of liver biopsy in local settings can be limited by poor reliability and acceptance of the procedure by both healthcare physicians and patients [11]. Recently, non-invasive markers have gained momentum for evaluation of liver cirrhosis; over the recent two decades, various serological, ultrasound-based, and magnetic resonance (MR)-based markers were evaluated as potential alternatives for liver biopsy in the setting of liver cirrhosis [10]. Markers, such as serum biomarkers algorithm [12, 13], transient elastography [14], shear wave elastography [15], and MR elastography [16] exhibited high performance and reproducibility for evaluation of liver cirrhosis and prediction of clinical outcomes. Thus, non-invasive methods are increasingly accepted by healthcare physicians as reliable and well-validated methods for the assessment of liver cirrhosis [17]. Nonetheless, limited data are available regarding the acceptance and reliability of non-invasive methods

for the assessment of liver cirrhosis in developing countries with a high prevalence of liver cirrhosis, like Egypt. This survey-based study aimed to provide real-life data concerning the level of acceptance and reliability of non-invasive methods for the assessment of liver fibrosis and cirrhosis among hepatologists from Egyptian institutions.

## Materials and methods

### Study design and population

We performed a survey-based study that recruited hepatologists from various Egyptian institutions. The survey was sent to participants through an online website ([www.surveymonkey.com](http://www.surveymonkey.com)) after they gave their approval of participation in the present study via email. We utilized a non-probability, convenience, sampling technique to recruit eligible physicians. The preparation of the present manuscript runs in compliance with the STROBE statement [18].

### Data collection

The survey assessed the level of acceptance and reliability of different methods for assessment of liver fibrosis and cirrhosis among hepatologists. The survey consisted of 47 questions that were administrated in the English language. The first part consisted of 8 questions assessing the demographic characteristics, and the level of experience of participants. The second part, assessed the acceptability and reliability of liver biopsy amongst participants using 14, mainly 5-Likert scale, questions; while the third part assessed the acceptability and reliability of serum biomarkers and consists of 5 questions. The fourth part assessed the acceptability and reliability of radiological markers and consisted of 7 questions. Finally, the fifth part was used to assess the utilization of combination methods and participants' attitudes towards them. Before the implementation of the study, a preliminary pilot test for different sections of the questionnaire was done among twenty potential participants. This was performed to check the validity and clarity of the structured questions as well as to estimate the time needed to complete the survey. Accordingly, some questions about attitude and practice were restructured. The results of the pilot study were excluded from data analysis.

### Statistical analysis

Data were entered and validated using Microsoft Excel 2019, while the statistical analysis was done using the statistical package for the social sciences (SPSS, windows version 22). All continuous quantitative data were

presented in mean and standard deviation (SD). While categorical data were presented in frequencies and percentages.

## Results

The present cross-sectional study included 573 participants with an age range from 25 to 75 years old and male predominance (71.55%). Out of them, 58% were having more than 15 years of experience as a hepatologist. Most of the participants (61%) agreed that liver biopsy is still considered the gold standard for the assessment of hepatic fibrosis and cirrhosis. However, they admitted that only 44% of patients clearly accepted liver biopsy. Most of the participants did not think they need a liver biopsy for diagnosis of significant fibrosis and cirrhosis in viral hepatitis (56%), on the other hand, 45% of participants thought they still need a liver biopsy for diagnosis of significant fibrosis and cirrhosis in non-viral chronic liver diseases. Only 8% of participants saw discordance between results of liver biopsy (histopathology report) and clinical findings. If the histopathology report was discordant with clinical findings, most of the participants (60%) used non-invasive methods "radiological methods or serum biomarkers", 34.19% asked for a second opinion from another pathologist and 6.71% repeated liver biopsy. Most of the participants (88%) agreed that they can diagnose cirrhosis easily using clinical, laboratory, and radiological evaluation. On the other hand, 51.58% of participants diagnose significant fibrosis easily (clinically, laboratory, and radiologically). Interestingly, 66% of participants did not think a liver biopsy is required for diagnosing cirrhosis. On the other hand, (39%) a liver biopsy is required to diagnose significant hepatic fibrosis. The majority of participants (84%) thought they need a more practical alternative to liver biopsy to assess liver disease progression or response to treatment (Table 1).

The majority of participants (78.34%) knew non-invasive (blood/serum) fibrosis markers for assessment of hepatic fibrosis but only 37.79% of participants thought that serum biomarkers are reliable. Most of the participants (84.08%) thought serum biomarkers are acceptable by patients while only 38% used them for assessment of hepatic fibrosis. Most of the participants (66%) preferred to use transient elastography for assessment of hepatic fibrosis, 45% used a combination of serum biomarkers and elastography, 31.42% used blood/serum biomarkers alone, and 7.86% used magnetic resonance elastography. Most of the participants (95.42%) were familiar with radiological methods for non-invasive assessment of hepatic fibrosis. Sixty-two percent of participants thought that radiological methods are reliable, 89.1% thought that they are acceptable by patients and 78% considered radiological methods to be easily applicable in clinical practice.

The most commonly used methods for assessment were FibroScan, ultrasound, computed tomography, ultrasound-based elastography, magnetic resonance imaging (MRI), and MRI-based elastography respectively. Most of the participants (87.58%) considered radiological methods for non-invasive assessment of hepatic fibrosis easy to use (Tables 2 and 3).

Despite that, 65% of participants thought combinations of methods are more beneficial for non-invasive assessment of hepatic fibrosis than using a single method, only 39.37% of participants used them frequently. Forty percent of participants thought that radiological methods are easier to use for assessment of hepatic fibrosis followed by the combination of non-invasive methods, serum biomarkers, and liver biopsy respectively (Table 4).

## Discussion

In this web-based survey, we assessed the level of acceptance and reliability of liver biopsy and non-invasive methods for the assessment of hepatic fibrosis and cirrhosis among hepatologists. Our results demonstrated that the majority of Egyptian hepatologists still consider liver biopsy as the gold standard tool for diagnosis and staging of liver fibrosis and cirrhosis. Liver biopsy results had a high level of acceptance and reliability among Egyptian hepatologists. Liver biopsies were reported to have a modest level of acceptance among patients. Despite the high level of acceptance, most hepatologists stated that there is a need for less-invasive alternatives, especially when serial evaluation of liver fibrosis/cirrhosis is a need. Most of the participants in the present survey stated that they knew the utility of serum biomarkers and radiological tools as non-invasive methods for assessment of liver cirrhosis; these methods are widely accepted by the physicians and the patients and are considered as reliable and applicable tools. The participants agreed that there is a need for a national guideline that governs the utilization of non-invasive methods for the assessment of liver fibrosis.

Liver cirrhosis is a major public health burden in Egypt, which harbors the largest number of patients with chronic hepatitis C worldwide [19]; previous epidemiological studies demonstrated that Egypt is ranked as the first leading country regarding cirrhosis-related mortality worldwide [20]. Therefore, evaluation and monitoring of liver cirrhosis account for a considerable proportion of routine clinical practice of Egyptian hepatologists; nevertheless, limited data are available concerning the frequency and sequence of different tools for assessment of liver fibrosis. Previous reports demonstrated that the utilization of liver biopsy has been significantly declined in Egypt over the past decades [21]. Such findings can be attributed to the limitations of liver biopsy such as

**Table 1** Hepatologists' attitude towards the use of liver biopsy for diagnosis of significant fibrosis and cirrhosis

Variable	Patients (n = 573)
Do you think the liver biopsy is still the gold standard for diagnosing liver fibrosis? %	
Extremely likely (100%)	21.15
Very likely (75%)	39.92
Moderately likely (50%)	23.91
Slightly likely (25%)	11.07
Not at all likely (0%)	3.95
In your practice what percentage of patients accept liver biopsy? %	
Extremely likely (100%)	6.13
Very likely (75%)	37.55
Moderately likely (50%)	32.81
Slightly likely (25%)	22.53
Not at all likely (0%)	1.98
Do you think we still need a liver biopsy for the diagnosis of significant fibrosis and cirrhosis in viral hepatitis? %	
Extremely likely (100%)	4.35
Very likely (75%)	13.64
Moderately likely (50%)	26.88
Slightly likely (25%)	37.94
Not at all likely (0%)	18.18
Do you think we still need a liver biopsy for the diagnosis of significant fibrosis and cirrhosis in non-viral chronic liver diseases? %	
Extremely likely (100%)	10.67
Very likely (75%)	34.39
Moderately likely (50%)	27.67
Slightly likely (25%)	20.55
Not at all likely (0%)	7.11
How frequently do you see discordant results of liver biopsy histopathology reports with clinical findings? %	
Extremely likely (100%)	0.99
Very likely (75%)	6.52
Moderately likely (50%)	30.24
Slightly likely (25%)	59.68
Not at all likely (0%)	2.57
What do you do if the histopathology report is discordant with clinical findings? %	
Ask for a second opinion from another pathologist	34.19
Repeat liver biopsy	6.72
Use non-invasive methods "biomarkers"	19.57
Use non-invasive methods "Radiological"	39.53
Do you think that currently used histopathological scoring systems are satisfactory for clinical decisions? %	
Extremely likely (100%)	9.29
Very likely (75%)	59.88
Moderately likely (50%)	25.30
Slightly likely (25%)	4.94
Not at all likely (0%)	0.59
Do you diagnose cirrhosis easily? %	
Yes	88.45
No	11.55
How do you diagnose cirrhosis? "choose all that apply"%	
Clinically	51.58
Laboratory tests	50
Radiological methods	53.95
All of the above	62.85
Do you diagnose significant fibrosis easily? %	
Yes	51.58
No	48.42

**Table 1** (continued)

Variable	Patients (n = 573)
How do you diagnose significant fibrosis? "choose all that apply" %	
Clinically	22.92
Laboratory tests	34.19
Radiological methods	44.66
All of the above	38.93
Do you think a liver biopsy is required for diagnosing cirrhosis? %	
Extremely likely (100%)	2.77
Very likely (75%)	8.50
Moderately likely (50%)	21.94
Slightly likely (25%)	45.45
Not at all likely (0%)	21.34
Do you think we need a more practical alternative to liver biopsy to assess liver disease progression or response to treatment? %	
Extremely likely (100%)	47.83
Very likely (75%)	36.17
Moderately likely (50%)	10.08
Slightly likely (25%)	4.15
Not at all likely (0%)	1.78

**Table 2** Hepatologists' attitude towards the use of serum markers for diagnosis of significant fibrosis and cirrhosis

Variable	Patients (n = 573)
Do you know non-invasive (blood/serum) fibrosis markers for assessment of hepatic fibrosis? %	
Extremely likely (100%)	42.46
Very likely (75%)	35.88
Moderately likely (50%)	13.59
Slightly likely (25%)	6.37
Not at all likely (0%)	1.70
Do you think non-invasive (blood/serum) fibrosis markers for assessment of hepatic fibrosis are reliable? %	
Extremely likely (100%)	3.82
Very likely (75%)	33.97
Moderately likely (50%)	47.56
Slightly likely (25%)	12.95
Not at all likely (0%)	1.70
Do you think non-invasive blood/serum fibrosis markers "biomarkers" for assessment of hepatic fibrosis are acceptable by patients? %	
Extremely likely (100%)	43.95
Very likely (75%)	40.13
Moderately likely (50%)	12.31
Slightly likely (25%)	2.76
Not at all likely (0%)	0.85
Do you use non-invasive blood/serum fibrosis markers "biomarkers" for assessment of hepatic fibrosis? %	
Extremely likely (100%)	15.92
Very likely (75%)	22.29
Moderately likely (50%)	19.75
Slightly likely (25%)	23.57
Not at all likely (0%)	18.47
Which non-invasive methods for assessment of hepatic fibrosis do you use? Please choose all that apply %	
Blood/serum biomarkers	31.42
Transient elastography	66.24
Biomarkers and elastography	45.01
Magnetic resonance elastography	7.86

**Table 3** Hepatologists' attitude towards the use of radiological methods for diagnosis of significant fibrosis and cirrhosis

Variable	Patients (n = 573)
Are you familiar with radiological methods for non-invasive assessment of hepatic fibrosis? %	
Very familiar	58.12
Familiar	37.30
Not familiar	4.58
Do you think radiological methods are reliable for non-invasive assessment of hepatic fibrosis? %	
Extremely likely (100%)	10.89
Very likely (75%)	51.20
Moderately likely (50%)	32.90
Slightly likely (25%)	4.58
Not at all likely (0%)	0.44
Do you think radiological methods for non-invasive assessment of hepatic fibrosis are acceptable by patients? %	
Extremely likely (100%)	51.20
Very likely (75%)	37.90
Moderately likely (50%)	8.71
Slightly likely (25%)	1.74
Not at all likely (0%)	0.44
Do you think radiological methods for non-invasive assessment of hepatic fibrosis are easily applicable in clinical practice? %	
Extremely likely (100%)	32.68
Very likely (75%)	45.1
Moderately likely (50%)	18.52
Slightly likely (25%)	3.27
Not at all likely (0%)	0.44
Which radiological methods do you use for noninvasive assessment of hepatic fibrosis? "Please choose all that apply" %	
Ultrasound	59.48
Computed tomography	26.58
Magnetic resonance imaging	24.62
FibroScan	85.40
Ultrasound based elastography	25.05
MRI-based elastography	8.71
What are the limitations of using radiological methods for the assessment of hepatic fibrosis? Please choose all that apply %	
Cost	47.06
Exposure to radiation	14.38
Availability	60.13
Accuracy	45.53
I don't trust non-invasive methods	0.22
What is encouraging you for using radiological methods for the assessment of hepatic fibrosis? Please choose all that apply %	
Easy to use	87.58
Less costly than liver biopsy	41.61
Not convinced that liver biopsy is the gold standard	15.03
Patient refusal for liver biopsy	64.27

invasive nature and high risk of post-procedure complications [10]. However, it is still unclear whether the decline in the utilization and acceptance of liver biopsy is consistent among different institutions in the country. Some studies about these non-invasive methods, especially in Egypt, showed that APRI, FIB4, and GUCI can be used as good predictors of liver fibrosis in chronic hepatitis C

[22]. In this report, we highlighted that majority of Egyptian hepatologists still consider liver biopsy as the gold standard tool for diagnosis and staging of liver cirrhosis; the biopsy also had a high level of acceptance and reliability among the Egyptian hepatologists, despite the modest acceptance by the patients. To our knowledge, no previous published studies have assessed the acceptability and

**Table 4** Hepatologists' attitude towards the use of combination tools for diagnosis of significant fibrosis and cirrhosis

Variable	Patients (n = 573)
Do you use combinations of serum biomarkers and radiological methods for non-invasive assessment of hepatic fibrosis? %	
Extremely likely (100%)	13.20
Very likely (75%)	26.17
Moderately likely (50%)	15.88
Slightly likely (25%)	23.27
Not at all likely (0%)	21.48
Do you think combinations of methods are more beneficial for non-invasive assessment of hepatic fibrosis than using a single method? %	
Extremely likely (100%)	31.1
Very likely (75%)	34
Moderately likely (50%)	21.70
Slightly likely (25%)	10.29
Not at all likely (0%)	2.91
Which method do you think is easier to use for the assessment of hepatic fibrosis? %	
Liver biopsy	5.37
Radiological methods	40.27
Serum biomarkers	24.16
Combination of non-invasive methods	30.20

reliability of liver biopsy among Egyptian hepatologists. However, our results are contrary to reports from Europe [11] and Canada [23], which showed that many hepatologists have shifted to radiological tools for the evaluation and monitoring of chronic liver diseases.

As mentioned before, non-invasive markers have gained momentum for the evaluation of liver cirrhosis over the recent two decades and many of these tools were well-validated in large cohort studies [10, 12–16]. Recent reports demonstrated that there is a notable increase in the acceptance of non-invasive tools among hepatologists in routine clinical practice [24], which is attributed to the simplicity of these tools and the avoidance of complications associated with liver biopsy; besides, many of these tools are readily available, even in limited-resources area, and cheaper than standard liver biopsy procedure [25]. In the present survey, we found that non-invasive methods are gaining acceptance by Egyptian physicians and patients, and most of them consider these methods as reliable and applicable tools for predicting the course of liver cirrhosis. Notably, we found that hepatologists prefer radiological methods over serum biomarkers, and considered them as easier and cheaper methods for evaluation and staging of liver cirrhosis. This study, however, has some limitations. Although web-based surveys may have advantages related to the speed and cost of data collection as well as data quality, they may be biased by low and selective participation. The Likert scale, based on overall impression, may provide more variable results when applied across hepatologists and

gastroenterologists from different institutions; the potential effect of the institution, in addition to individual readers, warrants future evaluation. Areas that should be targeted in future research include validation of promising novel imaging technologies (ultrasound-based, and magnetic resonance (MR)-based markers), longitudinal studies to validate the performance of noninvasive surrogates for monitoring fibrosis progression (or regression) over time, the definition of the role of combined vs. sequential noninvasive test approaches to optimize accuracy, validation of non-invasive methods for screening fibrosis and cirrhosis in at-risk groups (e.g., diabetic patients) and in the general population and finally validation in special populations (e.g., pediatric subjects).

### Conclusion

In conclusion, liver biopsy is still considered as the most reliable method for evaluation and staging of liver cirrhosis by hepatologists in Egyptian institutions, despite the modest acceptance by the patients. Nonetheless, non-invasive methods are gaining acceptance by Egyptian physicians and patients, and most of them consider these methods as reliable and applicable tools for predicting the course of liver cirrhosis. Notably, we found that hepatologists prefer radiological methods over serum biomarkers, and considered them as easier and cheaper methods for evaluation and staging of liver cirrhosis. Owing to the scarcity in the published literature, further studies with a well-planned design and multinational collaboration are still needed.



## Abbreviations

MR: Magnetic resonance; STROBE: Strengthening the Reporting of Observational studies in Epidemiology; SPSS: Statistical Package for the Social Sciences; SD: Standard deviation; MRI: Magnetic resonance imaging; APRI: Aspartate aminotransferase-to-platelet ratio index; FIB4: Fibrosis-4 index; GUCI: Göteborg University Cirrhosis Index.

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## Authors' contributions

MA, MK, AE, and NA conceptualized the idea and designed the study. ME, AAE, HN, ZK, AE, ARE, MI, MAA, and AE collected the data. NA did statistical analysis. MA, HN, and ARE drafted the final manuscript. FE, FH, MH, and GE reviewed the manuscript for certain intellectual points. All authors read and approved the final manuscript.

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## Availability of data and materials

The dataset used in the current study are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

This study was done in accordance with the ethical standards of Helsinki Declaration and its later amendments. The study was approved by the Ethics Committee of the faculty of medicine, AL-Azhar University. Informed consent was obtained from all participants.

### Consent for publication

All authors agree to the journal rules for publications.

### Competing interests

The authors declare that they have no competing interests.

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