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Exploring the Use of Point of Care Ultrasound in Screening for Non-Alcoholic Fatty Liver Disease: A Systematic Literature Review and Meta-Analysis

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a major cause of cirrhosis and liver failure globally. Despite its broad impact, screening recommendations for NAFLD remain varied based between gastrointestinal societies. Point of care ultrasound (POCUS) has emerged as a new form of screening and diagnosing intrabdominal pathologies including NAFLD. We aimed to estimate the effectiveness of POCUS in screening for NAFLD compared to formal ultrasound when screening by general practitioners trained in ultrasonography. Data was collected from Cochrane, PubMed, Embase, and Google Scholar using search terms related to POCUS and NAFLD screening. Observational cross-sectional studies were included in our analysis. Reviewers evaluated articles for eligibility and extracted data for analysis. The risk of bias was assessed by reviewers using a validated risk of bias assessment tool. Discrepancies between authors were resolved by a third reviewer or by consensus. Our review found 3 studies (n = 428) that met our eligibility criteria. Our review found that POCUS was 93% sensitive and 98% specific when screening for NAFLD compared to formal ultrasound. We concluded that POCUS is an acceptable method of screening for NAFLD when used by general practitioners trained in ultrasonography. Further, more robust, studies are required to validate the findings of our review and elucidate further horizons on this emerging screening method.

Keywords: Non-alcoholic fatty liver disease, NAFLD, NASH, Liver failure, Point of care ultrasound, POCUS, Screening

Introduction

Non-alcoholic fatty liver disease (NAFLD) is a common cause of chronic liver disease worldwide. It refers to hepatic steatosis, seen in imaging or histology, as lipid accumulation without any other secondary cause such as excessive alcohol consumption, viral disease, or medication use. The prevalence of NAFLD is estimated to be between 20-30% in the general population and it is associated with obesity, metabolic syndrome, and insulin resistance. There has been a linear rise of NAFLD correlating with the rise of diabetes and metabolic syndrome in the United States. It is estimated that within the next 20 years, NAFLD will be the major cause of liver related morbidity and mortality as well as the leading indication for liver transplantation [1].

The pathogenesis of NAFLD involves the deposition of free fatty acids and triglycerides in the liver. It is hypothesized that insulin resistance is at the center of the development of steatosis which results in hepatic *de novo* lipogenesis and subsequent reduction of adipose tissue lipolysis with consequent increase of fatty acids and reactive oxidant species in the liver. Further injury occurs with endoplasmic reticulum stress coupled with mitochondrial dysfunction which occurs as a result of fat accumulation in the liver. Additionally, the production and secretion of adipokines and inflammatory cytokines as a consequence of adipose tissue dysfunction is thought to further contribute towards both insulin resistance and progression of fatty liver disease. Such combined mechanisms appear to provide an explanation for the association of obesity and metabolic syndrome with

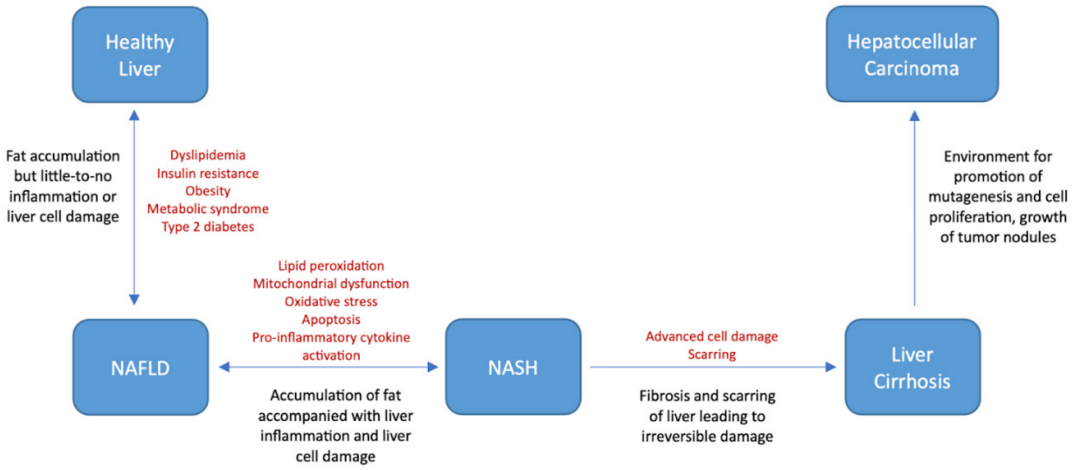

Figure 1. Progression of NAFLD to Liver Cirrhosis.

the development of NAFLD. The diversity of mechanisms and associations between metabolic syndrome and fatty liver disease has led an international group of experts to develop a new inclusive nomenclature termed metabolic dysfunction associated fatty liver disease (MAFLD) [2].

Much of the danger of NAFLD lies in its ability to progress to an inflammatory subtype referred to as non-alcoholic steatohepatitis (NASH). NASH is characterized by a pattern on liver histology of steatosis, lobular inflammation, and hepatocyte ballooning with or without perisinusoidal fibrosis. These consequences of NASH increase the risk of progression to liver cirrhosis, end-stage liver disease, and rarely hepatocellular cancer [3].

The prevalence of NAFLD varies globally across different populations and geographical regions [1]. The highest prevalence rates have been reported in Western countries, where the prevalence of NAFLD is estimated to be between 20-30% in the general population [4,5]. In North America, the prevalence of NAFLD is estimated to be around 24%, with a higher prevalence in Hispanic and non-Hispanic Black populations [6]. In Asia, the prevalence of NAFLD is also high, with estimates approximately 29% in different countries. In Asian populations, prevalence was highest amongst the Indonesian population at a prevalence of 51% contrasted with the lowest prevalence of 22% in Japan. The prevalence of NAFLD in Japan is lower than in Western countries but is increasing rapidly particularly in younger age groups [7]. In Africa and South America, the prevalence of NAFLD is less well studied but available data suggests it is also increasing. A recent systematic review estimated the prevalence of NAFLD in Africa to be around 13.5%, but the true prevalence may be higher due to limited data availability [8]. In Latin America, the prevalence of NAFLD is estimated to be approximately 24%, depending on the country and population [9].

Liver biopsy is currently the gold standard for the diagnosis of NAFLD. Liver biopsy allows for direct observation of hepatic structures in order to evaluate for the presence of fatty infiltration and local inflammatory changes which are the hallmark of NAFLD. Although liver biopsy is the gold standard, other screening modalities are preferred in the clinical setting due to their cost effectiveness and lack of complications such as biopsy associated bleeding [10]. Current non-invasive methods of screening of NAFLD include biomarkers and imaging. Multiple biomarker panels such as Fatty Liver Index (FLI), Hepatic Steatosis Index (HIS), Steato Test, Enhanced Liver Fibrosis (ELF) score, and NAFL screening score have been developed. These scoring systems utilize biomarkers such as alanine transaminase (ALT), aspartate aminotransferase (AST), and body mass index (BMI) in order to estimate the risk of NAFLD presence in patients. Such biomarker panels can be used in conjunction with imaging; however, they are unable to truly assess the level of steatosis [11].

Ultrasound imaging has emerged as a non-invasive method of screening for NAFLD. Ultrasound may be used to compare the echogenicity of the liver to the echogenicity of adjacent structures such as the kidney. Hyperechogenic liver tissue relative to renal echogenicity is among the most common ultrasonographic findings on screening [12]. A meta-analysis showed that ultrasound compared to biopsy had an 85% sensitivity and 94% specificity for moderate to severe steatosis [13]. However, a limitation of ultrasound is that it can often not detect the presence of steatosis when it involves less than 20% of liver parenchyma. Furthermore, ultrasound windows can be limited by the presence of morbid obesity [14].

Despite the known increase in rates of NAFLD around the world, and particularly in the United States, there is division amongst the major world bodies concerning NAFLD screening guidelines. The American Association for the Study of Liver

Diseases (AASLD), the European Association for the Study of the Liver (EASL), and the National Institute for Health and Care Excellence (NICE) lack a consensus on their respective screening recommendations [15]. While the EASL in 2016 and the NICE in 2021 both recommended screening patients with risk factors such as obesity or type II diabetes mellitus, the AASLD continues to cite lack of cost-effectiveness analyses to support screening for NAFLD in either the general population or in high-risk patients [15]. These recommendations appear to be based on the current fund of studies that predominantly use either formal ultrasound or liver biopsy for the diagnosis of NAFLD.

Recently however, point-of-care ultrasound has emerged as a more cost-effective and accessible option than either formal ultrasound or liver biopsy. The evaluation of the effectiveness of POCUS in screening for fatty liver disease may tip the scales towards recommendations for NAFLD screening if it emerges as an effective and reliable method for screening NAFLD. This paper aims to assess the currently available body of evidence and determine the current consensus with regards to the use of POCUS for the screening of fatty liver diseases such as NAFLD.

Materials and Methods

Search strategy

Two of our team members (O.H. & T.N.) conducted an independent search of cross-sectional and longitudinal studies published between January 1, 2010 and December 31, 2022 which evaluated the efficacy of POCUS as compared to formal ultrasound when screening for NAFLD. Our team systematically searched PubMed, Embase, Google Scholar, and Cochrane for eligible studies. Terms related to NAFLD and POCUS were combined with terms related to screening and formal ultrasound including "POCUS", "Bedside Ultrasound", "Ultrasound", "NAFLD", and "Screening".

Eligibility criteria

Inclusion criteria were comprised of the following: (a) study design: peer reviewed cross-sectional studies; (b) study population: adults aged 18 years or older; (c) examiner population: physicians conducting POCUS including primary care physicians; (d) comparison evaluation of formal ultrasound; (e) reported outcomes of presence or absence of fatty liver disease. Peer reviewed cross-sectional studies were included if data reported on the efficacy of both POCUS and formal ultrasound in detecting fatty liver disease when conducted by a physician. Studies did not require distinction between detecting NAFLD from other forms of fatty liver disease. Studies were excluded if manuscripts were unavailable in English, POCUS evaluation was conducted by a trained non-physician technician, or studies lacked comparison of POCUS evaluation with a formal ultrasound.

Evaluated studies were restricted to those with English manuscripts available. References which were identified from database searches were exported to Excel (Microsoft). Following duplicate and non-English publication removal, article titles from included references were screened for population, measured outcome, and relevance in subject matter to our study focus. Abstracts were then reviewed for inclusion criteria using a similar process. Full text articles were retrieved if screened abstracts were considered eligible by a minimum of one member of our team. Each full text article was evaluated independently by each member of our team for consideration of inclusion in our review. Following independent review, recommendations were made by each member concerning study inclusion. A 100% consensus was reached without disagreement for the included studies.

Data extraction

Two of our team members (O.H., Z.S.) conducted an independent extraction of the data from each included study. Extracted data included: study design, patient characteristics, patient sample size, intervention characteristics (POCUS or formal ultrasound), POCUS operator, and incidence of fatty liver disease diagnosis between POCUS and formal ultrasound evaluation. The primary outcome of our study was presence or absence of fatty liver disease.

Quality assessment

Included studies were evaluated for risk of bias using the Risk of Bias 2 (RoB 2) tool for the assessment of the risk of bias in randomized control trials [16]. Moreover, investigators utilized the standardized GRADE tool assessment when rating the quality of the included studies. The quality assessment of the outcomes was measured using the standardized GRADE assessment approach [17].

Statistical analysis

Data analysis was conducted using the RevMan software (Version 5.4.1; Cochrane Collaboration, Oxford, UK). Data concerning the primary outcome of fatty liver detection between the POCUS intervention group and the formal ultrasound group was collected and pooled. Sensitivities and specificities of the POCUS method were pooled into a forest plot for analysis. Random-effects models were applied to analyze between-study heterogeneity and assessed using a Receiver Operating Characteristic (ROC) curve.

Ethical statement

Our systematic literature review and meta-analysis was conducted following the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [18].

Results

Study selection

On initial search, a total of 137 studies were identified using our search terms. Following evaluation of titles, 121 studies were excluded from our analysis. Of the remaining 16 studies, we selected 3 for full text review following exclusion based on screening of available abstracts. The flowchart outlining this process is shown in **Figure 2**.

Characteristics of selected ultrasound studies

Our analysis included 3 studies, all of which were cross-sectional studies. Our total population studied was 428 ranging from sample sizes between 28 to 300 depending on the study. The average participant age between the studies was 59 with a narrow predominance on average of males at 53% (n=226). The GE Logiq E9 ultrasound system (GE Medical Systems, Milwaukee, WI, USA) was the most frequently used formal ultrasound system (n=2) while all POCUS devices varied in make and model from each other. The degree of training received by the operating physician conducting the POCUS examination ranged from non-board certification in ultrasound to formal board certification in ultrasound techniques as outlined in **Table 1**.

Fatty liver detection by POCUS compared to formal ultrasound

The prevalence of fatty liver disease was 17% (n=72) in the patients cumulatively recruited across all studies. The cumulative sensitivity for POCUS examination was 93% (95% CI: 85 – 98%), with a negative predictive value of 99%. Additionally, the specificity of POCUS for the detection of fatty liver disease was 98% (95% CI: 96 – 99%) with a positive predictive value of 91%. The highest number of false positive and false negative results was recorded in the Miles et al. study at n=7 and n=4 respectively [20]. The results of the studies are individually illustrated on a forest plot found in **Figure 3**. Assessment of heterogeneity plotted on a ROC curve demonstrated low heterogeneity between the included studies as seen in **Figure 4**.

Risk of bias

As illustrated in **Figures 5** and **6**, the risk of bias was low for two of the studies and one had moderate risk of bias. There was a low risk of applicability concerns in all three studies.

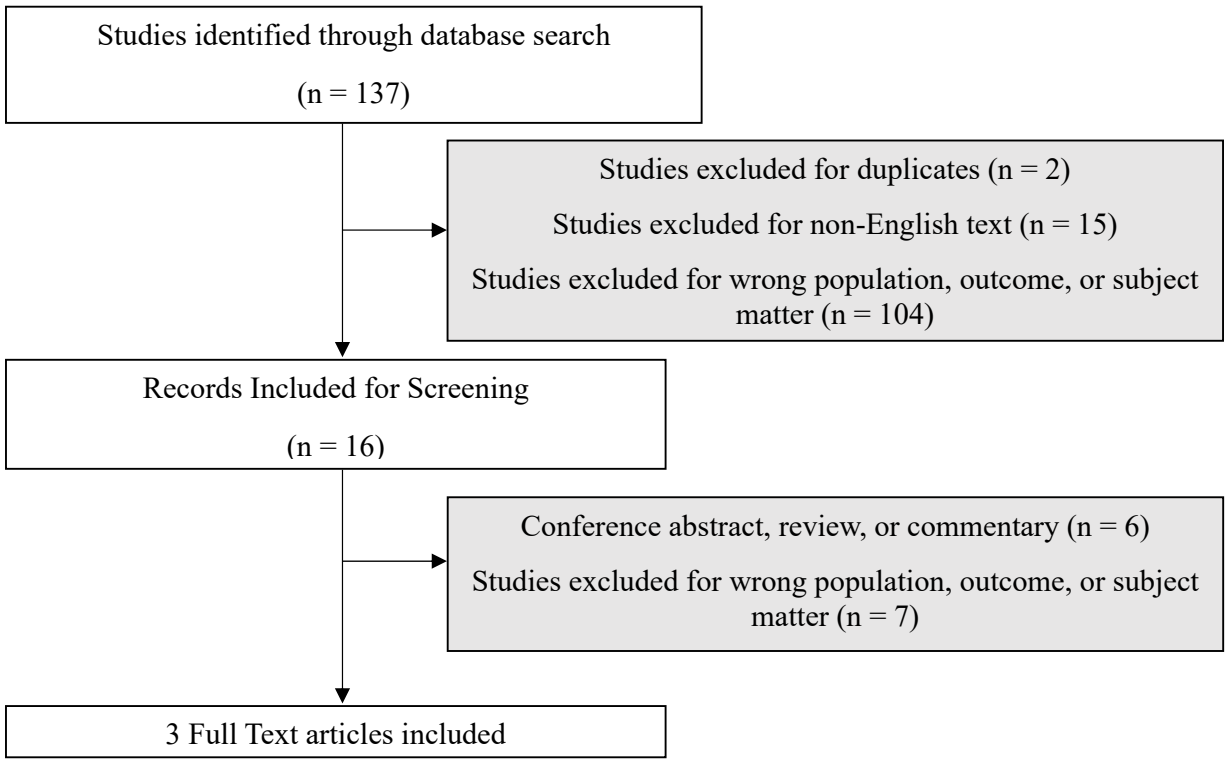

Figure 2. Study Selection Flowchart.

Table 1. Overall characteristics of the selected studies.

Author	Study Design	Country	N	Average Age (Range)	% Male	POCUS Operator Training	POCUS Device	Formal Ultrasound Device
Barreiros et al. 2019 [19]	Cross-Sectional	Germany	300	55 (18 - 96)	53%	Certification with the German Society for Ultrasound in Medicine	Vscan Dual Probe pocket device (GE Medical Systems, Milwaukee, WI, USA)	GE Logiq E9 ultrasound system (GE Medical Systems, Milwaukee, WI, USA)
Miles et al. 2019 [20]	Cross-Sectional	Canada	100	53 (N/A)	55%	Certification in POCUS via the Canadian Point of Care Ultrasound Society	Undefined Handheld Device using a 5–1 MHz phased-array probe	GE Logiq E9 ultrasound system (GE Medical Systems, Milwaukee, WI, USA)
Stock et al. 2015 [21]	Cross-Sectional	Germany	28	68 (29 - 94)	43%	Board certification by the National Ultrasound Society	Acuson P10 Portable Ultrasound System (Siemens Medical Solutions, Malvern, PA, USA)	Sonoline Antares ultrasound system (Siemens Medical Solutions, Malvern, PA, USA)

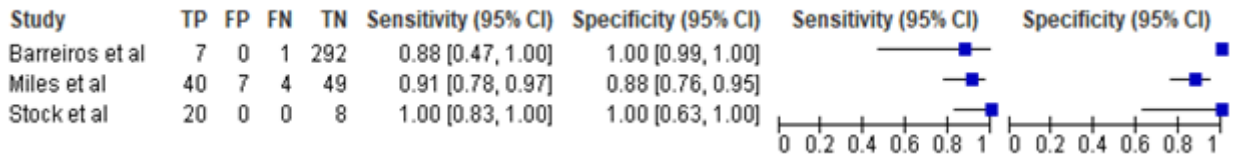

Figure 3. Forest plot of detection of fatty liver disease with POCUS with formal ultrasound as the gold standard. Each square represents the average value within its respective column with corresponding 95% confidence intervals.

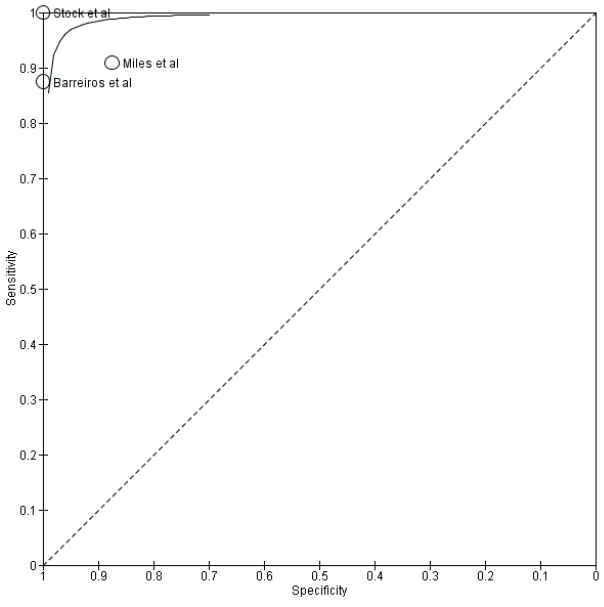

Figure 4. ROC curve plotting sensitivities and specificities of the included studies.

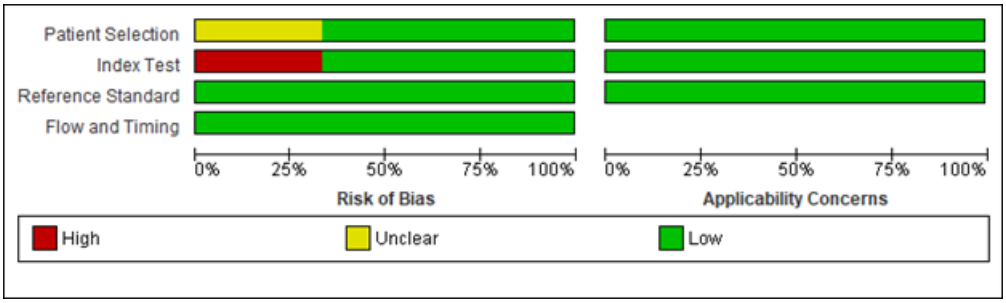

Figure 5. Cumulative risk of bias assessment.

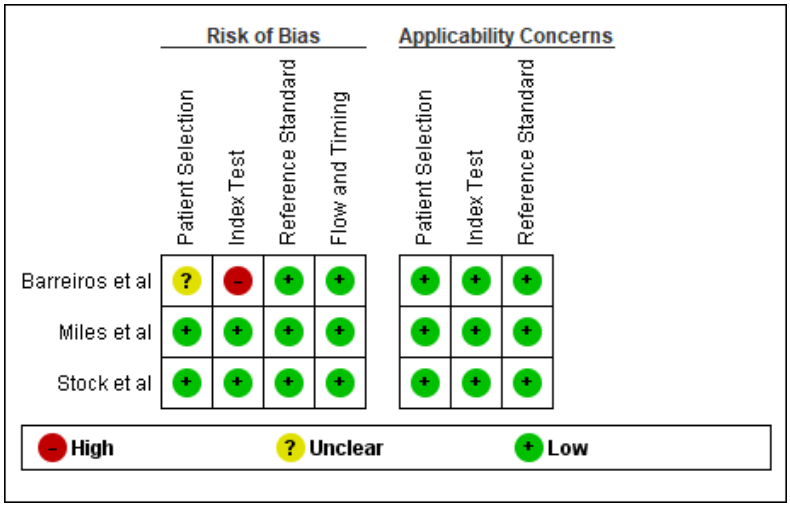

Figure 6. Risk of bias and applicability concerns stratified by study.

Discussion

A total of 3 studies with a population of 428 participants were included in our review. The included studies consistently demonstrated comparable diagnostic performance as demonstrated in the sensitivity and specificity exhibited by POCUS evaluations when compared to formal ultrasound. The use of POCUS as a screening tool for NAFLD and fatty liver disease holds various advantages including portability, ease of use, and cost effectiveness. These factors, combined with our findings, support POCUS as an option to consider when assessing recommendations for NAFLD screening.

One of the key strengths identified in our studies includes the high sensitivity of POCUS in detection of NAFLD. Hepatic steatosis, a key hallmark feature of NAFLD, was detected with a sensitivity of 93% (95% CI: 86-98%) with a specificity of 98% (95% CI: 96 – 99%) in discerning between NAFLD and other liver pathologies. These results were achieved even with POCUS operators of various levels of training.

Role of primary care physicians in screening with POCUS

Although primary care providers often represent the earliest healthcare contact for the detection of NAFLD, studies have shown a lack of awareness with regards to NALFD and at-risk patients [22]. Operator population is an important distinguishing feature of our study as the majority of operators were internal medicine physicians. The internal medicine physicians who conducted POCUS were able to achieve the high levels of sensitivity and specificity reported earlier. We believe this reflects the ability of primary care physicians to screen for NAFLD in the future while avoiding false positives, unnecessary interventions, reducing burden on the healthcare system, and providing an opportunity for earlier diagnosis and interventions for NAFLD.

The use of POCUS for NAFLD screening also presents advantages in terms of time efficiency and patient convenience. Unlike formal ultrasound, which typically requires specialized personnel and dedicated imaging appointments, POCUS can

be performed by trained healthcare providers at the bedside or in outpatient settings. This eliminates the need for additional visits and reduces the waiting time for patients, promoting a more streamlined and efficient diagnostic process. The included study by Miles et al. demonstrated an average reduction of 4 minutes of examination time when POCUS was used compared to formal ultrasound [20]. Moreover, POCUS has been demonstrated to be a more cost-effective and time-saving evaluation when compared to formal ultrasound for other conditions [23]. It is reasonable to suggest that POCUS for the screening of NAFLD may also be more cost-effective than formal ultrasound and affect future recommendations for NAFLD screening. More studies exploring the cost-effectiveness of POCUS compared to formal ultrasound for the diagnosis of NAFLD are needed though.

Possible interventions for screened populations

Screening for fatty liver disease could allow prompt detection of patients who would benefit from early non-pharmacological interventions of modifiable risk factors. These interventions include avoiding consumption of refined carbohydrates, animal proteins, high-fat diet, encouraging moderate-intensity aerobic exercise, weight loss, and the consumption of black coffee [24]. These lifestyle modifications are the cornerstone of NAFLD treatment and are also beneficial for other medical comorbidities. Despite there being no approved therapy for liver steatosis, many treatments for common comorbidities can have a positive impact on the liver and affect patient outcomes overall. For example, vitamin E in addition to medications that treat diabetes mellitus type II such as thiazolidinediones and GLP-1 agonists may improve steatosis [24-26]. Moreover, Semaglutide has shown possible benefit in slowing the progression of fibrosis [27,28].

Earlier detection of NAFLD in out-patient clinic settings is vital as it could prevent progression to worse outcomes. With detection and education, progression from NAFLD to NASH remains a reversible process. However, if high-risk individuals do not get screening or education on the importance of life-style modifications, as discussed above, they have the potential to progress to irreversible liver cirrhosis.

Limitations

Despite the promising findings supporting the effectiveness of POCUS in NAFLD screening, it is important to acknowledge some of the limitations of our review and those identified in the reviewed studies. Our review was limited to the scarce number of available studies evaluating our research question. More studies are required in order to further validate our findings and evaluate the validity of our study results.

Another limitation is the operator dependency of POCUS technique which can influence the diagnostic accuracy of the test. Proper training and experience are essential to ensure reliable interpretation and minimize interobserver variability. Therefore, establishing standardized protocols and guidelines for POCUS training and certification in NAFLD screening would be beneficial to enhance its overall performance and reproducibility. In reviewing our included studies, we could not establish a clear baseline protocol for each study when performing the POCUS examination. Our study was limited by its retrospective nature as we could not control training and examination performance differences by enacting a training and examination protocol. This remains an area which would benefit from further study.

Additionally, while the studies included in this review consistently demonstrated comparable diagnostic performance between POCUS and formal ultrasound, there is still a need for further research to validate these findings. Larger prospective studies with well-defined patient populations and standardized imaging protocols are warranted to confirm the effectiveness of POCUS in NAFLD screening. Moreover, the studies included in our review did not contain a direct comparison of POCUS to liver biopsy which is considered the gold standard for NAFLD diagnosis. Our studies were limited to comparisons to formal ultrasound. Long-term follow-up studies assessing the impact of POCUS-based screening on patient outcomes, such as the progression of liver disease and the development of related complications, would provide valuable insights into the clinical utility of POCUS in the management of NAFLD.

Conclusion

In conclusion, this systematic literature review supports the effectiveness of POCUS as a reliable method for screening for fatty liver disease and NAFLD when compared to formal ultrasound. The comparable diagnostic performance, high sensitivity, and specificity of POCUS in detecting hepatic steatosis make it a promising tool for early detection and intervention in NAFLD. Moreover, its portability, accessibility, and potential cost-effectiveness make POCUS a valuable screening option, particularly in resource-limited settings. However, further research is needed to validate these findings, establish standardized protocols, and evaluate the long-term impact of POCUS-based screening on patient outcomes.

Conflicts of Interests

No conflicts of interest to report by the corresponding author or co-authors.

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