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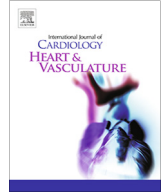
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Diagnostic accuracy of cardiac testing for coronary artery disease in potential liver transplant recipients: A systematic review and meta-analysis



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ABSTRACT

Background: The incidence of coronary artery disease (CAD) in Liver transplant (LT) patients is much higher than prior estimates and the morbidity and mortality are significant in this group of patients. Coronary angiography is the gold standard for detection of CAD, a non-invasive test that allows appropriate risk stratification would be preferred. In this systematic review and meta-analysis, we sought to assess the pooled diagnostic accuracy of various noninvasive cardiac imaging tests in detecting CAD in patients listed for LT.

Methods: We performed a systematic review and meta-analysis of studies comparing sensitivity and specificity of non-invasive tests to that of coronary angiography in diagnosing coronary artery disease in patients undergoing liver transplantation.

Results: Five studies (616 participants) evaluated myocardial perfusion imaging (MPI); five studies (1243 participants) dobutamine stress echocardiography (DSE); and three (87 participants), other tests. MPI had a pooled sensitivity of 0.62 (95% CI 0.37, 0.83), specificity of 0.60 (95% CI 0.39, 0.79), diagnostic odds ratio (DOR) of 2.5 (95% CI 1.7, 5.64) and Area under the curve (AUC) 0.649. DSE had a pooled sensitivity of 0.25 (95% CI 0.09, 0.51), specificity of 0.68 (95% CI 0.44, 0.84) and DOR of 0.7 (95% CI 0.12, 3.84).

Conclusions: Our results show that both MPI and DSE are not effective screening tools for detecting CAD in patients with end-stage liver disease (ESLD). Future studies are needed to evaluate the role of real-time myocardial contrast echocardiography (RTMCE) and coronary artery calcium score (CAC) with coronary CT angiography in patients with ESLD.

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1. Introduction

A total of 8250 adult liver transplants (LT) were performed in the United States (US) in 2018; 75.6% of all transplants were performed in patients ≥ 50 years of which 23.4% were aged 65 years or older [1]. The prevalence of coronary artery disease (CAD) is considerable in this population. Recent reports suggest a higher CAD prevalence in LT recipients than prior estimates [2]. CAD is associated with increased mortality and morbidity in LT patients, with a 1-year mortality as high as approximately 40% [2–4]. End-stage liver disease (ESLD) is a state of high cardiac output, low systemic vascular resistance, bradycardia; decreased responsiveness to beta-adrenoceptor agonists, and increased circulating inflammatory mediators with cardio-depressant properties [4]. Cirrhotic cardiomyopathy, present in 40–50% of patients with cirrhosis, may be masked by reduced afterload and electrophysiological abnormalities. Post LT, heart is suddenly exposed to altered hemodynamics and stress [4–6]. While coronary angiography is the gold standard for assessment of CAD, performing invasive cardiac catheterization on all patients listed for LT is not cost-effective and is associated with complications especially in patients with coexisting renal dysfunction [7,8]. Non-invasive cardiac tests have been used for detecting significant CAD and evaluating perioperative risk in patients with ESLD. However, the optimal screening method in this select group has not been defined. Currently, there is no consensus among various society guidelines about which non-invasive cardiac testing modality should be preferred for risk stratification in these patients before LT. American Association for the Study of Liver Diseases (AASLD) recommends use of non-invasive stress echocardiography as the initial screening test and invasive cardiac catheterization as clinically indicated (Grade 1B) [9]. European Association for the Study of the Liver (EASL) recommends electrocardiography and echocardiography in all patients undergoing liver transplantations (Grade II-3). Further, EASL recommends cardiopulmonary exercise testing in patients with multiple risk factors and those older than 50 years. In patients unable to achieve target heart rate during exercise testing, pharmacological stress test is the test of choice (Grade II-3) [10]. In this meta-analysis, we aim to assess the pooled diagnostic accuracy of common noninvasive cardiac imaging tests in detecting CAD in patients listed for LT.

2. Materials and methods

This systematic review and meta-analysis was conducted in accordance to the Quality of Reporting of Meta-analysis statement guidelines [11] and the PRISMA-DTA (Preferred Reporting Items for a Systematic Review and Meta-analysis of Diagnostic Test Accuracy Studies) Statement [12].

2.1. Search strategy

On May 10, 2020, a PubMed (MEDLINE) and EMBASE search encompassing (cardiac evaluation techniques) OR (liver transplantation) OR (coronary artery disease (CAD)) (Appendix 1) was conducted, with no restriction on date and species-specific search strategies and thesaurus were ratified such as

Medical Subject Heading terms and Emtree for MEDLINE and EMBASE respectively. To maximize the sensitivity of our search, methodology filters were eschewed because even the aptly sensitive filters deemed missing relevant articles [13,14].

2.2. Study selection

Two reviewers independently screened the titles, the abstracts and the full text of the articles generated by literature search. References of each included study were cross-checked for other relevant studies. Inclusion criteria were retrospective and prospective study designs reporting on cardiac test accuracy of the non-invasive test compared to coronary angiography, the gold standard for CAD diagnosis. Almost all CAD diagnostic tests were included entailing stress echocardiography or myocardial perfusion imaging (MPI) (either exercise or pharmacologically induced), exercise stress test (EST), electron beam computerised tomography (EBCT), conventional echocardiography, digital subtraction fluorography (DSF), carotid intima-medial thickness test (CIMT), CT coronary angiography, magnetic resonance angiography, and cardiac magnetic resonance imaging. Studies were approved as relevant if their participants were candidates for LT meanwhile the diagnostic tests were performed. Using coronary angiography as a standard, the definition of coronary artery stenosis was at least 50% narrowing of at least one epicardial coronary artery and severe coronary artery stenosis was defined as having $\geq 70\%$ stenosis. Corresponding authors of studies that missed reporting 2x2 data tables were e-mailed for more information. Such studies were excluded on failure to receive clarification from their corresponding authors after reminders.

3. Results

3.1. General information-selection of eligible studies

We screened 8278 titles and abstracts, 4962 from MEDLINE and 3316 from Embase. Of those, we excluded 8199 reports during the first phase of our selection process. During the second phase (full-text review), we excluded 71 studies. The results of electronic database searching are outlined in (Fig. 1). 19 studies met our inclusion criteria. However, only 10 studies were eligible for the meta-analysis. Five studies compared DSE with reference standard (coronary angiography), five studies compared MPI with reference standard (coronary angiography). Seven studies were not included in the meta-analysis as only index test positive patients underwent coronary angiography (Findely et al (2005), Biabhav et al (2017), Malik et al (2016), Kong et al (2015), Kemmer et al (2014), Jodocy et al (2012), Tsutsu et al (2006)) [15–21].

3.2. Characteristics of MPI studies

Three of five included studies of MPI were conducted in US. One was conducted in Canada and the other in Turkey. Most studies were performed at university hospital and were single center studies. The number of included patients in these studies ranged from

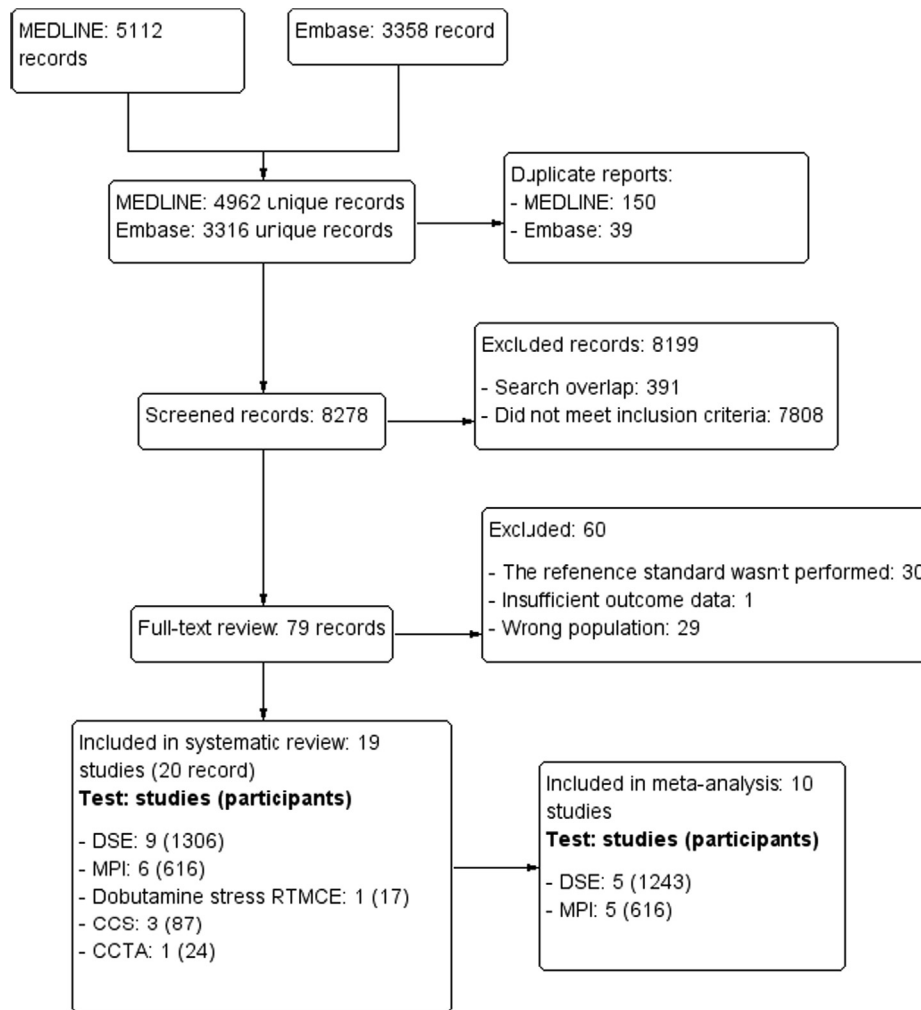


Fig. 1. Flow chart of studies selection during literature search.

Myocardial perfusion imaging (MPI)

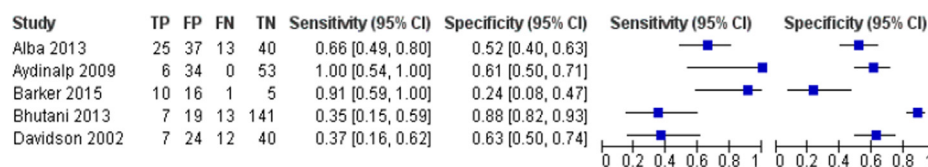


Fig. 2. Forest of plot of myocardial perfusion imaging studies.

32 to 293 (median, 93). Myocardial perfusion was evaluated using technetium-99m (Tc-99m), thallium 201 or tetrofosmin isotopes based upon the patient’s body mass index and chest diameter in most studies. Most studies preferred exercise during stress testing in all patients; however, patients who were unable to exercise received intravenous dipyridamole. Only one study used adenosine and regadenoson as vasodilator agents (Bhutani et al) [22].

MPI was compared with coronary angiography in five studies (616 participants) (Alba 2013, Aydinalp 2009, Barker 2015, Bhutani 2013, and Davidson 2002) [23–26]. (Fig. 2). Using the univariate model, the pooled sensitivity was 0.58 (95% CI 0.47, 0.68) and specificity 0.68 (95% CI 0.63, 0.73). The pooled summary estimates showed that MPI had a diagnostic odds ratio (DOR) of 2.3 (95% CI

1.46, 3.76) and area under the curve (AUC) 0.649. Using the bivariate model, the pooled sensitivity 0.62 (95% CI 0.37, 0.83) and specificity 0.60 (95% CI 0.39, 0.79). MPI was associated with DOR of 2.50 (95% CI 1.17, 5.64). Three studies of five studies avoided partial verification bias. The pooled estimates of these studies were 0.44 (95% CI 0.29, 0.60) for sensitivity and 0.75 (95% CI 0.70, 0.80) for specificity. The DOR remained unchanged at 2.49 (95% CI 1.30, 4.74) and the AUC 0.739, with positive likelihood ratio of 1.74 (95% CI 1.23, 2.47) and negative likelihood ratio of 0.74 (95% CI 0.56, 0.97). There is a substantial heterogeneity among the five studies (Fig. S3). One study (Kremmer 2014) [17] was excluded from the meta-analysis in which 4 participants with positive MPI underwent coronary angiography. In this study, patients with a negative MPI were not

subjected to the reference standard (coronary angiography); thus, a true specificity could not be calculated.

We analyzed five studies using the MPI tool in a cumulative 616 patients awaiting liver transplant. Ayndinalp et al. prospectively evaluated 93 liver transplantation candidates to determine the sensitivity and specificity of MPI in the detection of CAD [24]. Only reversible perfusion defects were considered positive; fixed defects and normal perfusion were deemed negative. Their analysis showed MPI to hold 100% sensitivity and 61% specificity for severe CAD which in turn was defined as stenosis of 70% or greater or greater than 50% with a positive MPI (reversible perfusion defects). Davidson et al., on the other hand, reported the sensitivity of MPI to be 37% with a specificity of 63% after retrospectively evaluating 83 liver transplantation candidates [26]. They also defined clinically relevant CAD on coronary angiography as a stenosis of 70% or greater, however, all single positron emission computed tomography (SPECT) scans defects were interpreted as positive regardless of size, severity, or reversibility (fixed or reversible). Alba et al., studied 115 patients undergoing MPI and coronary angiography with positive test defined as having 1 or more area(s) of ischemia seen on MPI and/or 50% or greater coronary artery stenosis on angiography. The sensitivity and specificity of MPI to identify CAD was found to be 66% and 52% respectively [23]. Bhutani et al. retrospectively analyzed 414 patients with end-stage liver disease who underwent coronary angiography and MPI before liver transplantation [22]. Like Davidson et al., they had interpreted all defects on MPI as positive regardless of size, severity, or reversibility. All the above studies included in our analysis evaluated pre-liver transplant patients with no known history of CAD and all patients underwent MPI followed by coronary angiography regardless of the MPI results. The main difference among the studies however was the interpretation/definition of a positive MPI test. This probably explains the variability in their results. In the fifth study by Baker et al., 244 patients with advanced liver disease were divided into 3 study cohorts; those with a positive MPI, those with a negative MPI, and those with the negative MPI having coronary angiography [25]. Our analysis included only those patients who underwent both MPI as well as coronary angiography (n = 32; positive MPI = 26, negative MPI = 6); outcome being MPI with a sensitivity of 91% and a specificity of 24%.

3.3. Characteristics of DSE studies

All of the included studies were conducted in US and performed at single center university hospitals. The number of included patients were ranged from 18 to 64 (median, 59). Three of these were retrospective and one was prospective. All studies only enrolled the patients who are candidates for liver transplantation and were referred for cardiac evaluation for suspected CAD. DSE was performed according to institutional protocol, with intravenous dobutamine infusion administered at incremental doses until the target heart rate or study end point were achieved.

Five studies (1243 participants) identified DSE (Donovan 1996, Harinsein 2008, Sinpelisky 2014, Doytchinova 2019, Kutkut 2019) [27–31]. Presence of wall motion abnormalities during the stress

test was considered a positive result for diagnosing CAD (Fig. 3). The pooled sensitivity of DSE was 0.27 (95% CI 0.07, 0.12) and the pooled specificity was 0.88 (95% CI 0.71, 0.78). Generally, DSE was associated with DOR of 0.79 (95% CI 0.06, 9.76). Using the bivariate model, the pooled sensitivity 0.25 (95% CI 0.09, 0.51) and specificity 0.68 (95% CI 0.44, 0.84). DSE was associated with DOR of 0.7 (95% CI 0.12, 3.84). All five studies used a reference test diagnostic threshold of $\geq 50\%$ stenosis. Generally, there was a strong evidence of heterogeneity (Fig. 4S) among these five studies. Four records (60 participants), weren't included in the meta-analysis (Plotkin, Baibhav, Malik, Findlay) [3,15,19,21], as in these studies, patients with a negative DES were not subjected to the reference standard (coronary angiography); thus, a true specificity could not be calculated.

Five studies were included in our analysis that endorsed DSE as a preferred cardiac test, in a pooled population of 1243 patients. As with our MPI study selection criteria, our objective was to identify patients who underwent both the screening as well as the gold standard test in order to extrapolate the sensitivity and specificity data. Donovan et al. evaluated 165 patients with ESLD, suitable for liver transplantation, who underwent DSE as part of pre-operative cardiac assessment [27]. Only 11 patients were noted to have wall motion abnormality, and out of those 9 patients underwent coronary angiography. Cardiac catheterization was also performed in 9 patients without a notable ischemic response on DSE. Only 3 patients in the former group had coronary stenosis of 50% or greater. In the latter group, only one patient had significant coronary artery stenosis, thereby yielding a sensitivity of 75% and a specificity of 57% were observed which could be limited by extremely small study group (n = 18). In a retrospective analysis of 105 liver transplant candidates who had both DSE and angiography, Harinsein et al. observed sensitivity and specificity of DSE to be 17% and 88% respectively in CAD with obstruction $>50\%$ or greater. Only 64 patients who were able to meet target heart rate on DSE and who did not have prior history of CABG, were included in the primary study group [28]. Snipelisky and colleagues identified a cohort of 64 patients who underwent angiography within 1 year of DSE. Catherization results were classified as mild ($<50\%$ stenosis), moderate (50–70% stenosis), and severe ($>70\%$ stenosis). Out of 38 patients with regional wall abnormalities seen on DSE, only 12 patients were found to have moderate to severe CAD, while 16 patients had mild CAD. On the other hand, out of 35 patients with non-ischemic DSE results, 17 had documented stenosis of more than 50% on cardiac catheterization. The analysis showed a sensitivity of 41% and a specificity of 47% [29]. In a retrospective study by Doytchinova et al, data from 633 liver transplantation candidates was analyzed to determine the test performance of DSE in end stage liver disease. Patients with positive or equivocal DSE or with a normal test in the presence of risk factors were referred for coronary angiography. Beta blocker was held 3 days prior to the DSE, and atropine was administered either during the rest and/or the stress phase of the test, in order to achieve the target heart rate. The study analysis yielded a sensitivity and specificity of 19% and 90% respectively of DSE in detecting CAD with obstruction $>50\%$ or greater. The sensitivity of DSE in this

Dobutamine stress echocardiography (DSE)

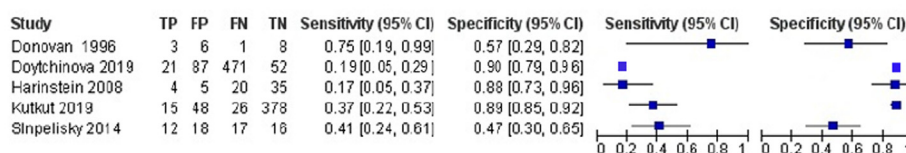


Fig. 3. Forest of plot of dobutamine stress echocardiography studies.

study was again low and did not improve after attaining the target heart rates [34]. Another recently published retrospective analysis conducted by Kutkut et al., showed a sensitivity of DSE to be 37% in detecting significant CAD in ESLD patients. Out of the 41 patients who were subsequently diagnosed with CAD on angiography, 15 were screened positive and 26 had a negative DSE. There were 378 patients who had normal DSE and cardiac catheterization. Only 48 patients had false positive results with DSE yielding a specificity of 89% [35].

4. Discussion

Our results show that MPI has a higher overall sensitivity and accuracy, though modest, compared to DSE. Both the tests, on the other hand, are found to have comparable, statistically significant, moderate specificities. There was no good data to assess the validity of other tests, like the coronary artery calcium (CAC) score or coronary CT angiography compared with the gold standard invasive coronary angiography, in patients awaiting liver transplant. Another promising test modality that brings in the use of both perfusion imaging and the DES is the RTMCE that appears to be a useful tool in predicting cardiovascular mortality in patients with advanced liver disease.

A high heterogeneity was observed in the pooled analysis of both MPI and DSE testing and is likely due to lack of a reference standards. Several artefacts and interpretation pitfalls can potentially compromise MPI results. Moreover, the hemodynamic changes seen in patients with liver disease may confound the results of MPI in this select group of patients, however to a lesser degree when compared to DSE. Firstly, the MPI relies on myocardial perfusion and not on inducible ischemia to detect coronary artery disease. As is understood from the physiological standpoint, advanced liver disease causes a perennial state of vasodilation. This may hinder additional adenosine-induced vasodilatation and can potentially decrease the diagnostic yield of MPI in liver disease patients. Secondly, the interpretation is dependent on both the size and intensity of the defect. However, in most of the studies, MPI scan defects were interpreted as positive regardless of size, severity, or reversibility (fixed or reversible).

DSE is one of the standard diagnostic modalities for chest pain evaluation and pre-operative risk assessment when evaluating unselected patients for ischemic heart disease. The sensitivity of DSE is directly proportional to the maximal heart rate achieved during the stress. The use of beta-blocking agents like propranolol, in patients with advanced liver disease, can result in an inability to achieve target heart rates making DSE an ineffective screening tool in this patient population. Low sensitivity of the DSE in patient undergoing liver transplant evaluation in our analysis is consistent with the observations published by Nguyen et al. [32] as well with the ACC/AHA guidelines [33]. Also, the high variability in the results in the studies included can be attributed to the operator dependency, both with respect to data acquisition and test interpretation. Besides the operator dependency and lack of a reference standard, the heterogeneity in the sensitivity and specificity amongst the selected studies could have resulted from a selection bias, duration of follow-up, prevalence of CAD in different centers and in different points in time, as well as the etiology of the liver disease. DSE sensitivity in the study by Doytcinova et al was calculated to be 16.3% ($n = 8/49$) in patients analyzed in early years of the study versus 39.1% ($n = 9/23$) when the analysis was performed for patients admitted in the recent years. As we know, the prevalence of CAD is on the rise in the general population and as well as in advanced liver disease patients. Also, there is a higher prevalence of CAD in patients with advanced liver disease from non-alcoholic steatohepatitis (NASH), compared to those from other

etiologies, and whose prevalence is steadily rising in conjunction with the obesity epidemic [34]. Thus, the older studies may have a lower prevalence of CAD and differing etiologies of liver diseases compared to the newer ones. In addition, there is an increasing number of patients receiving liver transplants at a more advanced age due to improvements in surgical techniques, organ preservation, and perioperative care, together with a sizeable number of deceased and living donors entering the transplant pool [35].

Dobutamine stress real-time myocardial contrast echocardiography (RTMCE) has the capability of quantifying both myocardial blood volume and velocity on a regional basis. It can thereby measure 'relative' reduction in myocardial perfusion (a product of myocardial blood volume and velocity) using myocardial contrast parameters, at both rest and during reversible ischemia generated by stress [36]. In addition, RTMCE is able to delineate subendocardial wall-thickening abnormalities, thereby improving the sensitivity of wall motion analysis during stress [37]. Porter et al., in a prospective trial, found RTMCE to be a better modality for detecting resting wall motion abnormalities when compared to DSE [38]. DSE can only analyze transmural wall thickening, whereas the RTMCE can detect wall thickening abnormality confined to the sub-endocardium, even in patients who have apparent normal transmural wall thickening during stress [38]. When compared to MPI, RTMCE can be performed at the bedside and provides quick interpretation by assessing both the perfusion and the contractility simultaneously and in real time. It also provides better quantification of LV volume and high resolution images when compared to the conventional MPI, obviating the exposure to radiation, thereby standing out as a promising modality [39]. This is complemented by the results of our statistical analysis that indicate that the DSE and MPI obtained by myocardial scintigraphy are of limited use as a screening tool in patients with ESLD.

Another imaging modality, which is non-stress based is CAC and coronary CT angiography. CAC values >400 has been associated with worse cardiac outcome after LT [40], but there have been several confounders such as DM, advance age, associated with high CAC. Although CAC scoring has emerged as a widely available, consistent, and reproducible means of assessing risk for major cardiovascular outcomes, more studies are required to assess the predictive value of CAC for perioperative outcomes in LT patients. Coronary CT angiography requires slow heart rate, absence of arrhythmia and normal renal function but requires contrast administration. Patients with ESLD often have coexisting renal impairment. In normal population, a normal coronary CT angiography effectively excludes obstructive CAD, but routine pre-operative coronary CT angiography has a low yield in LT patients [41]. There have been no previous studies to determine the diagnostic accuracy of coronary CT angiography with invasive coronary angiography for the detection of CAD in LT recipients.

5. Limitations

Although our review could identify only 5 studies involving DSE and 5 studies involving MPI, all of these were carefully selected to avoid any negative impact on our pooling model. We were conscientious and deliberate about our study selection and consequently may have compromised on the sample size. However, it was imperative that we select specific studies that were well-conducted, reproducible, transparent, and had an unpretentious statistical analysis in line with our strict and rigorous inclusion criteria. We also aimed at avoiding the small study effect by removing publication bias and employed well-established statistical methods to counter heterogeneity and variability. Another limitation is the inability to stratify pooled analysis based on individual etiologies of the end stage liver disease such as NASH vs Hepatitis C

and other comorbidities such as end-stage renal disease. These underlying and co-existing conditions have been known to contribute to the development of CAD.

6. Conclusions

In conclusion, the results of our systematic review show that both, MPI and DSE, are ineffective screening tools for detecting CAD in patients undergoing liver transplant evaluation. We also re-iterate the need for further studies to evaluate the role of RTMCE, CAC and/or coronary CT angiography in patients with advanced liver disease, which appear to be a promising and potentially a more reliable future modality. With the advent of efficacious HCV treatment and ever-rising incidence of obesity and diabetes, we foresee an upward shift in the proportion of patients with advanced age and non-alcoholic steatohepatitis being evaluated for transplant surgery, and consequently, there is an emergent need for an optimal screening method in this select group.

Declaration of Competing Interest

The authors report no relationships that could be construed as a conflict of interest.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2021.100714>.

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