Screening of Cardiovascular Disease in Nonalcoholic Fatty Liver Disease: Whom and How?

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Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease worldwide. Patients with NAFLD are at a higher risk of developing cardiovascular disease (CVD). In fact, CVD-related mortality is more common in patients with NAFLD in comparison to liver-related mortality. This association is related to the common metabolic risk factors such as obesity, dyslipidemia, diabetes, and hypertension shared by both NAFLD and CVD, and also there is independent association of NAFLD with CVD because of risk factors such as insulin resistance, systemic inflammation, and atherogenic dyslipidemia. While there is abundant literature on association of NAFLD with CVD, there is sparse literature regarding the screening for CVD in patients with NAFLD. In the current review article, we discuss as to which patients with NAFLD to screen and how to screen for CVD. (J Clin Exp Hepatol 2019;9:506–514)

Nonalcoholic fatty liver disease (NAFLD) is a spectrum of diseases that covers nonalcoholic fatty liver (NAFL) or simple steatosis, nonalcoholic steatohepatitis (NASH), cirrhosis, and hepatocellular carcinoma. NAFLD is one of the leading causes of liver disease and cirrhosis. It is associated with extrahepatic diseases that include cardiovascular disease (CVD).[1] The association of NAFLD with CVD is related to the common metabolic risk factors such as obesity, diabetes mellitus (DM), hypertension, and dyslipidemia;[2] however, multiple studies have shown that NAFLD is also independently associated with CVD despite presence of confounders (metabolic risk factors).[3] CVD has been shown to be the most common cause of death in patients with NAFLD, and this risk is more in patients with NASH as compared with simple steatosis or NAFL.[4–10] Majority of these studies have shown that risk of mortality is more in these patients as compared with controls,[4–8] while few studies have shown independent association with CVD but not higher risk of mortality.[9,10] Although CVD is more common cause of death in NAFLD, role of cardiovascular risk screening is not clear with conflicting views in literature.[11,12] As NAFLD is very common, it is not possible to screen all patients for CVD, and patients with higher risk of CVD should be selected for screening while patients with lower risk of CVD may be managed with risk factors modification alone which should improve their CVD risk as well. In the current review, we aim to review the literature regarding these questions: whom and how to screen for CVD among patients with NAFLD?

WHY NAFLD IS INDEPENDENTLY ASSOCIATED WITH CVD?

Although NAFLD and CVD are associated with metabolic risk factors, several potential links, which are independent of other risk factors, make NAFLD important for pathogenesis of CVD. These possible links which may cause atherosclerosis acceleration including genetics, atherogenic dyslipidemia, chronic inflammation, and imbalance of procoagulant and anticoagulant factors. In addition to NAFLD, insulin resistance, oxidative stress, and adiponectin imbalance also contribute to CVD.[3,10,13–18] Atherogenic dyslipidemia is characterized by high triglycerides and low high-density lipoprotein (HDL), which is frequently present in NAFLD. Some changes in low-density lipoprotein (LDL) particles are also important; NAFLD is associated with small dense LDL and oxidized LDL which are more atherogenic. DeFilippis et al. compared 569 patients with NAFLD (diagnosed by computed tomography) to 2793 non-NAFLD patients. The authors showed that NAFLD was independently associated with higher triglycerides and lower HDL.[14] In addition, patients with NAFLD had higher LDL particle concentration

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Abbreviations: BMI: Body Mass Index; CAD: Coronary Artery Disease; CI: Confidence Interval; CVD: Cardiovascular Disease; DM: Diabetes Mellitus; DSE: Dobutamine Stress ECHO; HDL: High-Density Lipoprotein; hs-CRP: High-Sensitivity C-Reactive Protein; ILTS: International Liver Transplantation Society; LDL: Low-Density Lipoprotein; NAFLD: Nonalcoholic Fatty Liver Disease; NAFL: Nonalcoholic Fatty Liver; NASH: Nonalcoholic Steatohepatitis; OR: Odds Ratio
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with lower particle size, and the lipoprotein abnormalities in NAFLD were associated with severity of hepatic steatosis.[14] In another study, these lipid abnormalities occurred more commonly in patients NASH in comparison to NAFL.[15] Serum and liver inflammatory markers are also increased in patients with accelerated atherosclerosis,[11] consistent with association of NAFLD with high-sensitivity C-reactive protein (hs-CRP) which represents subclinical inflammation and is a marker of CVD. Nigam et al. from Delhi (India) showed that increase of hs-CRP level by 1 mg/dl was associated with risk of having NAFLD by 1.7 times when compared with controls.[16] NAFLD is associated with increase in proinflammatory cytokines that promote lipolysis [tumor necrosis factor alpha (TNF-α)] causes insulin resistance). These proinflammatory cytokines may also cause endothelial dysfunction.[17,18] Adiponectin works as insulin sensitizer, antiatherosclerotic, and antiinflammatory agent. NAFLD is associated with low adiponectin which is associated with more extensive necroinflammation.[17,18] Tripodi et al. showed that patients with NAFLD had a procoagulant imbalance that increases from the less severe (steatosis) to more severe (NASH and cirrhosis) forms of the disease. This imbalance was caused by increased factor VIII and reduced protein C. This imbalance may also play a role in the causation of CVD in patients with NAFLD.[19]

HOW MUCH IS THE INCREASED RISK OF CVD IN NAFLD?

Targher et al. recommended evaluation of CVD in all NAFLD patients, while Ghouri et al. concluded that evidence is insufficient to consider NAFLD patients as high risk for future CVD.[11,12] Results of different studies are affected by age of study population as individuals with higher age are at more risk for CVD, race, and presence of other metabolic risk factors. A recent meta-analysis by Wu et al. included 34 studies (21 cross-sectional studies and 13 cohort studies) comprising of 164,494 participants and showed that NAFLD was associated with higher incident (HR = 1.37) and prevalent [odds ratio (OR) = 1.81] CVD but not with higher overall mortality or CVD-related mortality.[20] Analysis of specific CVDs revealed that NAFLD was associated with increased risk of prevalent (OR = 1.87) and incident (Hazard ratio = 2.31) coronary artery disease (CAD), prevalent and incident hypertension, and prevalent (OR = 1.32) atherosclerosis. The authors concluded that NAFLD was associated with increased risk of major adverse cardiovascular events.[20] Kapuria et al. included 12 studies in another meta-analysis that used coronary artery calcium as real world marker for atherosclerosis. NAFLD was diagnosed by ultrasound or CT. The meta-analysis included 42,410 subjects including 16,883 patients with NAFLD. The authors concluded that mean coronary artery calcium score was significantly higher in NAFLD, OR being 1.64 [95% confidence interval (CI) = 1.42–1.89]. This association remained significant in subgroup analyses, also for studies with >1000 subjects and a coronary artery calcium score cut-off of >100.[21]

These meta-analysis also highlights limitations of our current understanding of NAFLD and CVD. It is well known from multiple studies that NAFLD is associated with increased risk of CVD, but it is not possible to estimate exact risk in absence of gold standard diagnostic test for both NAFLD and CVD. The studies included in this meta-analysis used ultrasound (in majority) or CT for diagnosis of NAFLD, and only 3 studies used liver biopsy to diagnose NAFLD. The diagnosis of CVD was also based on different tests. Ultrasound and CT may not diagnose milder forms of steatosis, and liver biopsy cannot be done for general population as it is invasive and carries risk of morbidity/mortality. Similarly, there is no gold standard test available for diagnosis of CVD that can be performed on general population, as angiography cannot be done for all subjects. Recent data show that magnetic resonance estimated proton density fat fraction (MR-PDFF) and MR elastography has good correlation with biopsy and can be used to diagnose NAFLD, but the data are lacking in the setting of CVD.[22,23]

INDIANS ARE AT MORE RISK OF CVD

South Asians and Indians have CVD at early age as compared with Western population.[24,25] The Interheart study was conducted across 52 countries and all inhabited continents. This study included 15,152 cases and 14,820 controls. The median age of South Asians was 53 years at first presentation of acute myocardial infarction as compared with 63 years for patients from Western Europe, China, and Hong Kong. South Asians also had higher proportion of cases with myocardial infarction at ≤40 years as compared with China and Hong Kong, South America, and Europe.[24] Gupta et al. studied CVD risk factors such as smoking, hypertension, dyslipidemia, diabetes, and metabolic syndrome across various age groups in urban Indians. While adolescents and 20–29 year age group had low prevalence of risk factors, there was a rapid escalation of these risk factors in 30–39 years age group.[26] Indian are predisposed to metabolic risk factors at a lower body mass index (BMI), and the cutoffs for defining overweight and obesity are lower as compared with Western population.[27]

Indian population also have significant prevalence of NAFLD. Several Indian studies have shown 17–32% incidence of NAFLD in urban Indian population based on ultrasound.[28–30] In fact, a recent ultrasound-based study in healthy blood donors of Chandigarh found that 528 out of 986 (53.5%) donors had NAFLD, and at least one component of metabolic syndrome was present in 96% (506 of 528) of subjects with NAFLD.[31] We published our experience of liver donor liver biopsies; 50.4% of

apparently healthy prospective liver donors had NAFL.[32] NAFLD contributes significantly to liver disease–related morbidity in India[33] and has a different clinicopathological profile from West.[34]

WHOM TO SCREEN FOR CVD AMONG PATIENTS WITH NAFLD?

Current guidelines do not answer this question. American association for the study of liver diseases (AASLD) guidelines[1] recommend that "patients with NASH cirrhosis have high prevalence of CVD; therefore, careful attention should be paid to identifying CVD, whether clinically apparent or occult, during the transplant evaluation process"; however, there are no recommendations for patients who are not candidates for liver transplantation. There are insufficient prospective data at present to support screening of CVD in all patients with NAFLD.[35] Position Paper of the Indian National Association for the Study of the Liver, Endocrine Society of India, Indian College of Cardiology and Indian Society of Gastroenterology states that "routine cardiovascular evaluation in all patients with NAFLD cannot be recommended". The CVD evaluation is suggested selectively in those with old age or having metabolic risk factors. Detailed cardiovascular evaluation is recommended in NASH-related cirrhosis or with hepatocellular carcinoma before liver transplantation.[27] The International Liver Transplantation Society (ILTS) has proposed consensus statements regarding end-stage liver disease due to NASH and liver transplantation. The ILTS has suggested the following: liver transplant candidates with NASH should be considered at high risk of developing cardiovascular events before and after transplantation (quality of evidence: high; strength of recommendation: strong) and a multidisciplinary team evaluation including a cardiologist and anesthetist should be done. There was not enough evidence to support a different approach (quality of evidence: moderate; strength of recommendation: strong) or a specific algorithm (quality of evidence: moderate; strength of recommendation: moderate IIa) to pretransplant cardiovascular assessment.[36]

Advantage of screening and thus prevention of a disease depends on baseline risk. A 50% risk reduction at baseline risk of 5% means only 2.5% absolute reduction of disease, while a 50% risk reduction leads to 15% absolute reduction if baseline risk is 30%. In absence of a gold standard test that is applicable to general population, a positive screening test may be false positive in very low risk patients, while a negative test may be false negative in patients with high risk, and these false results contribute to further unnecessary investigations. It should also be noted that lifestyle modifications or treatment of NAFLD-related factors (DM, obesity, and dyslipidemia) results in improvement of CVD risk also, thus patients with low risk for CVD may not benefit from cardiovascular screening. Age has been shown to be an important risk factor for CVD, as atherosclerosis develops gradually, and it takes many years for disease to become symptomatic. Patients with advanced fibrosis have higher risk of CVD. Kim et al. analyzed 11,154 participants from the United States National Health and Nutrition Examination Survey conducted in 1988–1994; the mean follow-up was 14.5 years. The authors diagnosed NAFLD by ultrasonography and used NAFLD fibrosis score, the aspartate transaminase (AST)-platelet ratio index, and the FIB-4 score as indirect markers of liver fibrosis. The majority of NAFLD patients (34% of cohort) had simple steatosis (71%), while 28% had suggestion of intermediate (25%) or high (3%) level of liver fibrosis. The mortality within defined follow-up period was not higher for simple steatosis, but it increased with increase in fibrosis and was mainly because of cardiovascular causes.[37] Targher et al. studied CVD outcomes in a meta-analysis of 16 studies including 34,043 adult individuals; 36.3% of cohort had NAFLD. The study population had 2600 CVD outcomes at a median period of 6.9 years. Patients with NAFLD had more CVD events with an OR of 1.64, and the OR increased to 2.58 for severe (suggestion of NASH or fibrosis) NAFLD.[38]

NAFL or NASH to cirrhosis transition takes many years, and thus patients with NASH-related cirrhosis are at higher risk of CVD and should be screened. While many studies have shown that cardiovascular events are higher in patients with NASH, less data are available for patients with NASH-related cirrhosis as patients with cirrhosis may have less ischemic events,[39] although not all studies have shown that patients with cirrhosis have less CVD events.[40] Two types of data suggest more prevalence of CVD in patients with NASH-related cirrhosis. Patients with NASH-related cirrhosis have higher prevalence of CVD diagnosed during evaluation for liver transplantation and have higher cardiovascular events in peritransplant or posttransplant period as compared with other etiologies.

Kadayifci et al. compared 60 patients with NASH-related cirrhosis to 60 patients with other etiologies. The NASH-related group had higher prevalence of CAD (21.6%) as compared with other etiologies (5%), p = 0.005.[41] Kalaitzakis et al. also showed more prevalence of CAD in alcoholic and NASH groups as compared with other groups. The NASH group was older and had diabetes or hypertension more often.[42] Van den Berg et al. described data of 169 patients. The patients in NASH group had more CVD (29.4%) as compared with others (11.1%) and were older, more obese, and had more prevalence of diabetes and metabolic syndrome.[43] Several studies have shown significant risk of coronary events in patients with NASH cirrhosis. Vanwagner et al. compared cardiovascular events in 115 NASH and 127 alcoholic transplant recipients. As expected, patients in NASH cirrhosis group had more BMI, dyslipidemia, and hypertension. Twenty-six

percent cases in NASH group had any cardiovascular event at < 1 year after liver transplantation as compared with 8% in alcohol group, p≤0.001. On multivariate analysis, NASH was a significant risk factor [OR = 4.12 (95% CI = 1.91–8.90)] for a cardiovascular event at <1 year after LT, even after controlling other risk factors such as age, sex, smoking, diabetes, CVD, and metabolic syndrome. The majority (70%) of these events occurred in the perioperative period and were associated with significant (50%) mortality.[44] In another study of 389 adult liver transplant recipients, cardiovascular morbidity and mortality rates were 15.2% and 2.8% in first year after transplantation. An etiology of NASH or cryptogenic cirrhosis had a significant association with postoperative myocardial ischemia in correspondence analysis.[45] Wang et al. analyzed outcomes of liver transplantation for NASH in a meta-analysis. The authors included 9 studies; 717 patients with NASH as etiology were compared with 3520 without NASH. The patients with NASH had a higher risk of death from cardiovascular complications after liver transplantation (OR = 1.65).[46] Thus, patients with NASH-related cirrhosis have higher prevalence of CVD.

HOW TO SCREEN FOR CVD IN NAFLD?

The patients with NAFLD can be divided in 2 groups regarding CVD evaluation. One group comprises of patients with NASH cirrhosis, and another group comprises of asymptomatic patients with NAFLD (without cirrhosis). There are no good data/recommendations for screening patients with NASH cirrhosis who are not candidates for liver transplantation. Patients with NASH cirrhosis have a significantly higher prevalence of CAD and have a higher risk of perioperative or postoperative cardiovascular events that are associated with significant risk of mortality. NASH-related cirrhosis has also been shown as a predictor for presence of CAD.[42–46] Table 1 summarizes methods for CAD evaluation in pretransplant setting. Dobutamine stress ECHO (DSE) is commonly used, but it is only reliable if at least 85% of the predicted maximum heart rate is achieved; 19%–50% of patients do not achieve this heart rate because of use of beta blockers, discomfort, or chronotropic incompetence. DSE is very good to rule out the possibility of future coronary event; however, it does not rule out presence of CAD and has shown poor sensitivity in some of the studies.[47–50]

CT coronary angiography requires stable low heart rate, is less invasive than conventional angiography, and negative predictive value is excellent. Coronary angiography is gold standard for coronary evaluation; however, complications are higher as compared with controls.[51] Single photon emission computed tomography can also be used to detect myocardial ischemia. Studies have shown contradicting combination of poor sensitivity (not picking up CAD)[52] with good specificity (true negatives) and good sensitivity with poor specificity (false positives).[53] A recent meta-analysis showed that DSE, myocardial perfusion imaging, and coronary angiography do not satisfactorily predict perioperative cardiac events.[50]

Hogan et al. suggested an algorithm for evaluation of CAD in pretransplant evaluation. The authors recommended coronary angiography if >2 of following risk factors are present: age >50 years, history of NAFLD, type 2 diabetes mellitus (T2DM), hypertension, family history of CAD, smoking, or known CAD. Patients with 1 or 2 risk factors can be taken for DSE, and coronary angiography can be reserved for patients with abnormal DSE.[47] Several studies have compared DSE to coronary angiography, and poor sensitivity and positive predictive value has been shown.[48,49] A recent systemic review of 29 studies has confirmed the poor sensitivity of DSE. The authors showed that age >60 years and background cardiac disease were most consistent risk factors for adverse cardiovascular outcomes after LT. Unfortunately, the number of patients with NASH in this study were very few (8.8%), thus limiting its impact on outcomes.

Table 1 Pretransplant Evaluation for Patients With NASH Cirrhosis (Based on References 47–52).

Test	Advantages	Disadvantages
Dobutamine stress ECHO	Less invasive than angiography, no risk of bleed/contrast nephropathy	Predict the absence of medium- to long-term risk of cardiovascular events after LT, specificity 99%, to predict the absence of coronary artery disease, negative predictive value 75%, thus poor to rule out coronary artery disease, reliable to predict cardiovascular events, and not optimal in presence of beta blockers and anemia What constitutes positive? Sometimes needs to terminate prematurely because of pain, inadequate heart rate No good relation with angiography
CT coronary angiography	Good sensitivity and excellent negative predictive value	Radiation, risk of contrast nephropathy, and does not predict perioperative cardiac events with great accuracy
Conventional angiography	Gold standard	Risk of contrast nephrotoxicity, invasive, and risk of hematoma

NASH, nonalcoholic steatohepatitis.

Table 2 Screening of CVD in Asymptomatic Individuals[a] (Based on Reference 56,57).

Methods	ACC/AHA category of recommendation	Comments
Risk prediction by scores and family history	Class I, level of evidence: B	Risk scores should be race specific
Genetic prediction	Class III, level of Evidence: B	Pathogenesis of CVD is complex and many environmental and genetic factors
Lipoproteins, apolipoproteins, particle size/density beyond a standard fasting lipid profile	Class III, level of evidence: C	Added benefit was not present in all studies
HbA1c	Class IIb in asymptomatic adults without a diagnosis of diabetes	Level of evidence: B
hs-CRP	Class IIa—men >50 years or women >60 years without other risk factors, to select for statin therapy Class IIb—asymptomatic intermediate risk Level of evidence: B	Should not be done in low-risk men (<50 years) or women (<60 years), should not be done for high-risk adults, level of evidence: B
Electrocardiography (ECG) at rest	If there are risk factors (IIa) such as diabetes/hypertension, IIb without risk factors, level of evidence: C	Also provides information of arrhythmias, no randomized study in asymptomatic
Exercise ECG	Class IIb, if intermediate risk, including sedentary adults considering vigorous exercise, Level of evidence: B	Exercise capacity and heart rate recovery are stronger predictors than ECG changes
Resting ECHO	IIb if hypertension (to look for left ventricular hypertrophy), level of evidence: B	Class III for asymptomatic, without hypertension, level of evidence: C
Carotid intima media thickness	IIa if intermediate risk Level of evidence: B	Increased in hypertension also, correlates more with stroke than myocardial infarction, and need of highly standardized protocols
Peripheral arterial flow mediated dilation	Class III, level of evidence: B	Technical challenges with results
Stress ECHO	Class III for low/intermediate risk, level of evidence: C	Primarily used for symptomatic, to know prognosis in a known coronary artery disease
Myocardial perfusion imaging	Class 3 for low/intermediate risk, level of evidence: C	CLASS IIb for asymptomatic adults with diabetes, strong family history, or high risk in previous investigations Level of evidence: C
Coronary calcium	IIa if intermediate risk, IIb if low-intermediate risk, not recommended for low risk (<6% at 10 years Level of evidence: B	Generally not present in men <40 years or women <50 years, ideal score is 0, no ideal cutoff, risk increases with increasing score, adds to prediction of Framingham risk score
CT coronary angiography	Class III Level of evidence: C	Radiation, no good data in general population/asymptomatic
MRI of plaque	Class III Level of evidence: C	Not enough data in asymptomatic

CVD, cardiovascular disease; NAFLD, nonalcoholic fatty liver disease; MRI, magnetic resonance imaging; hs-CRP, high-sensitivity C-reactive protein. Class of recommendation: Class I (benefit>>>risk), class IIa (benefit >> risk), class IIb (benefit > risk), class III (no benefit, or harm), level of recommendation: A (data from population studies, multiple randomized studies, or meta-analysis), B (data from limited population, single randomized study, or series), and C (limited population, consensus/expert opinion, case studies, standard of care).
[a]Applicability to patients with NAFLD is not studied.

However, diabetes, BMI, and metabolic syndrome conditions frequently associated with NASH were associated with adverse cardiovascular events in some studies.[54] We agree with algorithm suggested by Hogan et a. that NAFLD should be considered as a risk factor for CAD during cardiovascular evaluation.

While all patients with NASH-related cirrhosis undergoing evaluation for liver transplantation should have

CVD evaluation, this decision is difficult in asymptomatic patients. In general, a significant number of patients who experience nonfatal myocardial infarction or sudden death had no prior symptoms. Risk scores have been suggested to estimate risk of CVD at 10 years. The risk scores (risk calculators) are easy and should be used for risk stratification. Risk is stratified as low (<6%) at 10 years, low to intermediate (6–10% in 10 years), intermediate (10–20% in 10 years), and high (>20% in next 10 years). The risk scores predict a good number of future CVD events.[55–57] Table 2 provides summary of methods to screen CVD in asymptomatic patients based on American Heart Association guidelines.[57] Although these guidelines are for asymptomatic individuals and applicability for patients with NAFLD is not known, these tests should be applicable for NAFLD also. There are many risk calculators. Framingham risk score (FRS) is one of the most widely used, but these calculators are applicable to original population (development cohort).[57,58] It is well known that Indians are more predisposed for CVD; however, there are no Indian risk scores. QRISK score, which is a UK score, allows option of Indian origin of an individual.[59] These risk scores describe risk of future cardiac events as low, intermediate, or high (>20% risk at 10 years). There are many risk scores which are different because of differences in studied population, different definitions of CVD endpoints, and different mathematical algorithms. Mostly, these scores are a combination of age, gender, lipids, hypertension (HTN), DM, smoking, and family history.[60] There is considerable variability in results across various risk scores.[61] Few small studies have evaluated risk scores in NAFLD versus non-NAFLD patients, and these studies have shown a higher 10-year CHD risk as determined by the FRS or by Prospective Cardiovascular Munster study score. However, these were single time point studies with no follow-up.[62–65] As NAFLD independently adds to risk of CVD, it should be a part of these risk scores for better CVD risk assessment; however, there is paucity of data regarding impact of NAFLD on these risk scores. Treeprasertsuk S et al. followed a total of 309 NAFLD patients for 11.5 ± 4.1 years. The overall calculated 10-year CHD risk was higher in the NAFLD cohort predicted by the FRS ($p < 0.0001$) when compared with same age and gender. New onset CHD occurred in 34 patients, and FRS was the only variable significantly associated with new onset CHD on multivariate analysis. The FRS accurately predicted the higher 10-year CHD risk in NAFLD patients.[66] It should be noted that patients with NAFLD and diabetes have higher risk of CVD, and this group should be evaluated more carefully.[67,68] As highlighted in manuscript by 2 meta-analysis,[20,21] the OR of CAD in patients with NAFLD is not very high. It should be noted that the majority of studies are based of imaging that may not diagnose mild steatosis. Thus, some of controls may also have NAFLD, and absolute risk of CVD may be slight lower than reported. If an individual with NAFLD without cirrhosis has low risk of CVD based on risk scores, the risk will not become high even after adjustment for NAFLD. We believe that patients with low risk by risk-scores should be managed with life style modification that should improve their CVD risk also. Patients with intermediate or high risk by risk scores should be referred to a cardiologist for evaluation of CVD.

Table 3 Current Status of Our Understanding About NAFLD and CVD.

What is established	Patients with NASH or NASH-related cirrhosis are at higher risk of incident and prevalent CVD in comparison to patients NAFL or simple steatosis Despite presence of metabolic risk factors that contribute to both NAFLD and CVD, NAFLD is independently associated with CVD Both these diseases take many years to develop into symptomatic disease, thus offer opportunity to prevent clinical disease Indians are more predisposed to CVD
What we do not know	Quantum of increased risk for CVD in patients with NAFL, NASH, and NASH cirrhosis Where to NAFLD and its spectrum (NAFL, NASH, and NASH cirrhosis) in the assessment of CVD risk scores
What should be done	MR-PDFF (to diagnose NAFLD) and MR elastography (for fibrosis assessment)–based longitudinal studies Addition of NAFL, NASH, and NASH cirrhosis to CVD risk scores, to improve CVD prediction and to look for amount of increased risk

NAFLD, nonalcoholic fatty liver disease; NAFL, nonalcoholic fatty liver; NASH, nonalcoholic steatohepatitis; CVD, cardiovascular disease.

Table 3 summarizes current status and future aspects of CVD screening in patients with NAFLD. The current literature is not sufficient to make a conclusive statement regarding optimal screening strategy in asymptomatic patients with NAFLD without cirrhosis.

CONCLUSIONS

NAFLD is epidemic of current era. As it adds to risk of CVD independent of other metabolic risk factors, it is important to identify risk of CVD in these patients. While low risk patients can be managed by risk factor modification, we believe that patients with intermediate or high risk or with NASH cirrhosis should be referred to cardiologist for evaluation of CVD. Identification of significant risk should lead to prevention of CVD morbidity/mortality. Patients with NASH-related cirrhosis undergoing liver transplantation evaluation should be screened for significant CAD, and stress echocardiography and CT coronary angiography are useful modalities in this cohort. Conventional angiography is

reserved for patients with combination of risk factors for CAD. How to screen asymptomatic NAFLD without significant fibrosis is not clear with each modality having some limitations. The current understanding of exact risk imparted by NAFLD is limited by lack of good studies.

CONFLICTS OF INTEREST

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