Nonalcoholic fatty liver disease (NAFLD) is now the most common chronic liver disease in the United States with a prevalence of 10%-30% using different screening tests. NAFLD encompasses a wide spectrum of hepatic conditions ranging from simple steatosis (nonalcoholic fatty liver [NAFL]) to nonalcoholic steatohepatitis (NASH), which can progress to cirrhosis and end-stage liver disease. NAFLD has become a major cause of cirrhosis in Western countries and is predicted to overtake hepatitis C as the leading cause for liver transplantation within the next 10-20 years.

Several lines of evidence suggest a strong association between NAFLD and coronary artery disease (CAD). First, prevalence of NAFLD is significantly higher in patients having co-existing obesity, diabetes mellitus, or metabolic syndrome, all of which are established risk factors for CAD. Second, NAFLD and CAD share several common environmental and genetic factors. Third, studies have demonstrated that...
NAFLD is associated with more severe symptomatic coronary atherosclerosis and is even considered an independent risk factor for CAD.\(^{(12,13)}\) Finally, cardiovascular disease has been identified as the most common cause of death in NAFLD patients with advanced liver fibrosis.\(^{(4,14,15)}\)

Similar to the progression of NAFL to NASH in a percentage of patients, subclinical atherosclerosis, defined as the presence of coronary arterial atherosclerosis in asymptomatic individuals, is a prodrome that can progress to clinically evident CAD.\(^{(16,17)}\) Improved cardiovascular diagnostic modalities, such as carotid intima-media thickness (CIMT),\(^{(18,19)}\) carotid-femoral pulse velocity,\(^{(20)}\) and coronary calcium scoring,\(^{(18,21-23)}\) have resulted in an improved ability to detect subclinical atherosclerosis, understand its natural history, and have a meaningful impact on clinical care. A consistent methodology for measuring brachial artery flow-mediated dilation has not yet been adopted, and CIMT, although useful to assess atherosclerosis, cannot quantify the degree of calcification in atherosclerotic plaque. Therefore, of these various modalities, coronary artery calcium (CAC) scoring has emerged as an economical, sensitive, and specific method to screen for CAD, with an increased risk for prevalent coronary heart disease observed at all levels of a CAC score >0.\(^{(6,7,24,25)}\) A large registry analysis demonstrated that higher CAC scores increase all-cause mortality after adjusting for traditional risk factors, with risk-adjusted relative risk ratios for a CAC score ranging between 2.2-fold and 12.5-fold for scores 11 to >1,000, respectively.\(^{(26)}\) This provides strength to the growing evidence that progressive coronary atherosclerosis, albeit subclinical, is an important predictor of mortality and that CAC scoring is an effective tool to assess cardiovascular risk.

Recently, several studies have evaluated the association of subclinical atherosclerosis with NAFLD.\(^{(27,28)}\) Although these studies uniformly demonstrate an association of subclinical atherosclerosis with NAFLD, they lack a unified method of detecting subclinical atherosclerosis or use modalities not readily available in clinical practice. A recent study by Jaruvongvanich and colleagues\(^{(29)}\) demonstrated an association between atherosclerosis measured by CAC scores and NAFLD in populations that included known CAD. However, the question remains whether subclinical atherosclerosis is actually associated with NAFLD. There has not been a meta-analysis evaluating the association of subclinical atherosclerosis alone, as defined by the CAC score, with NAFLD.

In this study, we focus on the association of NAFLD with subclinical atherosclerosis by CAC scoring and determine the risk conferred by NAFLD on CAD.

### Materials and Methods

This systematic review followed a developed protocol (Supporting Information S1) and was reported according to the meta-analyses of observational studies in epidemiology guidelines.\(^{(30)}\)

### ELIGIBILITY CRITERIA

Both cross-sectional and cohort studies reporting hepatic steatosis by imaging and evidence of subclinical atherosclerosis by CAC scoring were included in this meta-analysis. CAC scores were reported using the scoring system proposed by Agatston.\(^{(31)}\) Hepatic steatosis could be identified either by computed tomography (CT) or by ultrasonography (US). Inclusion and exclusion criteria were determined a priori to the literature search (Supporting Information S1). Studies that included patients who presented with symptoms of CAD, such as acute chest pain, or subjects who had a history of prior CAD were excluded to maintain the integrity of the definition of subclinical atherosclerosis.
SEARCH STRATEGY
MEDLINE, EMBASE, and OVID searches were conducted to identify studies published between 1980 and 2017 that associated NAFLD with subclinical atherosclerosis. The search terms and their variation for NAFLD used included “fatty liver”, “Non-alcoholic fatty liver disease”, “NASH”, “NAFLD”, “non-alcoholic fatty liver disease”, and “non-alcoholic”. The search terms and their variation for subclinical atherosclerosis and the CAC score included “coronary calcium, subclinical atherosclerosis”, “preclinical atherosclerosis”, “spiral CT”, “mDCT”, “coronary artery disease”, “cardiac imaging techniques”, “multi-slice CT”, “cardiac CT”, and “multidetector CT”. The search strategy for MEDLINE is provided in Supporting Information S2. Studies were not limited by language and standard citation, and related article chasing was used. Study authors were contacted if additional data were needed. Abstracts and unpublished studies were not considered for review or data extraction.

STUDY SELECTION AND DATA EXTRACTION
Two review authors (V.T. and D.K.) independently screened studies and abstracts of the studies identified by electronic searches using the Covidence platform (https://www.covidence.org/home). Study quality was assessed using the Newcastle-Ottawa Scale modified for cross-sectional studies, with a score more than 5 indicating higher quality. The study by Sinn et al. is a cohort study; therefore, quality assessment was performed using the original Newcastle-Ottawa Scale. The same review authors performed data extraction. A third investigator (C.K.) resolved any disagreements in study selection, quality assessment, and data extraction.

The data abstracted included demographics (including age, sex, and body mass index [BMI]), baseline risk factors for metabolic syndrome (hypertension, diabetes mellitus, dyslipidemia, smoking, exercise levels), serum aminotransferases (alanine aminotransferase [ALT], aspartate aminotransferase [AST]), number of subjects with and without NAFLD, number of subjects divided into groups based on CAC scores as well as with and without subclinical atherosclerosis, and number of subjects with and without calcified plaques. Additional information collected included country of origin of the study, type of study (cohort, cross-sectional), and outcomes assessed.

DATA SYNTHESIS AND STATISTICAL ANALYSIS
The primary summary measure was level of CAC in subjects with NAFLD by imaging. Other data pooled for analysis included ALT, AST, and BMI, if available, in subjects with or without coronary artery calcifications.

The rate of coronary artery calcification in subjects with NAFLD was analyzed using both fixed and random effects models using the DerSimonian–Laird estimator and Hartung–Knapp–Sidik–Jonkman method to estimate pooled odds ratio (OR) and 95% confidence intervals (95% CI). Similarly, pooled analysis of continuous variables, including aminotransferase and BMI, were assessed to estimate mean difference (MD) and 95% CI. Using the chi² test, statistically significant heterogeneity was defined as \( P < 0.10 \). Further, \( I^2 \) was assessed to evaluate for true variability between the two arms, and a result >50% was identified as significant.

Subgroup analyses, for studies with more than >1,000 subjects, CAC score cutoffs of 0 versus >100, study location (Western versus Asian), and method of assessment of hepatic steatosis (US versus CT) were also performed to explore sources of heterogeneity (Supporting Information S5).

Publication bias was assessed through Egger’s regression test for funnel plot asymmetry. Lastly, visual evaluation of the funnel plot asymmetry was performed. Primary analyses were done using RStudio (version 0.99.484); subgroup analyses were performed using Review Manager (version 5.3.5).

Results
STUDY LEVEL DATA
The initial search generated a total of 1,620 studies, using (((“Non-alcoholic Fatty Liver Disease”[Mesh]) OR fatty liver)) AND atherosclerosis, with 208 potential relevant papers retrieved for detailed assessment using Covidence software (Fig. 1). Among these, 29 studies were eligible for full text screening; 12 studies were included in the final analysis. The characteristics of each study and the Newcastle-Ottawa Scale for quality assessment are given in Table 1. A total of 42,410 subjects were assessed in these studies, comprising 16,883 patients with NAFLD and 25,527 without. The mean age was 52.9 years, with most studies having a predominance of male subjects. Hepatic steatosis was assessed by CT scan-based liver to spleen
attenuation ratios in five studies and by US (diagnosed by increased liver echogenicity) in seven studies. We note that four studies used a higher CAC score of >100 compared to a CAC score >0 in the rest. Common risk factors adjusted for in most of the studies were age, sex, and components of the metabolic syndrome. Some studies also adjusted for ethnicity, physical activity, socioeconomic level, and alcohol intake. One study recruited only male subjects and another only female subjects.

**RISK OF CAC IN SUBJECTS WITH NAFLD**

Data from the 12 studies were synthesized to evaluate the risk of CAC score between subjects with and without NAFLD. Mean CAC score was significantly higher in subjects with NAFLD compared to those without, with a pooled OR with random effects model of 1.64 and 95% CI of 1.42–1.89 (Fig. 2). All the evaluated studies demonstrated a similar increase in odds of a high CAC score in patients with NAFLD, with an OR as high as 2.84 in one study. There was significant heterogeneity between the studies ($I^2$, 72%; $P < 0.01$). Subgroup analyses were subsequently performed based on the number of subjects in the study ($>1,000$ versus $<1,000$), origin of population of study (Asian versus non-Asian), and method of detection of liver steatosis (CT versus US) (Supporting Information S5). Five out of 12 studies had less than 1,000 subjects) with a total of 3,128 subjects. Subgroup analysis performed for these studies demonstrated a similar trend of a higher CAC score in subjects with NAFLD (OR, 1.96; 95% CI, 1.59–2.40; $I^2$ 0% for studies with $<1,000$ subjects and OR, 1.54; 95% CI, 1.34–1.77; $I^2$ = 80% for studies with $>1,000$ subjects). Studies with $>1,000$ subjects showed significant heterogeneity. Test for subgroup differences yielded chi$^2$ = 3.54, $P =$
| Study            | Design                                                                 | Number of Subjects | Age (Mean ± SD) | Sex (% Males) | NAFLD Determination | CAC Definition    | Plaques (Calcified) | Risk Factors Adjustment                                                                 | Study Quality |
|------------------|------------------------------------------------------------------------|--------------------|-----------------|---------------|---------------------|-------------------|-------------------|---------------------------------------------------------------------------------------|--------------|
| Chen et al.      | Cross-sectional                                                       | 295                | 52.6 ± 11       | 65%           | CT (L:S ratio)      | CAC >100          |                   | smoking, hypertension, diabetes, dyslipidemia, age, sex, smoking, dyslipidemia, hypertension, diabetes | ***********  |
| Chhabra et al.   | Cross-sectional                                                       | 377                | 62.3 ± 8.5 vs 55.9 ± 9.5 | 51.90%       | CT (L:S ratio)      | CAC >100          |                   | age, sex, smoking, dyslipidemia, hypertension, diabetes                               | *********    |
| Juarez-Rojas et al. | Cross-sectional                                                       | 765                | 55 ± 9 vs 54.3 ± 10 | 47%           | CT (L:S ratio)      | CAC >0            |                   | age, smoking, BMI, total cholesterol, CRP                                             | *********    |
| Al Rifai et al.  | Cross-sectional                                                       | 3,976              | 61.2 ± 9.6 vs 63.3 ± 10.5 | 45.10%       | CT (L:S ratio)      | CAC >0            |                   | age, gender, ethnicity, smoking, LDL, statin, education                              | **********   |
| Jung et al.      | Cross-sectional                                                       | 1,218              | 52.5 ± 8 vs 51 ± 10 | 49.50%       | US                  | CAC >100          |                   | age, gender, BMI, waist to hip ratio, uric acid, BP, TGs, HDL, DM, statin            | ********     |
| Kang et al.      | Cross-sectional                                                       | 772                | 55 ± 9 vs 45.8 ± 8.4 | 68%           | US                  | CAC >100          | 59%               | age, smoking, HTN, DM2, LDL, HDL, metabolic syndrome                                 | ***********  |
| Kim et al.       | Cross-sectional                                                       | 4,023              | 57.5 ± 9 vs 56.4 ± 9.6 | 60.70%       | US                  | CAC >0            |                   | age, sex, BMI, waist circumference, alcohol, smoking, cholesterol, HTN, DM2, HDL, CRP, TGs | **********   |
| Kim et al.       | Cross-sectional study                                                 | 919                | 59.5 ± 6 vs 57 ± 7 | 0%            | US                  | CAC >0            |                   | age, BMI, hypertension, diabetes, hyperlipidemia, insulin resistance                 | *********    |
| Kim et al.       | Cross-sectional analysis of longitudinal cohort data                   | 1,575              | 40.0 ± 5.3 vs 39.8 ± 5.5 | 89.6%       | US                  | CAC >0            |                   | age, sex, diabetes, cholesterol, hypertension, smoking, BMI                          | ********    |
| Lee et al.       | Cross-sectional                                                       | 21,335             | 40.85 ± 6.5 vs 40.15 ± 7 | 100%         | US                  | CAC >0            |                   | age, diabetes, HTN, smoking, physical inactivity                                    | ***********  |
| Sinn et al.      | Cohort study                                                          | 4,731              | 52.1 ± 7.2 vs 52.3 ± 7.1 | 91%         | US                  | CAC >0            |                   | age, sex, smoking, alcohol consumption, hypertension, hyperlipidemia, diabetes        | *********    |
| Van Wagner et al. | Cross-sectional analysis of longitudinal cohort data                   | 2,424              | 50.5 ± 3.7 vs 49.9 ± 3.6 | 42.70%       | CT (L:S ratio)      | CAC >0            |                   | age, sex, race, socioeconomic level, alcohol intake, physical activity score           | ***********  |

*NAFLD vs non-NAFLD; †CAC vs non-CAC; ‡ stands for study quality.

Abbreviations: BP, blood pressure; CRP, C-reactive protein; DM, diabetes mellitus; HDL, high-density lipoprotein; HTN, hypertension; LDL, low-density lipoprotein; L:S, liver to spleen ratio; TG, triglyceride.
0.06, $I^2 = 71.8\%$ (Supporting Information S5-1). A similar analysis was performed in studies with higher CAC score cut-off values of $>100$ (four studies with 2,622 subjects) and lower CAC score cut-off values (eight studies with a total of 39,748 subjects) (Fig. 3). NAFLD continued to be a risk factor for subclinical atherosclerosis even in the subgroup with a high CAC cut-off value (OR, 2.11; 95% CI, 1.61–2.76; $I^2 = 0\%$). Test for subgroup differences showed heterogeneity between the two subgroups ($\chi^2 = 3.89$, $P = 0.05$, $I^2 = 74.3\%$).

When studies were grouped into the origin of the study population, eight studies with a total number of 24,742 subjects were performed in Asian populations, with a prevalence of subclinical atherosclerosis in subjects with NAFLD (OR, 1.64; 95% CI, 1.40–1.93). There were four studies performed in non-Asian populations (7,542 subjects), with similar results noted (OR, 1.64; 95% CI, 1.19–2.26). Although both subgroups were heterogeneous, test for subgroup differences showed no heterogeneity ($\chi^2 = 0.01$, $P = 0.92$, $I^2 = 0\%$).

Finally, subgroup analysis was performed based on the method of detection of liver steatosis (CT versus US). Seven studies (34,573 subjects) used US to detect hepatic steatosis, with an increased prevalence of CAC in NAFLD (OR, 1.64; 95% CI, 1.42–1.90). The other five studies with 7,837 subjects used CT as a tool to detect hepatic steatosis, and a similar relationship between NAFLD and CAC was noted (OR, 1.73; 95% CI, 1.27–2.36). Test for subgroup differences showed minimal heterogeneity ($\chi^2 = 0.09$, $P = 0.77$, $I^2 = 0\%$).

**SERUM AMINOTRANSFERASE LEVELS IN SUBJECTS WITH CORONARY ARTERY CALCIFICATION**

Only four studies reported serum aminotransferase levels for a total of 5,467 subjects. Almost all studies individually reported an association of elevated ALT with CAC with the exception of one study. (38) Higher AST levels were associated with increased subclinical atherosclerosis (MD, 1.77; 95% CI, 1.19–2.34). A trend with ALT levels was observed, with elevated ALT levels in patients with increased subclinical atherosclerosis (MD, 1.89; 95% CI, –3.44 to 7.21); however, this was not significant (Fig. 4). Sensitivity analyses were performed by excluding the cohort study from the pooled analysis, with similar results. Further, studies with only male, (42) only female, (43) and then both subjects were excluded from the pooled analysis; this yielded similar results, albeit with a slightly increased heterogeneity. Additionally, analysis was repeated after excluding the cohort study (Sinn et al. (34)) from the analysis, with similar results (Supporting Information S6).

FIG. 2. Forest plot showing relationship of NAFLD with subclinical atherosclerosis.
EVALUATION FOR PUBLICATION

BIAS

The funnel plot did show asymmetry; this was confirmed with a nonsignificant Egger’s test. The studies were heterogeneous (Supporting Information S4).

Discussion

In this pooled analysis evaluating 12 published studies with an aggregate of 42,410 patients, we evaluated the association of NAFLD with subclinical atherosclerosis. By examining “real-world” clinical biomarkers, namely CAC scoring for subclinical atherosclerosis and US or CT for NAFLD, we demonstrated an increased prevalence of subclinical atherosclerosis in subjects with NAFLD compared to subjects without hepatic steatosis, after adjusting for risk factors predisposing to CAD. This is the first meta-analysis that evaluates the association of subclinical atherosclerosis as defined by CAC scoring with the presence of NAFLD in subjects without known CAD compared to subjects without hepatic steatosis, after adjusting for risk factors predisposing to CAD. This is the first meta-analysis that evaluates the association of subclinical atherosclerosis as defined by CAC scoring with the presence of NAFLD in subjects without known CAD compared to subjects without hepatic steatosis, after adjusting for risk factors predisposing to CAD. This is the first meta-analysis that evaluates the association of subclinical atherosclerosis as defined by CAC scoring with the presence of NAFLD in subjects without known CAD compared to subjects without hepatic steatosis, after adjusting for risk factors predisposing to CAD. This is the first meta-analysis that evaluates the association of subclinical atherosclerosis as defined by CAC scoring with the presence of NAFLD in subjects without known CAD compared to subjects without hepatic steatosis, after adjusting for risk factors predisposing to CAD.

Although a recent meta-analysis\(^{29}\) suggests an association between subclinical atherosclerosis and NAFLD, our study provides more definitive evidence as it was performed in patient populations without existing CAD; also, the availability of two additional studies after the previous meta-analysis was published further strengthens this association. Moreover, we report similar results in subgroup analyses that differentiated larger studies from studies with small sample sizes.

In our study, a significantly higher mean AST was observed in the cohort with coronary artery calcification; ALT levels trended higher in patients with coronary artery calcification; however, when only non-U.S. populations (i.e., more homogeneous) were studied, this was a significant association. Further study needs to be performed to evaluate the role of an elevated AST value in patients at a high risk of developing coronary atherosclerosis.

Despite the general concordance of our results with previous studies, the results from this study seemingly differ from two other studies. First, Van Wagner and colleagues\(^{22}\) observed a weakening in the relationship between NAFLD and subclinical atherosclerosis after adjusting for abdominal or general obesity. Second, a subgroup analysis evaluating the association of NAFLD and CAC score in 398 black and white individuals from the Multi-Ethnic Study of Atherosclerosis (MESA)
cohort at a single center in North Carolina did not find an association between NAFLD and CAC score.\(^{(46)}\) However, in the larger cross-sectional analysis of the entire MESA cohort, a significant relationship was identified between NAFLD and subclinical atherosclerosis even after adjusting for obesity and metabolic syndrome. These contrasting observations can be explained on the basis of the population characteristics of each individual study; the patients in Van Wagner’s study were younger, potentially explaining the weak association between NAFLD and CAC score, and the patients in the MESA subgroup were small in number and from a uniform group of individuals. In contrast, larger studies including ethnically diverse populations have demonstrated that Hispanics, followed by Asians, have the strongest association of NAFLD with subclinical atherosclerosis.\(^{(36)}\) There has also been an emerging association of NAFLD with “nontraditional” cardiovascular risk factors, such as elevated uric acid levels, decreased vitamin D, and adiponectin levels.\(^{(47-49)}\) Experimental data have demonstrated an increased transcription of several candidate genes responsible for atherogenesis in NASH but not NAFLD, which suggests a putative association of severity of NASH with the development of atherosclerosis.\(^{(9,41)}\) A similar incremental rise from NAFLD to NASH in inflammatory markers C-reactive protein, interleukin-6, tumor necrosis factor, and transforming growth factor \(\beta\) has been described in a few studies.\(^{(49,50)}\) Early NAFLD models have described messenger RNA up-regulation of the inflammasome components nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3, pyrin domain and apoptosis-associated speck-like protein containing a CARD, and caspase. Although significant, these markers only result in incomplete inflammasome activation, but there is an increase in expression of inflammasome components that would lead to more complete activation in NASH.\(^{(21)}\)

Unlike NAFLD, there is a paucity of prospective studies on the natural history of subclinical atherosclerosis progression. Despite a single conflicting study,\(^{(19)}\) most of the published literature has demonstrated progression of subclinical atherosclerosis over relatively short periods of time.\(^{(48,49)}\) Notably, one interesting
finding is that this progression occurred over months rather than years, indicating that there may be other unknown factors apart from simple aging involved that could contribute to this rapid progression. With recent research suggesting that the presence of NAFLD is associated with increased progression of coronary atherosclerosis, further study in this area may yield novel results along with potential changes in the way both diseases are managed.

This study, while strong for its numbers and evaluation of clinically available tests for subclinical atherosclerosis and NAFLD, is limited by the inherent limitations of US or CT in determining hepatic steatosis and estimations of hepatic fat as well by the inability of these modalities to differentiate between simple steatosis and NASH. While US remains the most widely used imaging method to detect steatosis, its accuracy is diminished considerably in mild hepatic steatosis. Similarly, while the CT scan has a better diagnostic yield for focal steatosis, using it as a tool for detecting hepatic steatosis has several limitations, including unnecessary radiation exposure. Additionally, the CAC score cut-off values for subclinical atherosclerosis in asymptomatic subjects varied between studies with a range from <0 to <100. While a CAC score >100 is clearly linked to adverse cardiovascular outcomes, the association between low CAC (>0-10) and adverse cardiovascular events is less defined. Next, the analyzed studies were performed in heterogeneous populations with varying levels of normal cutoffs for transaminases, and this could affect the association of transaminases with increased coronary calcification. We attempted to contact several authors of studies where dichotomization of study subjects based on CAC score was not presented; however, we received only one response. The studies included in the meta-analysis had a high level of heterogeneity. On the basis of subgroup analyses, this heterogeneity can probably be explained by the use of different cutoffs for CAC and studies with large versus small numbers of study subjects. We also excluded non-English language citations. Finally, given that our meta-analysis included smaller studies, there remains a risk for selection and ascertainment bias.

In conclusion, NAFLD appears to be associated with subclinical atherosclerosis by CAC scoring. Further prospective studies are needed to establish whether a causative relationship exists between NAFLD and coronary atherosclerosis and whether management of subclinical atherosclerosis will impact coronary or hepatic outcomes.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1199/full.