GJMT Global Journal of Medical Therapeutics

Open Access Systematic Review

Subclinical Left Ventricular Systolic Dysfunction Assessed Using Myocardial Strain Measured by Speckle Tracking in Non-Alcoholic Fatty Liver Disease – Systematic Review

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How to cite this article: Ismaiel A, Al Srouji N. Subclinical Left Ventricular Systolic Dysfunction Assessed Using Myocardial Strain Measured by Speckle Tracking in Non-Alcoholic Fatty Liver Disease – Systematic Review. Glob J Med Therap. 2020;2(2):1-8.

***Abstract*-- Background and Aims:** Multiple studies demonstrated that non-alcoholic fatty liver disease (NAFLD) is associated with several structural and functional cardiovascular complications. The aim of this systematic review is to evaluate subclinical left ventricular (LV) systolic dysfunction in NAFLD assessed with myocardial strain measured by speckle tracking echocardiography (STE). **Methods:** We performed a systematic search on PubMed and EMBASE with predefined keywords searching for observational studies published till 19 March 2020. NAFLD diagnosis was accepted if confirmed by biopsy or imaging techniques and LV systolic function evaluation by STE. Full articles that fulfilled our inclusion and exclusion criteria were included in the systematic review. The National Heart, Lung, and Blood Institute (NHLBI) quality assessment tools were used for evaluation of included studies. **Results:** Eleven observational studies (9 cross-sectional studies, 1 case-control, 1 longitudinal cohort) were included with a total study population of 5,851 subjects. All included studies evaluated left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS). Only two studies rated as "good" demonstrated that NAFLD patients had a reduced LVEF, out of which, one study was conducted on type 2 diabetic patients, while the other study was a population-based longitudinal cohort. Moreover, eight studies, out of which four were rated "good", two as "fair" and two as "poor" demonstrated that GLS was significantly reduced in NAFLD. On the other hand, the remaining three studies that reported a non-significant difference in GLS were conducted on type 2 diabetic patients in two of the studies, one rated as "fair" and one as "good". Furthermore, the third study was involving only NAFLD patients comparing drinkers with non-drinkers, being rated as "good". **Conclusions:** NAFLD patients are at increased risk to develop subclinical LV systolic dysfunction assessed with myocardial strain measured by speckle tracking, despite having normal LVEF values and remaining asymptomatic. This association remains to be confirmed in more studies involving diabetic patients in the presence and absence of NAFLD.

Keywords: Non-alcoholic fatty liver disease, NAFLD, Subclinical Left Ventricular Systolic Dysfunction, Myocardial Strain, Speckle Tracking Echocardiography, Systematic Review.

1. INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), characterized by hepatic fat deposition in the absence of significant alcohol consumption or other secondary causes, is currently the most common chronic liver disease worldwide [1]. It is leading to a significant increase in morbidity and mortality with several intra-hepatic and extra-hepatic manifestations. The main cause of death in NAFLD is attributed to cardiovascular disease (CVD). At the moment, there are no approved therapies for NAFLD [2, 3].

Several studies demonstrated that NAFLD is associated with several structural and functional cardiovascular (CV) complications. Structural modifications include left ventricular hypertrophy, increased epicardial fat thickness and valvular calcifications [2]. Moreover, functional alterations comprise diastolic dysfunction in addition to conduction defects, prolonged QTc interval, as well as cardiac arrhythmias of both atrial and ventricular origin [4].

Several echocardiographic parameters have been developed to estimate the left ventricular (LV) systolic function, among which left ventricular ejection fraction (LVEF) seems to be the most evaluated parameter with overwhelming clinical utility for this purpose [5]. Nevertheless, it is associated with several limitations. Instead of directly evaluating the systolic function, it uses an indirect estimate of myocardial contractile function that can be influenced by several factors such as loading conditions and heart rate. Moreover, this method can't detect minor contractile function modifications. Accordingly, LVEF is not a convenient method for assessing subclinical myocardial damage, a finding that is associated with significant prognostic implications in several pathologies.

Lately, the development of a novel non-invasive ultrasound imaging technique, speckle-tracking echocardiography (STE), has improved and eased the quantitative assessment of global and regional myocardial function regardless of the insonation angle and cardiac translational movements. Subsequently, this

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Received: 23 March 2020
Accepted: 24 April 2020
Published: 30 April 2020

imaging method facilitates the detection of early LV dysfunction in subjects with preserved LVEF [6]. STE allows a direct quantification of myocardial contraction overcoming several limitations present in LVEF assessment. Strain is evaluated using STE reporting a percentage difference in the length of a myocardial segment over a specific period of time [5].

Several studies demonstrated that NAFLD isn't associated with a reduction in LVEF, the most common method used to assess LV systolic function, while more recent studies reported subclinical LV systolic dysfunction assessed using more advanced techniques. Accordingly, we decided to conduct the first systematic review to the best of our knowledge evaluating subclinical LV systolic dysfunction in NAFLD assessed with myocardial strain measured by STE through performing a systematic literature search.

2. METHODS

2.1 Data Sources and Search Strategy

We aimed to review all the current evidence published on PubMed and EMBASE reporting observational studies evaluating the association between NAFLD and subclinical LV systolic dysfunction assessed with myocardial strain measured by STE. The following keywords "global longitudinal strain" OR GLS OR strain OR "speckle tracking system" OR "speckle tracking" AND "non-alcoholic fatty liver disease" OR "nonalcoholic fatty liver disease" OR NAFLD were used for our search looking for full articles published till 19.03.2020. We used filters to exclude studies conducted on infants, pediatrics, adolescents, animals, in vitro and conference abstracts without placing any duration, country or language restrictions. Afterwards, a screening evaluation was performed assessing the titles and abstracts. Furthermore, studies that fulfilled our inclusion and exclusion criteria underwent a qualitative synthesis. Eligibility of the evaluated studies was conducted and data extraction from the eligible studies was performed by two authors (A.I and N. A) independently, while resolving any discrepancies by mutual consensus. Data that was extracted included author names, publication year, country, study design, total study population, mean age, gender, NAFLD diagnosis, NAFLD percentage, LV assessment method, LVEF, available strain parameters, in addition to a summary of the study conclusions.

2.2 Eligibility Criteria

Inclusion criteria of original articles were as follows: (1) Full article studies of observational cohort population-based / hospital-based, cross-sectional or case-control designs, that assessed subclinical LV systolic dysfunction evaluated with myocardial strain measured by STE; (2) NAFLD diagnosis confirmed by evaluating hepatic steatosis using liver biopsy or imaging techniques such as ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI) in the absence of other secondary causes of hepatic steatosis or significant alcohol consumption; (3) Absence of other causes of chronic liver disease (CLD) or liver cirrhosis; (4) Adults ≥18 years with no restrictions to gender, race or ethnicity; (5) Human studies only; and (6) Studies published in English, German or Romanian languages.

Exclusion criteria were as follows: (1) Secondary causes of hepatic steatosis or significant alcohol consumption; (2) Presence of any type of hepatitis viruses; (3) Other known causes of CLD; (4) Confirmed cirrhosis of any etiology; (5) End stage liver disease patients that are awaiting liver transplantation; and (6) Editorials, letters to the editor, case reports, conference abstracts, literature and systematic reviews, practice guidelines, commentaries, abstracts published without a full article.

2.3 Quality assessment

Quality of the included studies was evaluated using quality assessment tools from the National Heart, Lung, and Blood Institute (NHLBI) [7]. Two tools were used for observational cohort and cross-sectional studies as well as case-control studies. We used this evaluation tool in order to assess bias risk and internal validity in a similar method. Two authors (A.I and N.A) performed the evaluation independently. In case of disagreement, a consensus was reached through a discussion.

3. RESULTS

3.1 General Results

The PRISMA flow diagram demonstrating the conducted search strategy is described in **Figure 1**. The initial search using the previously mentioned keywords yielded a total of 127 results on PubMed. Human filter on PubMed search was applied reducing the total number of studies to 51 studies. Moreover, EMBASE database had a total of 421 results using the previously mentioned keywords. Several filters were applied, including studies only on EMBASE (186 studies), while excluding studies on embryo (1 study), newborn (2 studies), children (6 studies), adolescents (4 studies) and young adults (1 study). Furthermore, filters to exclude non-human studies (28 studies) as well as animal experiments (22 studies), animal tissues (16 studies), animal cells (9 studies), in vitro studies (6 studies) and mouse models (2 studies) was performed. Conference abstracts (48 abstracts) and conference reviews (2 reviews) were also excluded using search filters. A remaining number of 7 studies remained from the EMBASE search for screening. Furthermore, two additional records were identified through other sources and included for screening. A total of 60 studies (51 studies from PubMed, 7 from EMBASE and 2 from other sources) were included for evaluation. Out of these 60 studies, 1 duplicate was identified and excluded, as well as 42 other studies that were excluded with reasons (14 animal studies, 13 irrelevant topics, 7 literature reviews, 4 studies conducted on pediatrics / adolescents, 2 studies involving patients with liver cirrhosis, 1 systematic review and 1 case report). A total of 17 studies were eligible for full article evaluation, out of which, 6 studies were excluded with reasons. Studies evaluating LV systolic dysfunction using methods other than STE were excluded (2 studies), as well as studies that didn't evaluate the LV parameters (2 studies). Moreover, 2 studies were excluded as they were not evaluating patients according to the presence or absence of

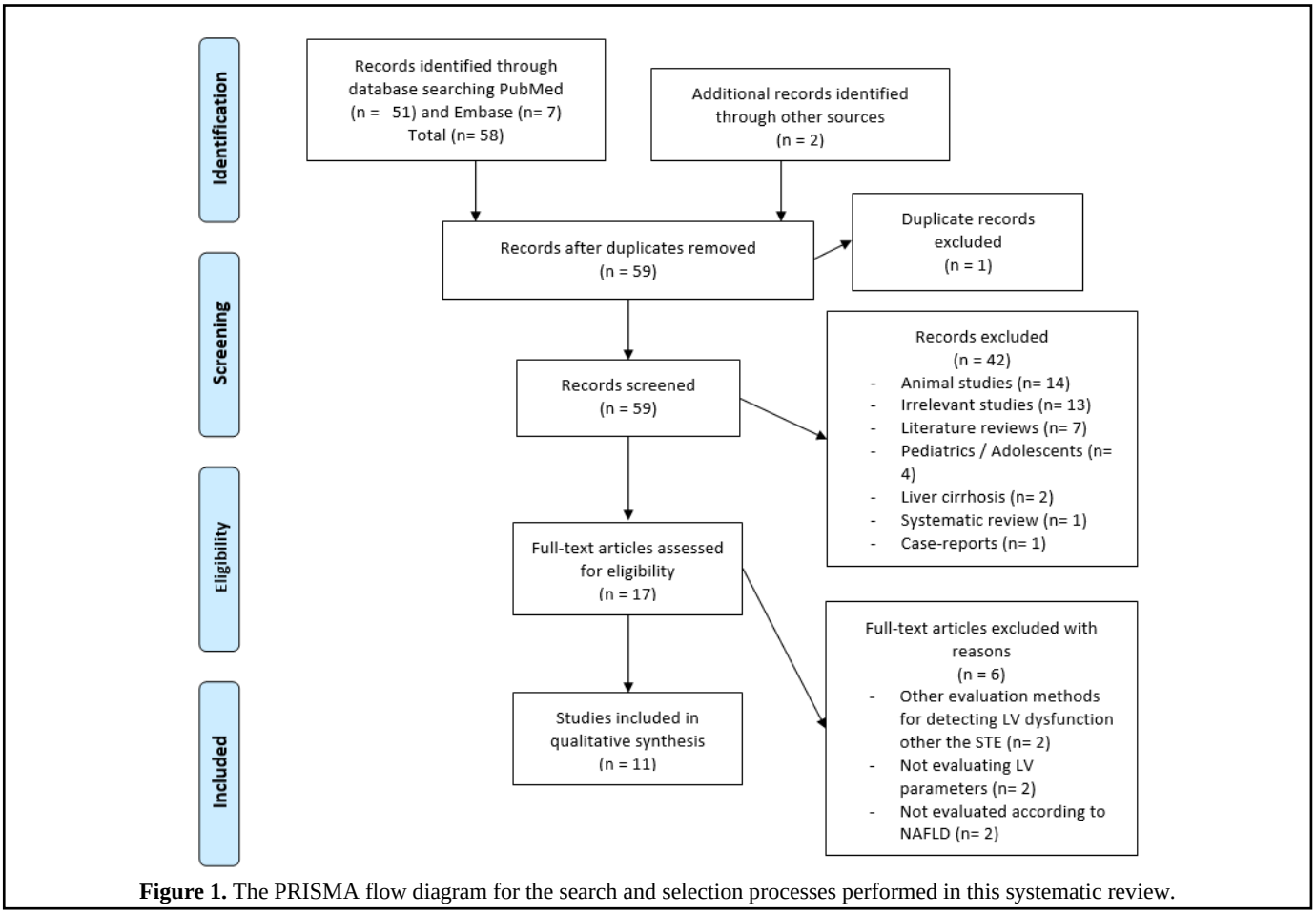

Figure 1. The PRISMA flow diagram for the search and selection processes performed in this systematic review.

NAFLD. Finally, a total of 11 studies were included for qualitative synthesis in this systematic review [8-16].

A summary of the main characteristics of included studies in this systematic review are demonstrated in **Table 1**. This systematic review evaluates a total number of 5,851 subjects. The eleven included studies were composed of nine cross-sectional studies (3,964 subjects), one case-control study (60 subjects) and one longitudinal cohort study (1,827 subjects) were included. Males subjects were 2,612 (45%) subjects while females were 3,239 (55%) subjects. Moreover, 1,346 (23%) subjects were confirmed to have NAFLD. Studies were conducted in USA (n= 3), Italy (n= 2), Iran (n= 2), Turkey (n= 2) and China (n= 2).

3.2 Non-alcoholic Fatty Liver Disease Diagnosis

In this systematic review, five studies diagnosed NAFLD using ultrasonography [8, 11, 12, 15, 17], three studies used liver biopsy, the gold standard method [9, 10, 16], while three studies used CT [13, 14, 18].

3.3 Evaluation of Left Ventricular Systolic Function in NAFLD

STE was used with two-dimensional trans-thoracic echocardiography (TTE) in the majority of studies (n= 8) [8-10, 12-14, 16, 18], while two studies used three-dimensional TTE [15, 17] and one study used four-dimensional TTE [11]. All studies evaluated LVEF and global longitudinal strain (GLS), out of which, only two studies reported a significant association between a reduced LVEF and NAFLD [12, 18]. On the other hand, eight studies reported that GLS was demonstrated to be significantly reduced in NAFLD patients [9-11, 13, 15-18]. The other three studies that didn't demonstrate a reduction in GLS in NAFLD included two studies that evaluated only type 2 diabetic patients [8, 12] and one study that evaluated drinkers and non-drinkers in NAFLD patients [14].

Out of the four studies that evaluated subclinical LV systolic dysfunction in diabetic patients with and without NAFLD, three reported that LVEF wasn't significantly reduced in diabetic patients with and without NAFLD [8, 15, 17], while one study concluded that diabetic patients with NAFLD had a reduced LVEF compared to patients without NAFLD [12]. Moreover, GLS was demonstrated to be significantly reduced in diabetic patients with NAFLD in only two out of the four studies evaluating diabetic patients [15, 17].

Five cross-sectional studies diagnosed NAFLD using ultrasonography. Bonapace S et al. reported in a study involving 50 type 2 diabetic patients that NAFLD was associated with a reduced GLS and strain rate, even after adjusting for cardiometabolic risk factors [8]. Furthermore, Khoshbaten M et al. concluded that asymptomatic NAFLD patients were associated with a significantly reduced GLS [11]. A study conducted by Mantovani A et al. on type diabetic patients did not demonstrate a significant reduction in GLS in NAFLD patients, while LVEF was significantly reduced [12]. Moreover, Wang Q et al. demonstrated in a study involving 120 subjects that diabetic patients with

Table 1. Subclinical Left Ventricular Dysfunction Assessed with Myocardial Strain Measured by Speckle Tracking

First Author / Year / Country	*Study Design*	*Study Characteristics*	*Main Findings*
Bonapace S et al. / 2012 / Italy [8]	Cross-sectional	• **Total Subjects:** 50 (NAFLD – 32; Controls – 18) • **NAFLD:** 64% • **Mean age (years):** NAFLD 64.8 ± 4; Controls 63.0 ± 6 • **BMI:** Without NAFLD 28.6 ± 3.5; NAFLD 28.6 ± 3.3 (p value= 0.98) • **NAFLD diagnosis:** Ultrasonography • **Gender (males):** 38 (76%) • **LV dysfunction assessment:** Tissue doppler echocardiography with myocardial strain measurement **LVEF (%):** NAFLD 73.7 ± 7.2; Controls 71.3 ± 6.9 (p value= 0.29) Measurements of LV G-LS and strain rate were present in 45 patients (29 with NAFLD and 16 controls). **G-LS (%):** NAFLD – 15.5 ± 3.0; Controls – 16.1 ± 2.9 (p value= 0.70) **G-SRsys (/s):** NAFLD – 1.03 ± 0.15; Controls – 1.01 ± 0.13 (p value= 0.78) **G-SRearly (/s):** NAFLD 0.84 ± 0.22; Controls 0.94 ± 0.20 (p value= 0.19) **G-SRlate (/s):** NAFLD 0.90 ± 0.21; Controls 1.0 ± 0.18 (p value= 0.12) **E/SRearly (m):** NAFLD 0.77 ± 0.21; Controls 0.63 ± 0.19 (p value= <0.05)	Type 2 diabetic patients with NAFLD presented with a reduced LV G-LS, strain rate and increased E/SRearly. All of these findings remained significant after adjustment for cardiometabolic risk factors.
Karabay CY et al. / 2014 / Turkey [9]	Cross-sectional	• **Total Subjects:** 76 (NAFLD – 55; Controls – 21) • **NAFLD:** 72% • **Mean age (years):** NAFLD 42.9 ± 10.0; Controls 40.5 ± 7.8 • **BMI:** Controls 27.3 ± 3.6; Simple Steatosis 28.3 ± 3.7; Borderline NASH 30.6 ± 3.5; Definitive NASH 32.2±1.4 (p value= 0.001) • **NAFLD diagnosis:** Liver biopsy • **Gender (males):** 43 (60%) • **LV dysfunction assessment:** 2D-STE analysis **LVEF (%):** Simple steatosis 62.4 ± 6.5, Borderline NASH 62.2 ± 10.3, Definitive NASH – 59.2 ± 5.4; Controls 62.5 ± 4.5 (p value= NS) **G-LS (%):** Simple steatosis – 17.0 ± 1.2, Borderline NASH – 17.1 ± 2.2, Definitive NASH – 17.7 ± 2.7; Controls – 19.8 ± 3.1 (p value= 0.005) **G-SRsys (/s):** Simple steatosis – 0.87 ± 1.3, Borderline NASH – 0.92 ± 0.17, Definitive NASH – 1.0 ± 0.22; Controls – 1.2 ± 0.54 (p value= 0.05) **G-SRearly (/s):** Simple steatosis 1.2 ± 0.20, Borderline NASH 1.1 ± 0.30, Definitive NASH 1.3 ± 0.33; Controls 1.2 ± 0.19 (p value= NS) **G-SRlate (/s):** Simple steatosis 0.91 ± 0.19, Borderline NASH 0.87 ± 0.27, Definitive NASH 0.99 ± 0.18; Controls 0.95 ± 0.13 (p value= NS)	NAFLD patients presented with subclinical myocardial dysfunction in relation to the presence of insulin resistance. Nevertheless, no significant findings were demonstrated between different subgroups of NAFLD using 2D-STE.
Baktır AO et al. / 2015 / Turkey [10]	Cross-sectional	• **Total Subjects:** 56 (NASH – 28; Controls – 28) • **NASH:** 50% • **Mean age (years):** NASH 41.6 ± 9.8; Controls 41.2 ± 9 • **BMI:** NASH 27.7 ± 1.6; Controls 26.7±1.7 (p value= 0.053) • **NASH diagnosis:** Liver biopsy • **Gender (males):** 32 (57%) • **LV dysfunction assessment:** 2D-STE analysis **LVEF (%):** NASH 66.7 ± 5.2; Controls 65.7 ± 2.4 (p value= 0.385) **G-LS (%):** NASH – 18.88 ± 1.51; Controls – 23.73 ± 2.34 (p value= <0.001) **G-SRsys (/s):** NASH – 1.14 ± 0.20; Controls – 1.73 ± 0.28 (p value= <0.001) **G-SRearly (/s):** NASH 1.20 ± 0.38; Controls 2.35 ± 0.55 (p value= <0.001) **G-SRlate (/s):** NASH 1.45 ± 0.55; Controls 1.68 ± 0.53 (p value= 0.106)	LV longitudinal and radial systolic functions may be altered in NASH patients despite the absence of an apparent reduction in LVEF. STE may be useful in detecting subclinical LV impairment in NASH patients.
Khoshbaten M et al. / 2015 / Iran [11]	Cross-sectional	• **Total Subjects:** 60 (NAFLD – 30; Controls – 30) • **NAFLD:** 50% • **Mean age (years):** NAFLD 39.97 ± 6.84; Controls 40.53 ± 8.08 • **BMI:** NAFLD 27.33 ± 2.41; Controls 24.95 ± 1.74 (p value= <0.001) • **NAFLD diagnosis:** Ultrasonography • **Gender (males):** 36 (60%) • **LV dysfunction assessment:** 4D echocardiography and STE **LVEF (%) by 2DE:** NAFLD 54.81 ± 6.72; Controls 57.43 ± 7.3 (p value= 0.79) **LVEF (%) by 4DE:** NAFLD 55.83 ± 8.03; Controls 59.75 ± 5.4 (p value= 0.59) **G-LS (%):** NAFLD – 18.96 ± 2.31; Controls – 20.27 ± 1.72 (p value= 0.016)	G-LS was significantly reduced in asymptomatic NAFLD patients compared to controls assessed using STE.
Mantovani A et al. / 2015 / Italy [12]	Cross-sectional	• **Total Subjects:** 222 (NAFLD – 64; Controls – 158) • **NAFLD:** 29% • **Mean age (years):** NAFLD 68.6 ± 7; Controls 66.9 ± 7 • **BMI:** Without NAFLD 27.4 ± 3; NAFLD 29.3 ± 5 (p value <0.005) • **NAFLD diagnosis:** Ultrasonography • **Gender (males):** 156 (70%) • **LV dysfunction assessment:** Tissue doppler echocardiography and STE **LVEF (%):** NAFLD 62.8 ± 6; Controls 65.4 ± 7 (p value= <0.05) **G-LS (%):** NAFLD – 15.9 ± 3.0; Controls – 16.2 ± 2.3 (p value= 0.64) **G-SRsys (/s):** NAFLD – 1.02 ± 0.25; Controls – 1.05 ± 0.15 (p value= 0.47) **G-SRearly (/s):** NAFLD 1.05 ± 0.27; Controls 1.14 ± 0.26 (p value= 0.10) **G-SRlate (/s):** NAFLD 1.16 ± 0.36; Controls 1.08 ± 0.23 (p value= 0.20) **E/SRearly (m):** NAFLD 0.68 ± 0.24; Controls 0.55 ± 0.20 (p value= <0.005)	Type 2 diabetic patients with NAFLD with preserved systolic function are independently associated with echocardiographic features of early LVDD.
VanWagner LB et al. / 2015 / USA [13]	Cross-sectional	• **Total Subjects:** 2,713 (NAFLD – 271; Controls – 2,442) • **NAFLD:** 11% • **Mean age (years):** Overall Sample 50.1 ± 3.6; NAFLD 50.5 ± 3.7; Controls 50.1 ± 3.6 • **BMI:** Overall 30.4 ± 7.2; No NAFLD 29.7 ± 6.9; NAFLD 36.2 ± 7.5 (p value <0.0001) • **NAFLD diagnosis:** CT • **Gender (males):** 1,118 (41%) • **LV dysfunction assessment:** Tissue doppler echocardiography with myocardial strain measurement **LVEF (%):** NAFLD 62.0 ± 7.7; Controls 61.6 ± 7.0 (p value= 0.42) **G-LS (%):** NAFLD – 14.2 ± 2.4; Controls – 15.2 ± 2.4 (p value= 0.0001)	NAFLD is independently associated with subclinical myocardial remodeling and dysfunction, as well as worse absolute G-LS even after adjusting for cardiometabolic risk factors.

Table 1 (Continued). Subclinical Left Ventricular Dysfunction Assessed with Myocardial Strain Measured by Speckle Tracking

First Author / Year / Country	*Study Design*	*Study Characteristics*	*Main Findings*
VanWagner LB et al. / 2017 / USA [14]	Cross-sectional	• **Total Subjects:** 570 (NAFLD – 570: Non-drinkers – 238; Drinkers – 332) • **NAFLD:** 100% • **Mean age (years):** Overall Sample 50.4 ± 3.6; Non-drinkers 50.5 ± 3.7; Drinkers 50.2 ± 3.6 • **BMI:** Overall NAFLD 35.5 ± 7.3; Non-drinkers 37.3 ± 8.1; Drinkers 34.3 ± 6.4 (p value <0.0001) • **NAFLD diagnosis:** CT • **Gender (males):** 308 (54%) • **LV dysfunction assessment:** Tissue doppler echocardiography with myocardial strain measurement **LVEF (%):** NAFLD 69.4 ± 8.6; Non-drinkers 69.8 ± 8.8; Drinkers 69.2 ± 8.4 (p value= 0.41) **G-LS (%):** NAFLD – 14.4 ± 2.3; Non-drinkers – 14.1 ± 2.4; Drinkers – 14.5 ± 2.2 (p value= 0.06)	Middle aged NAFLD patients didn't present with a CV risk reduction or improvement in subclinical markers of CVD associated with alcohol use.
Wang Q et al. / 2018 / China [15]	Cross-sectional	• **Total Subjects:** 120 (NAFLD + Diabetes – 40; Diabetes Only – 40; Controls – 40) • **NAFLD:** 33% • **Mean age (years):** NAFLD + Diabetes 64.4 ± 79; Diabetes Only 60.8 ± 8.1; Controls 61.9 ± 6.9 • **BMI:** Controls 24.74 ± 2.07; Diabetes Only 24.50 ± 2.58; Diabetes + NAFL 25.73 ± 2.97 • **NAFLD diagnosis:** Ultrasonography • **Gender (males):** 62 (52%) • **LV dysfunction assessment:** Echocardiography with 3D STE **LVEF (%):** NAFLD + Diabetes 58.73 ± 6.67; Diabetes Only 58.46 ± 8.52; Controls 57.75 ± 6.00 (p value= NS) **G-LS (%):** NAFLD + Diabetes – 14.28 ± 3.08; Diabetes Only – 17.32 ± 2.43; Controls – 19.86 ± 2.59 (p value= 0.001)	Diabetic patients with NAFLD presented with a worse LV dysfunction compared with NAFLD patients without diabetes and controls, suggesting that combining conventional and 3D STE could detect these asymptomatic preclinical abnormalities.
Zamirian M et al. 2018 / Iran [16]	Case-control	• **Total Subjects:** 60 (NAFLD – 30; Controls – 30) • **NAFLD:** 50% • **Mean age (years):** NAFLD 38.4 ± 5; Controls 36.9 ± 4.5 • **BMI:** NAFLD 25.84 ± 2.16; Controls 25.73 ± 2.29 (p value= 0.848) • **NAFLD diagnosis:** Liver biopsy • **Gender (males):** 31 (52%) • **LV dysfunction assessment:** 2D transthoracic echocardiography with STE **LVEF (%):** NAFLD 56.7 ± 4.6; Controls 57.1 ± 5.2 (p value= 0.753) **G-LS (%):** NAFLD – 19.3 ± 2; Controls – 21.2 ± 1.4 (p value= <0.001)	NAFLD patients develop subclinical cardiovascular structural and functional modifications. LV systolic dysfunction is better evaluated using the more sensitive G-LS compared to LVEF in NAFLD patients.
Dong Y et al. / 2020 / China [17]	Cross-sectional	• **Total Subjects:** 97 (NAFLD – 67; Controls – 30) • **NAFLD:** 74% • **Mean age (years):** Mild NAFLD 45.3 ± 5.4; Moderate-Severe NAFLD 47.2 ± 9.7; Controls 48.5 ± 10.0 • **BMI:** Controls 24.4 ± 2.6; Mild NAFLD 25.5 ± 3.2; Moderate-Severe NAFLD 27.3±3.8 (p value= 0.019) • **NAFLD diagnosis:** Ultrasonography • **Gender (males):** 69 (71%) • **LV dysfunction assessment:** 3D transthoracic echocardiography with STE **LVEF (%):** Mild NAFLD 59.3 ± 3.7; Moderate-Severe NAFLD 58.9 ± 4.5; Controls 60.3 ± 5.0 (p value= 0.169) **G-LS (%):** Mild NAFLD – 17.9 ± 3.1; Moderate-Severe NAFLD – 14.1 ± 4.1; Controls – 19.0 ± 2.6 (p value= 0.001)	In a study conducted on type 2 diabetic patients, conventional echocardiography in combination with 3D-STE demonstrated a better assessment method for evaluating LV function in NAFLD. Moreover, LV dysfunction severity in patients with moderate-to-severe NAFLD assessed using ultrasonography was worse than in patients with mild and absent NAFLD.
VanWagner LB et al. / 2020 / USA [18]	Longitudinal cohort	• **Total Subjects:** 1,827 (NAFLD – 159; Controls – 1,668) • **NAFLD:** 9% • **Mean age (years):** Overall Sample 50.0 ± 3.6; NAFLD 50.4 ± 3.6; Controls 49.9 ± 3.6 • **BMI:** Overall 30.2 ±7.2; No NAFLD 29.6 ± 6.9; NAFLD 36.0 ± 7.4 (p value <0.0001) • **NAFLD diagnosis:** CT • **Gender (males):** 719 (39%) • **LV dysfunction assessment:** Tissue doppler echocardiography with myocardial strain measurement **LVEF (%):** NAFLD 58.9 ± 6.5; Controls 60.2 ± 5.3 (p value= 0.005); **LVEF 5-year interval difference:** NAFLD – 3.0 ± 7.9; Controls – 1.5 ± 7.5 (p value 0.02) **G-LS (%):** NAFLD – 13.9 ± 2.7; Controls – 15.3 ± 2.8 (p value= 0.0001) **G-LS 5-year interval difference:** NAFLD 0.001 ± 3.0; Controls – 0.04 ± 3.2 (0.88)	NAFLD was independently associated with an increased alteration in strain (odds ratio: 2.2, 1.1–4.7) after performing multivariable analyses and adjusting for heart failure risk factors. Nevertheless, adjustment for BMI attenuated the association to non-significance.

BMI – **Body mass index;** CT – **Computed tomography;** CV – **Cardiovascular;** CVD – **Cardiovascular disease;** E/SRearly – **E/global longitudinal diastolic strain rate during the early phase of diastole;** G-LS – **Global longitudinal strain;** G-SRearly – **Strain rate in early diastole;** G-SRlate – **Strain rate in late diastole;** G-SRsys – **Strain rate in systole;** LV – **Left ventricular;** LVDD – **Left ventricular diastolic dysfunction;** LVEF – **Left ventricular ejection fraction;** NAFLD – **Non-alcoholic fatty liver disease;** NASH – **Non-alcoholic steatohepatitis;** NS – **Non-significant;** STE – **Speckle tracking echocardiography.**

NAFLD present with subclinical LV systolic dysfunction assessed by myocardial strain [15]. They also reported that BMI was only associated with GLS (p value= 0.009). A cross-sectional study conducted by Dong Y et al. involving 97 type 2 diabetic patients demonstrated that GLS values were significantly reduced in NAFLD, being worse according to hepatic steatosis grading, while BMI was only associated with global area strain (p value= 0.008) [17].

Two cross-sectional studies and one case-control study confirmed the diagnosis of NAFLD by liver biopsy. Karabay CY et al. conducted a cross-sectional study involving 76 subjects demonstrating subclinical myocardial dysfunction evaluated using 2D-STE in relation to insulin resistance in NAFLD patients, without a significance difference between subgroups of NAFLD [9]. Moreover, a cross-sectional study conducted by Baktır AO et al. including 28 patients with NASH and 28 controls concluded that despite the normal LVEF in NASH patients, LV longitudinal and radial systolic functions may be altered [10]. A case-control study involving 60 subjects conducted by Zamirian M et al. concluded that LV systolic function is better evaluated using GLS compared to LVEF in NAFLD patients [16].

Two cross-sectional studies and one longitudinal cohort study conducted by VanWagner LB et al. evaluated NAFLD using CT. First study involved 2,713 subjects, concluding that subclinical myocardial remodeling and dysfunction are association independently with NAFLD [13]. They also suggested that obesity may play an essential role in the observed association between NAFLD and subclinical myocardial dysfunction. The second study was conducted only on NAFLD patients while comparing drinkers with non-drinkers [14]. They demonstrated that alcohol wasn't a

protective factor against CVD, neither did it improve subclinical markers of CVD. The third study was a follow-up for 5 years for previously evaluated subjects, concluding that NAFLD prospectively and independently associated with an increased alteration in strain, even after performing multivariable analyses and adjusting for heart failure risk factors [18]. However, they reported that the association between NAFLD and longitudinal strain was attenuated in models with HF risk factors and either BMI or VAT.

3.4 Quality Assessment of Included Studies

NHLBI quality assessment tool for observational cohort and cross-sectional studies as well as for case-control studies was used to evaluate the included studies as demonstrated in **Supplementary Tables 1 - 2**. Quality of each study was rated as "good", "fair, or "poor". Five studies were rated as "good" [13-15, 17, 18], four were rated as "fair" [8, 10, 12, 16], while two studies were rated as "poor" [9, 11]. A clear objective or research question was clearly stated in all included studies. All but three studies performed measurements for key potential confounding variables and statistical adjustments [9, 11, 16]. Subclinical LV systolic dysfunction evaluated using myocardial strain was reported to be associated with NAFLD in all but three studies, out of which, two involved type 2 diabetic patients were rated as "fair" in addition to one study rated as "good" that included only NAFLD patients while comparing drinkers with non-drinkers. Moreover, all studies demonstrated that NAFLD wasn't associated with a reduction in LVEF compared to controls except two studies, one involving type 2 diabetic patients rated as "fair" [12] and the other with longitudinal design including a population-based cohort rated as "good" [18].

4. DISCUSSION

Currently, to the best of our knowledge, this systematic review is the first to evaluate subclinical LV systolic dysfunction assessed with myocardial strain measured by STE in NAFLD. A total of eleven studies (nine cross-sectional studies, one longitudinal cohort and one case-control study) were included in our systematic review with a total study population of 5,851 individuals. We demonstrated that NAFLD patients have an increased risk of developing subclinical LV systolic dysfunction, despite being asymptomatic with normal LVEF values.

Several findings were reported in our systematic review that require further discussion. Firstly, we noticed that most studies assessing subclinical LV dysfunction in NAFLD using STE in the current literature were of cross-sectional design, while only one was a longitudinal cohort and one case-control study. This prevents us from being able to confirm any causal association between NAFLD and subclinical LV systolic dysfunction. Furthermore, metabolic syndrome and obesity, being well known risk factors associated with NAFLD and CVD have been associated with subclinical LV systolic dysfunction in several studies in the current literature [19, 20]. As demonstrated in most studies included in our systematic review, NAFLD was associated with a significantly increased BMI. Therefore, subclinical LV systolic dysfunction reported to be associated with NAFLD might have been due to an epiphenomenon of metabolic syndrome and obesity. Accordingly, more prospective studies are required in order to better evaluate this association.

Secondly, we reported that five included studies used ultrasonography to diagnose NAFLD, three used liver biopsy and histology, being the gold standard to assess hepatic steatosis [21] and three used CT. Ultrasonography is the most frequently performed investigation to evaluate hepatic steatosis with a sensitivity of 84.8 % and specificity of 93.6% [22]. Moreover, CT was reported by Park et al. to have a sensitivity of 82% and a specificity 100% [23].

Thirdly, only two studies demonstrated that LVEF was significantly reduced in NAFLD compared to controls [12, 18]. One of these studies was conducted on type 2 diabetic patients, and therefore, they might present with several other CV manifestations associated with microvascular and macrovascular complications related to their diabetes [24]. Therefore, generalizability of these findings on non-diabetic NAFLD patients isn't possible. Moreover, the other study was a population based longitudinal cohort demonstrating that LVEF was reduced significantly in NAFLD patients compared to controls.

Fourthly, subclinical LV systolic dysfunction was assessed in the included studies using STE by measuring myocardial strain, out of which, three studies didn't report a reduction in GLS in NAFLD [8, 12, 14]. This can be explained by the fact that two of these studies were also conducted only on type 2 diabetic patients that might present with other CV complications, which limits the generalization of these results on non-diabetic subjects. The third study was actually conducted only on NAFLD patients and compared alcohol drinker with non-drinkers [14]. Therefore, both groups presented with NAFLD which can explain why both groups had similar CV manifestations without a significant difference in GLS values.

Fifthly, risk of bias and methodology assessment performed using the NHLBI quality assessment tools demonstrated that five included studies were rated as "good", four as "fair" and only two were rated as "poor". Accordingly, most included studies were demonstrated to have a low risk of bias with minor methodological flaws. Moreover, interpreting the results of the other studies with an increased risk of bias and methodology flaws should be performed with caution.

Several potential limitations should be mentioned regarding this systematic review. First, most included studies are of cross-sectional design. Only one longitudinal cohort study with a 5-year follow up period evaluating subclinical LV systolic dysfunction in NAFLD through myocardial strain measurements was found in the current literature. Therefore, causality between NAFLD and subclinical LV systolic dysfunction can't be confirmed. Second, we included any study that used histopathological or imaging methods to confirm the presence of hepatic steatosis. We didn't exclude studies that used other methods other than the gold standard, being liver biopsy as we will be left with a small number of studies which will lead to less significant and generalizable results.

Despite the previously mentioned limitations, our study also has several important strengths. A comprehensive search conducted using two electronic databases was performed,

therefore summarizing the currently published literature in a non-biased manner. Moreover, included studies were mostly rates as "good" and "fair" for methodological assessment with a low risk of bias, minimizing biased results in studies included in this systematic review. To the best of our knowledge, this is the first systematic review to evaluate, outline and summarize that currently published data evaluating subclinical LV systolic dysfunction assessed with myocardial strain measured by STE in NAFLD.

5. Conclusions and Future Directions

In conclusion, NAFLD patients are of increased risk to develop subclinical LV systolic dysfunction assessed with myocardial strain measured by speckle tracking, despite being asymptomatic with normal LVEF values. Accordingly, we recommend the evaluation of subclinical LV systolic dysfunction in NAFLD patients due to the great prognostic significance, while supporting early lifestyle and therapeutic considerations in NAFLD patients in order to prevent or minimize further complications. The existence of significant subclinical LV dysfunction in type 2 diabetic patients comparing the presence or absence of NAFLD remains uncertain. Further high-quality studies of prospective design with longer follow up periods are required in order to assess whether NAFLD patients present worsening of their systolic function and reduction of myocardial strain values, in addition to search for potential pathogenic links that lead to subclinical LV systolic dysfunction in NAFLD.

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions: AI had the study idea, suggested methodology, performed the literature search, data extraction, helped with drafting the tables and wrote the manuscript. NA performed the literature search, data extraction, drafted the tables and contributed to the writing of the manuscript. All authors approved the final version of the manuscript.

Funding: No funding was obtained for this study.

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Supplementary Table 1. NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies

Criteria	Bonapace, S. et al. [8]	Karabay, C. Y. et al. [9]	Baktir, A. O. et al. [10]	Khoshbaten, M. et al. [11]	Mantovani, A. et al. [12]	VanWagner, L. B. et al. [13]	VanWagner, L. B. et al. [14]	Wang, Q. et al. [15]	Dong, Y. et al. [17]	VanWagner , L. B. et al. [18]
1. Was the research question or objective in this paper clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2. Was the study population clearly specified and defined?	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
3. Was the participation rate of eligible persons at least 50%?	CD	CD	CD	CD	CD	Yes	Yes	CD	CD	Yes
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Yes	CD	Yes	CD	Yes	Yes	Yes	Yes	Yes	Yes
5. Was a sample size justification, power description, or variance and effect estimates provided?	No	No	No	No	No	Yes	Yes	No	Yes	Yes
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	No	No	No	No	No	No	No	No	No	No
7. Was the time frame sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	No	No	No	No	No	No	No	No	No	Yes
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?	No	Yes	No	No	No	No	No	Yes	Yes	No
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
10. Was the exposure(s) assessed more than once over time?	No	No	No	No	No	No	No	No	No	Yes
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
12. Were the outcome assessors blinded to the exposure status of participants?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
13. Was loss to follow-up after baseline 20% or less?	NA	NA	NA	NA	NA	NA	NA	NA	NA	No
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?	Yes	No	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Rating	Fair	Poor	Fair	Poor	Fair	Good	Good	Good	Good	Good

Available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). CD, cannot determine; NA, not applicable; NR, not reported.

Supplementary Table 2. NHLBI Quality Assessment of Case-Control Studies

Criteria	Zamirian, M. et al. [16]
1. Was the research question or objective in this paper clearly stated and appropriate?	Yes
2. Was the study population clearly specified and defined?	Yes
3. Did the authors include a sample size justification?	No
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	Yes
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	Yes
6. Were the cases clearly defined and differentiated from controls?	No
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	NA
8. Was there use of concurrent controls?	No
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	No
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	Yes
11. Were the assessors of exposure/risk blinded to the case or control status of participants?	Yes
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?	No
Rating	Fair

Available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools). CD, cannot determine; NA, not applicable; NR, not reported.