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Original Article

Internal Medicine Section

Association between Non Alcoholic Fatty Liver Disease and Severity of Coronary Artery Disease in Patients Aged 45 Years and Below with Acute Coronary Syndrome

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ABSTRACT

Introduction: Coronary Artery Disease (CAD) is an important extrahepatic cardiovascular complication of Non Alcoholic Fatty Liver Disease (NAFLD).

Aim: To determine the prevalence of NAFLD in young (≤45 years) Acute Coronary Syndrome (ACS) patients, and to assess the association between severity of NAFLD and severity of CAD.

Materials and Methods: This cross-sectional study was conducted from May 2017-April 2018, with a total of 85 patients. CAD severity was determined by coronary angiogram while its complexity by SYNTAX score. Fatty liver was diagnosed and graded by liver ultrasound examination.

Results: The prevalence of NAFLD was 100%. Thirty-three (38.9%) had ST-Elevation Myocardial Infarction (STEMI), 32 (37.6%) had Non STEMI (NSTEMI) and 20 (23.5%) had unstable angina. There was no significant correlation between NAFLD steatosis grades and ACS subtypes (p=0.721), severity of CAD (p=0.822) and SYNTAX score (p=0.982). No association between NAFLD fibrosis score and ACS subtypes (p=0.232), severity of CAD (p=0.445) or SYNTAX score (p=0.839) were observed.

Conclusion: The NAFLD was extremely prevalent in young ACS patients. However, no significant association between severity of NAFLD and severity of CAD was found.

Keywords: Fibrosis score, Hepatic steatosis, Myocardial infarction, Prevalence, Young

INTRODUCTION

The NAFLD is an evolving public health problem worldwide. It is believed to be the most common cause of chronic liver disease in the United States with a recent estimated prevalence of 30% [1]. It is predicted to be among the chief indicators for liver transplant in the recent future [2]. The prevalence of NAFLD in Europe is found to be 23.7%, while in South Asia and South-East Asia ranges from 9-45%, and the prevalence in Malaysia is on the rise [3,4]. The latest estimated prevalence in Malaysia in a study by Goh SC et al., was 22.7%, which was considerably higher compared to Amarapurkar DN et al., of 17% [5,6]. The rise in prevalence is partly attributable to the emergence of the metabolic syndrome and its individual components such as diabetes mellitus, hypertension, hyperlipidaemia, and visceral obesity [7]. NAFLD is considered as the hepatic component of metabolic syndrome. Beside its hepatic complications in early adulthood, it also exerts serious extrahepatic complications such as cardiovascular disease, chronic kidney disease, endocrine disorders and rarely colorectal cancer.

In Malaysia, CAD is the major cause of death, with an estimated mortality of 20-25% [8]. Literature has shown that NAFLD is associated with increased CAD prevalence, which is manifested as ACS [9]. In addition to CAD, NAFLD is also shown to result in structural changes in the heart valves, for instance, mitral annulus calcification and aortic valve sclerosis. Moreover, it gives rise to left ventricular dysfunction and hypertrophy, and arrhythmias such as atrial fibrillation [10]. Evidence indicated that cardiovascular disease including ACS is the primary cause of morbidity and mortality in NAFLD [11].

The prevalence of ACS rises with increasing age and predominantly affects individuals aged more than 40 years. There is no scientific consensus regarding the definition of young patient with ACS. However, multiple studies that were conducted previously have been using a cut-off age of 40-45 years to define the 'young patient' with ACS [8,12-14]. There is an emerging increase in the proportion of adults hospitalised with young ACS, and it is a potential cause of morbidity and mortality in young adults. In Malaysia, Hoo FK et al., reported the prevalence of young ACS as 6.1% [8]. Previous data had shown a positive association between NAFLD and severity of CAD in older patients with ACS [15]. However, this relationship in young ACS patients is still unknown and local data pertaining to this is still lacking. Therefore, in the present study, the authors aimed to determine the prevalence of NAFLD in young patients presenting with ACS, and to assess any association between the severity of NAFLD and the severity of CAD in this cohort.

MATERIALS AND METHODS

This cross-sectional study was conducted from May 2017-April 2018. ACS is defined as a clinical spectrum of ongoing cardiac ischaemia, in which acute chest discomfort is usually the leading symptom. In line with previous studies [8,12-14], the authors had defined the young patients with ACS (therefore the inclusion criteria) as patients aged less than or equal to 45-year-old, who developed ACS. Written informed consent was obtained from all the participants. Ethical approval was received from Research Ethics Committee (Reference number: JEP-2017-545).

Inclusion criteria: All patients' ≤45 years, who presented to the hospital with ACS and underwent coronary angiogram were included in this study.

Exclusion criteria: Patients with documented chronic liver disease of any aetiologies. Patients with fatty liver due to secondary causes such as excessive alcohol consumption (>30 grams/day in men and >20 grams/day in women) and steatogenic medications (for example; amiodarone, methotrexate, steroids) were also excluded.

Sample size calculation: The sample size was calculated from Open Epi, version 3. Due to the lack of studies evaluating

the prevalence of NAFLD in young ACS, the sample size was calculated based on Baharvand-Ahmadi B et al., which reported the prevalence of NAFLD in ACS patients as 47% [16]. The calculated number of subjects was 96 patients with a confidence level of 95%. However, include 85 patients were included due to financial and time constraints.

Study Procedure

Socio-demographic data: Data on demographics, family history of ischaemic heart disease/sudden cardiac death, and personal history of alcohol intake, smoking and regular exercise is defined as exercise of at least 150-300 minutes of moderate intensity aerobic physical activity per week, or 75-150 minutes of vigorous intensity activity, or an equivalent combination of moderate and vigorous intensity activity as recommended by the 2018 Physical Activity Guidelines for Americans [17].

Cardiometabolic risk assessment: Cardio metabolic risks parameters included Body Mass Index (BMI), waist circumference, hypertension (defined as systolic blood pressure >140 mmHg and diastolic blood pressure> 90 mmHg according to the 8th Joint National Committee guideline-JNC8) [18], diabetes mellitus (HbA1c >6.3% based on Malaysian clinical practice 2015 guidelines), serum cholesterol subsets {Low Density Lipoprotein Cholesterol (LDL-C), High Density Lipoprotein Cholesterol (HDL-C) and Triglycerides (TG)}, renal function and urine protein index (u.PCI). BMI classification was performed as per Malaysian clinical practice guidelines [19]. Therefore, under-weight refers to BMI <18.5 kg/m^2, normal weight is for patients with BMI 18.5–22.9 kg/m^2, pre-obese for BMI of 23.0–27.4 kg/m^2 and obese when BMI is > 27.5 kg/m^2. Metabolic syndrome is defined based on International Diabetes Federation (IDF) criteria which include: central obesity (defined as waist circumference ≥90 cm in men and ≥80 cm in women for Asians, except for Japanese) plus two of the following four factors: TG ≥150 mg/dL (1.7 mmol/L), HDL cholesterol <40 mg/dL (1.03 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women, fasting glucose ≥100 mg/dL (5.6 mmol/L) or previously diagnosed with type 2 diabetes mellitus, and blood pressure >130/85 mmHg or on treatment for hypertension [20].

Coronary Artery Disease (CAD) assessment: Depending on the Electrocardiogram (ECG) finding and the level of cardiac biomarker (Troponin I), the study patients were classified into either unstable angina, NSTEMI or STEMI. Angiogram characteristics of CAD are categorised into Multi-Vessel Disease (MVD), Single-Vessel Disease (SVD), mild CAD, and no apparent CAD. MVD refers to narrowing of ≥50% in ≥2 of the major coronary arteries (left anterior descending, circumflex coronary artery or right coronary artery). SVD refers to narrowing of ≥50% in one of the major coronary arteries [21]. Mild CAD is defined as coronary luminal obstruction of 25-49%, while normal coronaries and minimal CAD refer to 0%, and <25% obstruction of the coronary artery lumen, respectively [22]. Additionally, the term "no apparent CAD" has been defined in previous literature as all coronary stenosis less than 20% or evidence of luminal irregularities [23]. No apparent CAD in this study included patients with normal coronaries, minimal coronary disease or coronary irregularities.

SYNTAX score: SYNTAX Score (SYNergy between Percutaneous Coronary Intervention (PCI) with TAXUS™ and Cardiac Surgery) is a validated angiographic tool to quantify the complexity of CAD as it considers the coronary artery anatomy and lesion's characteristics. The SYNTAX score is calculated by an open-access online computer program consisting of sequential self-guided questions. SYNTAX score of more than 34 is considered as a high score in which Coronary Artery Bypass Graft Surgery (CABG) was shown to be superior to PCI in terms of 2-year mortality [24].

Coronary angiograms were then reviewed by a cardiologist (who was blinded to the patient's ACS types and liver ultrasound findings) to assess the angiographic characteristics of CAD and to calculate the SYNTAX score. SYNTAX score was only calculated for the patients with ≥50% stenosis in coronary artery lumen, as it was not applicable for patients with mild CAD and no apparent CAD groups.

NAFLD assessment: Liver biochemistry, full blood count and viral screening (Hepatitis B and C serology) were performed at baseline. Ultrasound examination of the liver was performed for the study patients by the hepatobiliary interventional radiologist (who was blinded to study patients) to diagnose and grade the hepatic steatosis. The severity of steatosis was graded based on Saverymuttu SH et al., assessment method [25]. Fat infiltration in the liver was graded from grade 0 to grade 3 depending on the abnormally increased echogenicity of the liver parenchyma, the liver-kidney difference in echo amplitude, and echo penetration into hepatic deep structures and vasculature.

The NAFLD Fibrosis Score (NFS) was calculated for patients with proven fatty liver using the online NFS calculator. It is a validated non invasive tool to predict the degree of liver fibrosis in NAFLD patients [26]. Based on NFS, patients were categorised as low probability for advanced fibrosis (score < -1.455), indeterminate probability (score ≤ - 1.455 to ≤0.675), or high probability for advanced fibrosis (score > 0.675).

STATISTICAL ANALYSIS

Analysis was performed using International Business Machines (IBM) Statistical Package for the Social Sciences (SPSS) Statistics version 22.0 (IBM Corp., New York, USA). A p-value of <0.05 was considered statistically significant. Normality testing was done for all the continuous variables. Data are expressed as mean±Standard Deviation (SD) for the normally distributed continuous variables, as median (25th-75th IQR) for the non parametric continuous variables, and as frequencies for categorical variables. Non parametric data was analysed using Kruskal-Wallis test and Mann U Whitney test, whereas Analysis of Variance (ANOVA) was used for normally distributed variables. The categorical variables were analysed using Pearson Chi-square (χ^2) test where appropriate. Spearman correlation coefficient (r) was used to compare two continuous variables.

RESULTS

Baseline demographics and cardiometabolic characteristics: A total of 85 patients were included in the study. Majority of the patients were men (84.7%). The median age of the patients was 40-year-old (IQR 35-43). Majority of the patients (80%) were of Malay ethnicity, 75.3% were smokers, whereas 98.8% were strictly non alcohol consumers, and 77.6% were not performing a regular exercise [Table/Fig-1].

Patients characteristics	n (%)
Age, median (IQR) (years)	40 (35-43)
Gender	
Male	72 (84.7%)
Female	13 (15.3%)
Ethnicity	
Malay	68 (80.0%)
Chinese	11 (12.9%)
Indian	6 (7.1%)
Alcohol intake	
Yes	1 (1.2%)
No	84 (98.8%)
Smoking	
Yes	64 (75.3%)
No	21 (24.7%)
Physical Activity	
Yes	19 (22.4%)
No	66 (77.6%)

Family history of IHD/ sudden death	
Yes	35 (41.2%)
No	50 (58.8%)
BMI (kg/m^2), mean ± SD	29.78±6.68
Underweight	4 (4.7%)
Normal weight	9 (10.6%)
Pre-obese	23 (27.1%)
Obese	49 (57.6%)
Waist circumference (cm), mean±SD	98.4±15.0
Abdominal obesity	
Yes	63 (74.1%)
No	22 (25.9%)
Hypertension	
Yes	49 (57.6%)
No	36 (42.4%)
DM	
Yes	27 (31.8%)
No	58 (68.2%)
HbA1c (%), median (IQR)	5.7 (5.4-6.9)
Hyperlipidaemia	
Yes	56 (65.9%)
No	29 (34.1%)
Triglyceride, (mmol/L), median (IQR)	1.8 (1.3-2.9)
LDL-c, (mmol/L), mean±SD	3.56±1.5
HDL-c, (mmol/L), median (IQR)	0.95 (0.83-1.1)
Metabolic syndrome	
Yes	45 (52.9%)
No	40 (47.1%)

[Table/Fig-1]: Socio-demographic and cardiometabolic data of the patients (N=85).
IHD: Ischaemic heart disease; BMI: Body mass index; DM, Type 2 diabetes mellitus; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; IQR: Interquartile ranges; SD: Standard deviation

Coronary Artery Disease (CAD) assessment: Thirty-three patients (38.9%) presented with STEMI, 32 (37.6%) had NSTEMI, and 20 (23.5%) were diagnosed with unstable angina. Coronary angiogram showed 31 patients (36.5%) had MVD (only 1 patient had Left Main Stem (LMS) disease), 21 (24.7%) had SVD, 27 (31.8%) had mild CAD, whereas only 6 patients (7.1%) had no apparent CAD. Forty-nine patients (57.6%) underwent subsequent (PCI), whereas only 3 patients (3.5%) had CABG, and the rest 33 were treated with optimal medical therapy. Median SYNTAX score was 16 (IQR 9.0-22.3) [Table/Fig-2].

NAFLD assessment: Among all 85 young ACS patients, liver ultrasound examination detected the presence of hepatic steatosis in all of them (100%), of which 13 patients (15.2%) had grade 1, 36 (42.4%) had grade 2, and 36 (42.4%) had grade 3 hepatic steatosis. Based on NFS, 60 patients (70.6%) had low probability for advanced fibrosis, 24 (28.2%) were of indeterminate probability, whereas only 1 patient (1.2%) had high probability for advanced fibrosis [Table/Fig-3].

Socio-demographic and cardiometabolic data according to NAFLD grades: Analysis of the socio-demographic, cardiometabolic and CAD parameters according to NAFLD grades was performed and represented in [Table/Fig-4,5]. As the grade of hepatic steatosis increases, the higher proportion of patients with metabolic syndrome (23.1% vs 44.4% vs 72.2%, p=0.006) and hypertension (30.8% vs 50% vs 75%, p=0.002) were demonstrated. Moreover, there was an increasing trend of BMI (27 vs 28.2 vs 32.3, p=0.001), waist circumference (91.4 cm vs 96.3 cm vs 103 cm, p=0.008), HbA1c (5.6% vs 5.6% vs 6.1%, p=0.013) and TG levels (1.2 mmol/L vs 1.8 mmol/L vs 2.4 mmol/L, p=0.011) as the grade of NAFLD increases.

Parameters	n (%)
ACS	
STEMI	33 (38.9%)
NSTEMI	32 (37.6%)
Unstable angina	20 (23.5%)
Troponin I, median (IQR)	513.5 (28.3-12811.5)
Coronary angiogram	
No apparent CAD	6 (7%)
Mild CAD	27 (31.8%)
SVD	21 (24.7%)
MVD	31 (36.5%)
Intervention	
Medical therapy	33 (38.9%)
PCI	49 (57.6%)
CABG	3 (3.5%)
Ejection fraction, (%), median (IQR)	59 (42-65.5)
*SYNTAX Score, median (IQR)	16 (9 – 22.3)

[Table/Fig-2]: CAD parameters of the patients (N=85).
ACS: Acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; NSTEMI, Non ST segment elevation myocardial infarction; CAD: Coronary artery disease; IQR, interquartile ranges; SVD: Single-vessel disease; MVD: Multi-vessel disease; PCI: Percutaneous coronary intervention; CABG: Coronary artery bypass grafting; *SYNTAX score was calculated only for patients with significant coronary artery stenosis > 50 % in at least 1 vessel (total numbers of patients = 52)

Characteristics	n (%)
NAFLD	
Grade 1	13 (15.2%)
Grade 2	36 (42.4%)
Grade 3	36 (42.4%)
NAFLD fibrosis score	
Low probability or advanced fibrosis	60 (70.6%)
Indeterminate probability	24 (28.2%)
High probability for advanced fibrosis	1 (1.2%)
NAFLD fibrosis score, mean± SD	-2.389 ± 0.161
Liver Enzymes, (U/L), median (IQR)	
ALT	36 (23.0 - 47.5)
AST	22 (18.0 - 28.0)

[Table/Fig-3]: NAFLD assessment of the patients (N=85).
NAFLD: Non alcoholic fatty liver disease; ALT: Alanine transaminase; AST: Aspartate transaminase

CAD parameters according to NAFLD grades: There was no significant difference among NAFLD grades in terms of ACS subtypes (p=0.721), and angiographic severity of diseased vessels (p=0.822). Mean Troponin I was highest in grade 3 NAFLD with mean of 995 pg/mL, compared to grade 1 (mean TroponinI=176 pg/mL) and grade 2 NAFLD (mean Troponin I= 276 pg/mL), however, no statistical significance was observed (p=0.395). As mentioned earlier SYNTAX score was calculated only for patients with SVD and MVD (n=52). There was no significant difference in mean SYNTAX score among NAFLD grades (p=0.982) as shown in [Table/Fig-6]. All CAD parameters stratified by NAFLD grades are illustrated in [Table/Fig-5].

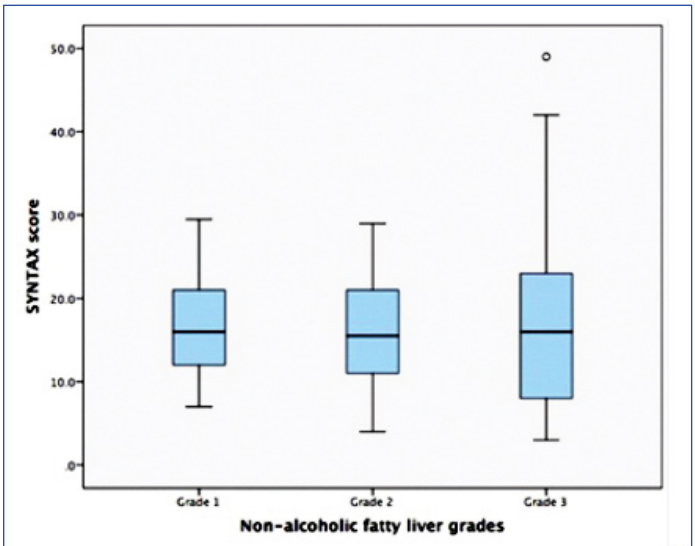
CAD parameters with NFS: Since only one patient fell in the high advanced fibrosis probability group based on NFS, the comparison of CAD parameters and NFS groups (high and low advanced fibrosis probability groups) was not done. However, NFS was tested in relation to ACS subtypes and angiographic severity of the coronary vessels and showed no significant difference (p=0.232) and (p=0.445), respectively. The authors also found no significant correlation between NFS and SYNTAX score (r=0.029, p=0.839).

Parameters	NAFLD grades			
	Grade 1 (n=13)	Grade 2 (n=36)	Grade 3 (n=36)	p-value
Gender, n (%)				
Male	12 (92.3%)	33 (91.7%)	27 (75.0%)	0.103
Female	1 (7.7%)	3 (8.3%)	9 (25.0%)	
Ethnicity, n (%)				
Malay	12 (92.3%)	27 (75.0%)	29 (80.6%)	0.634
Chinese	1 (7.7%)	5 (13.9%)	5 (13.9%)	
Indian	0 (0.0%)	4 (11.1%)	2 (5.6%)	
Age (years)	43 (39.2- 44.0)	39.5 (35.0-42.2)	40.0 (35.5-42.5)	0.182
Smoking, n (%)				
Yes	10 (76.9%)	29 (80.6%)	25 (69.4%)	0.544
No	3 (23.1%)	7 (19.4%)	11 (30.6%)	
Alcohol, n (%)				
Yes	1 (7.7%)	0 (0.0%)	0 (0.0%)	—
No	12 (92.3%)	36 (100%)	36 (100%)	
Family history of IHD or sudden death, n (%)				
Yes	7 (53.8%)	13 (36.1%)	15 (41.7%)	0.53
No	6 (46.2%)	23 (63.9%)	21 (58.3%)	
Exercise, n (%)				
Yes	5 (38.5%)	9 (25.0%)	5 (13.9%)	0.167
No	8 (61.5%)	27 (75.0%)	31 (86.1%)	
BMI (kg/m^2)	27.0±5.6	28.2±6.9	32.3±6.0	0.001*
Metabolic syndrome, n (%)				
Yes	3 (23.1%)	16 (44.4%)	26 (72.2%)	0.006*
No	10 (76.9%)	20 (55.6%)	10 (27.8%)	
Waist circumference, (cm)	91.4±15.1	96.3±14.0	103±15.0	0.008*
Hypertension, n (%)				
Yes	4 (30.8%)	18 (50.0%)	27 (75.0%)	0.002*
No	9 (69.2%)	18 (50.0%)	9 (25.0%)	
DM, n (%)				
Yes	4 (30.8%)	6 (16.7%)	17 (47.2%)	0.021*
No	9 (69.2%)	30 (83.3%)	19 (52.8%)	
HbA1c (%)	5.6 (5.4-6.6)	5.6 (5.4-6.0)	6.1(5.6-8.7)	0.013*
Hyperlipidaemia, n (%)				
Yes	8 (61.5%)	22 (61.1%)	26 (72.2%)	0.572
No	5 (38.5%)	14 (38.9%)	10 (27.8%)	
TG, (mmol/L)	1.2 (1.0-2.2)	1.8 (1.1-2.4)	2.4 (1.5-3.0)	0.011*
HDL-C, (mmol/L)	1.1 (0.9-1.2)	0.9 (0.8-1.0)	0.9 (0.8-1.0)	0.105
LDL-C, (mmol/L)	3.6±1.3	3.6±1.4	3.4±1.6	0.45
CKD, n (%)				
Stage 1	3 (23.1%)	12 (33.3%)	20 (55.6%)	0.084
Stage 2	7 (53.87%)	19 (52.8%)	7 (19.4%)	
Stage 3	1 (7.7%)	3 (8.3%)	4 (11.1%)	
Stage 4	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Advanced CKD/ ESRD	2 (15.4%)	2 (5.6%)	5 (13.9%)	
Urine protein creatinine index (urine PCI) (gm/day)	0.1 (0.02-0.8)	0.1 (0.1-0.2)	0.1 (0.1-0.5)	0.121
ALT, (U/L)	30.0 (21.2-49.5)	39.5 (26.5-46.0)	34.0 (21.5-48.0)	0.989
AST, (U/L)	22.5 (19.5-25.5)	21.0 (17.8-29.0)	22.0 (16.5-27.5)	0.771
NAFLD fibrosis score, n (%)				
Low probability of advanced fibrosis	8 (61.5%)	29 (80.6%)	23 (63.9%)	0.265
Indeterminate probability	5 (38.5%)	6 (16.7%)	13 (36.1%)	
High probability of advanced fibrosis	0 (0.0%)	1 (2.7%)	0 (0.0%)	

[Table/Fig-4]: Socio-demographic and cardiometabolic data of the patients according to NAFLD grades.
NAFLD: Non alcoholic fatty liver disease; IHD: ischaemic heart disease; BMI: body mass index; DM: type 2 diabetes mellitus; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; ALT: Alanine transaminase; AST: aspartate transaminase; * Significant; Pearson Chi-Square test: Parameters: Gender, Ethnicity, Smoking, Family history of IHD, Exercise, Metabolic syndrome, Hypertension, DM, Hyperlipidemia, CKD; Kruskal-wallis test: Parameters: Age, HBA1c, TG, HDL-C, Urine protein creatinine index, ALT, AST; One-way ANOVA test: Parameters: BMI, Waist circumference, LDL-C, NAFLD fibrosis score

Parameters	NAFLD grades			
	Grade 1 (n=13)	Grade 2 (n=36)	Grade 3 (n=36)	p-value
ACS				
STEMI	4 (30.8%)	16 (44.4%)	13 (36.1%)	0.721
NSTEMI	5 (38.4%)	11(30.6%)	16 (44.4%)	
USA	4 (30.8%)	9 (25.0%)	7 (19.4%)	
Troponin I (pg/mL)	176 (0.0-1719)	276 (19.5-16115)	995 (69-21877)	0.395
Vessels disease				
No apparent CAD	0 (0.0%)	2 (5.6%)	4 (11.1%)	
Mild CAD	4 (30.7%)	12 (33.3%)	11(30.5%)	0.822
SVD	3 (23.1%)	8 (22.2%)	10 (27.8%)	
MVD	6 (46.2%)	14 (38.9)	11 (30.6%)	
SYNTAX score	16.0 (9.5-22.0)	15.5 (10.5-21.4)	16.0(8.0-25.0)	0.982

[Table/Fig-5]: CAD parameters data of the patients according to NAFLD grades. ACS: Acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction; NSTEMI: Non ST segment elevation myocardial infarction; CAD: Coronary artery disease; SVD: Single-vessel disease; MVD: multi-vessel disease; Pearson Chi-Square test: Parameters: ACS, Vessels disease; Kruskal-Wallis test: Parameters: Troponin I, SYNTAX score



[Table/Fig-6]: Box plot illustrating the distribution of the SYNTAX score stratified by the ultrasound-graded of Non Alcoholic Fatty Liver Disease (NAFLD).

DISCUSSION

The exact pathophysiological mechanisms linking NAFLD and CAD is extremely complex and not well explained. Few theories elucidate the potential contributing factors. Firstly, NAFLD is a proinflammatory state associated increased release of the cytokines including C-reactive protein, interleukin 6 and Tumour Necrosis Factor-α (TNF-α) from the adipose tissues. Additionally, NAFLD is a hypercoagulable state where fibrinogen, tissue plasminogen activator 1 and Von Willebrand levels are raised. Ultimately, these factors could lead to endothelial dysfunction, which is the earliest process in atherosclerosis pathogenesis. NAFLD is also associated with a high level of oxidative stress which has an essential role in microvascular spasm. Lastly, NAFLD is associated with peripheral and hepatic Insulin Resistance (IR), which is a definitive contributor to atherosclerosis, exerting a state of steatogenesis and is associated with atherogenic dyslipidaemia, endothelial dysfunction and plaques formation [10].

This present study has demonstrated that young ACS occurs mainly in men which is similar with previous study [8]. It is presumed that in young females, oestrogen exerts an essential physiological role with its cardioprotective effect. This effect is due to the fact that oestrogen reduces the LDL-C, enhances endothelial release of nitric oxide by promoting the enzyme nitric oxide synthase and inhibits platelets aggregation [27]. Thus, lowers the incidence of ACS and cardiovascular mortality in women of reproductive age compared to men [28].

Alarmingly, the authors found that all young ACS study patients suffered from NAFLD. There is a paucity of literature studying the prevalence of NAFLD in young ACS patients. Baharvand-Ahmadi B et al., in Iran reported NAFLD prevalence of 47% in patients with CAD in the general age groups [16]. In Italy, Boddi M et al.,had examined NAFLD in STEMI patients in the age group between 18 to 80-year-old. They revealed a high prevalence of 87% of their studied population [29].

Assessment of the cardiometabolic factors in relation to the severity of NAFLD grades had been studied as well. In India, Majumder B et al., showed significantly increased frequency of diabetes mellitus, hypertension and metabolic syndrome along with higher BMI and TG levels in grade 2-3 NAFLD compared to grade 1 [30]. This study similarly showed a substantial association of hypertension, diabetes mellitus, metabolic syndrome with the severity of NAFLD grades. The authors also noticed that BMI, TG, waist circumference and HbA1c were significantly higher as the grade of NAFLD increases.

The authors found that in this young ACS cohort, compared to unstable angina, the frequency of myocardial infarction (STEMI and NSTEMI) increased as the NAFLD grade increased (69.2%, 75% and 80.5% for grade 1,2 and 3 NAFLD, respectively), however the differences were not statistically significant (p=0.721). Similarly, NFS was assessed in relation to ACS sub types but showed no significant correlation (p=0.232). This indicates that NAFLD grade and NFS do not reflect or predict the subtype of ACS in this group of patients. In fact, to the best of authors knowledge, studies investigating the relation of ACS sub types to the grades of NAFLD and NFS are lacking in the literature. Further studies with a larger population are needed to confirm these results.

Several studies had established a positive correlation between the presence of NAFLD and severity of CAD. Arslan U et al., found that the presence of NAFLD was significantly associated with MVD [31]. Even though MVD was the most common angiographic characteristic (36.5%) in the study population, the authors did not observe any correlation between the angiographic severity of CAD and NAFLD grades (p=0.822). This result signifies that the sonographic grade of NAFLD in young ACS patients does not predict the angiographic severity of CAD. However, this association between angiographic severity of CAD and the grades of NAFLD in ACS patients of general age group is proven in literature. Most of the studies used Gensini score as an assessment tool for the severity of CAD. Açıkel M et al., reported a higher means of Gensini score in grades 2-3 NAFLD compared to grade 1 (mean age 58.7±10.9) (p=0.007) [32]. Indistinguishably, Majumder B et al., stated that modified Gensini score was significantly higher in grade 2-3 NAFLD groups compared to grade 0 or 1 NAFLD [30]. The discrepancy between the current data and the previous studies is principally ascribed to the young age of present study populations, and the difference in CAD severity assessment method. Compared to elderly population, younger patients are proven to have a higher likelihood of SVD and non obstructive CAD (<50% coronary luminal stenosis) than MVD and obstructive coronaries [33]. Hence, the ageing process is one of the main determinants of CAD severity.

The NFS was tested in relation to ACS subtypes and angiographic severity of the coronary vessels and showed no significant difference (p=0.232) and (p=0.445), respectively. The authors also found no significant correlation between NFS and SYNTAX score (r=0.029, p=0.839). Madan SA et al., assessed the association of NFS with the angiographic severity of CAD in patients who underwent elective coronary angiogram [34]. Their data revealed that high NFS was a predictor of MVD. The contradicting result can be explained by the difference in the patient's age group as well

as the methodology. Currently, there is lack of studies assessing the association between NFS and angiographic severity of CAD in young ACS patients.

In a study by Ağaç MT et al.,it was shown that NAFLD group was associated with significantly higher SYNTAX score as compared to non NAFLD individuals [9]. Keskin M et al., evaluated the complexity of CAD between NAFLD grades in patients with STEMI using SYNTAX score. Their study population mean age was 59±12 years.They indicated that SYNTX score was significantly increased with higher grades of NAFLD [15]. In the current study, there was no significant difference in SYNTX score among NAFLD sonographic grades, with mean score of 16, 15.5 and 16 in grade 1, grade 2, and grade 3 NAFLD, respectively (p=0.982). This contrast in results is probably explained by the young patients age in present study, in addition to the relatively small number of patients with significant coronary artery stenosis (MVD and SVD) (n=52).

The SYNTAX score was evaluated in relation to NFS, and showed no association (r=0.029, p=0.839). This result is chiefly attributable to the young patient's age and lower prevalence of advanced fibrosis in our young ACS study population. Moreover, the median SYNTAX score of the study patients was 16, which is considered low SYNTAX score. Further studies are needed to assess and identify lower thresholds for these scores to be used as risk stratification methods in young patients.

The strength of this study is attributed to the fact that it is the first study to evaluate the association between the severities of NAFLD and CAD in young ACS patients. Although no similar study of NAFLD specifically done in young ACS patients previously, it might be interesting for the previous, studies to explore this relationship in their young ACS cohort [9,15].

Limitation(s)

Limitations of this study was the difficulty of finding a large cohort of ACS population of this young age group, as young ACS occurrence is not as common as in older population. Therefore, our negative finding of association between severity of NAFLD and severity of CAD in young ACS patients might be contributed by the relatively small sample size. However, the authors believe this study will provides some foundation for further studies to be done. As NAFLD is highly prevalent in individuals aged ≤45 years with ACS, it is worth to explore the prevalence of subclinical atherosclerosis in younger patient with NAFLD and without apparent cardiovascular disease.

CONCLUSION(S)

The NAFLD is highly prevalent in young ACS patients.This definitely will have major public health implication. However, there is no association between NAFLD and CAD severity in young ACS patients. While this could be attributed to the relatively small sample size, there is a possibility of different pathophysiology of young and older ACS, which merit further studies to be conducted.

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