Study of non-alcoholic fatty liver disease (NAFLD) by shear-wave elastoraphy in subjects with metabolic syndrome

Abstract:

Background: Non-alcoholic fatty liver disease (NAFLD) is well known to have a strong association with metabolic syndrome. The degree of liver fibrosis is related to the clinical course and prognosis. Shear-wave elastography (SWE) provides a precise non-invasive staging of the degree of liver fibrosis in NAFLD. **Aims and objectives:** To study Non-alcoholic fatty liver disease (NAFLD) by Shear-Wave Elastography (SWE) in subjects with metabolic syndrome (MetS). **Material and methods:** This was a single centre, retrospective, comparative study done on patients with MetS in 100 in a tertiary care hospital over period of 18 months from October 2019 to March 2021**.** Enrolled patients underwent conventional ultrasonography (USG), point SWE (pSWE), fasting blood sugar, post-prandial blood sugar, glycosylated HbA1c, lipid profile, LFTs. Appropriate statistical tests were applied using SPSS v21 for analysis and p-value<0.05 was considered statistically significant. **Results:** Mean age was 55.8 (SD±15.34). Majority belonged to age group 51-65 years (33%). Grade 3 fatty liver (steatosis) on USG had 3.39 times independently (OR:3.39,p=0.043) more chance of having significant fibrosis or cirrhosis(F3-F4) by SWE over those who do not have fatty liver (steatosis) on USG. Those with 4 components of MetS had 6 times (OR:6.04,p=0.003) and those with 5 components had 13.7 (OR:13.768,p=0.001) times more chance of having significant fibrosis or cirrhosis(F3-F4) by SWE over those who have 3 components independently. **Conclusion:** Increasing number of components of MetS and steatosis (fatty liver grade) on USG were independently associated with higher grades of fibrosis by SWE.

Keywords: Metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), shear-wave elastography (SWE), diabetes mellitus, hypertension, waist circumference, HbA1c

Introduction:

Non-alcoholic fatty liver disease (NAFLD) is known to be a major cause of liver disease worldwide.[1] It is a well-known fact that the degree of fibrosis is one of the most important parameters for the clinical course and prognosis in NAFLD.[2] In patients with mild lobular inflammation or fibrosis (irrespective of the severity) tend to have an increased risk of developing non-alcoholic steatohepatitis (NASH) compared to those patients with exclusive steatosis. A significant proportion of patients with NAFLD can develop fibrosing NASH in about 5-20 %. This is noticed in situations when metabolic factors continue to deteriorate.[3] metabolic syndrome is a strong risk factor for non-alcoholic fatty liver disease. Moreover when there is a disease of non-alcoholic fatty liver along with the metabolic syndrome,it is rare that the disease will be regressing.[4] Liver biopsy still remains to be the gold standard in the diagnosis of NAFLD and identifying NASH. The invasiveness of the procedure comes along with risks to the patient such as bleeding, injuries to other organs, vascular structures, and complications of anaesthesia.[5] Conventional ultrasonography (USG) identifies the third phase of liver cirrhosis quite accurately however fails to detect the second phase.[6] In case of advanced fibrosis and cirrhosis specifically, Point shear-wave elastography (pSWE) has proved to be a promising technique.[7]

Aim and objectives: To study Non-alcoholic fatty liver disease (NAFLD) by Shear-Wave Elastography in subjects with metabolic syndrome**.**

Material and methods: This study was conducted in KIMS Hospital, Medicine department over period of 18 months. *For the present research* 100 patients were observed. Research Duration is from October 2019 to March 2021 and the IEC approval had also taken(IEC protocol number: 216/2019-2020). *Inclusion criteria:* Patients with metabolic syndrome and above the age of 18 years. The patient with a history of alcohol consumption exceeding 40 grams/week in males and 20 grams/week in females, patients who are pregnant, on medications known to cause fatty liver disease (tamoxifen, corticosteroids, amiodarone, methotrexate and sodium valproate) were excluded from this study. Parameters included were- conventional ultrasonography of the liver (USG), point shear-wave elastography (pSWE), fasting blood sugar, post-prandial blood sugar, glycosylated HbA1c, lipid profile, liver function tests (LFTs). The presence of fatty liver was assessed using the conventional Ultrasonography. There is an application of Automatic median value which got generated by the ultrasound software. It established the elastography grade which can be given as follows < 4.6 = F0, 4.6-5.6 = F1, 5.7-7.0 = F2, 7.1-12.0 = F3 and > 12 = F4.[8] We aim find the relation of metabolic syndrome and its components with non-alcoholic liver disease (NAFLD) by use of shear-wave elastography.

Results: A total of 100 subjects were taken in the study and it was observed that population 11(11%), 30 (30%), 33 (33%) and 26 (26%) of the subjects were in the age group 18-35 years, 36-55 years, 51-65 years and 66 and above years in age respectively, majority lying in the age group of 51-65 years amongst which 68 (68%) and 32 (32%) of the subjects were males and females respectively. In the study population it has been found that 0%, 16%, 38% and 46% of the subjects had a body mass index (BMI)(kg/m^2) of <18.5 (Underweight), 18.5 – 24.99 (Normal), 25 – 29.99 (Overweight) and 30 & above (Obese) respectively, obese being the majority and no subjects who were underweight. In the study population 13%, 10%, 41%, 11% and 25% of the subjects had a grade of F0, F1, F2, F3 and F4 on shear wave elastography respectively. 51%, 19%,14% and 16% of the subjects had a grade of no fatty liver, grade 1 fatty liver, grade 2 fatty liver and grade 3 fatty liver on ultrasonography respectively. 23%, 51% and 26%of the subjects had NAFLD fibrosis score of < - 1.455 (No fibrosis), NAFLD fibrosis score of -1.455 – 0.67 (Indeterminate fibrosis) and NAFLD fibrosis score of >0.67 (Fibrosis) respectively. Here the mean age was 55.8 (SD±15.34),

mean systolic blood pressure (SBP) was 150.15 (SD±21.65), mean diastolic blood pressure was 91.64 (SD±11.93) and fasting blood sugar (FBS) was 160.72 (SD±54.96). The mean post-prandial blood sugar (PPBS) was 235.03 (SD±89.31), mean glycosylated haemoglobin (HbA1c) was 7.06 (SD±1.72), mean total cholesterol was 154.87 (SD±46.67) and mean triglycerides was 152.56 (SD±62.38). The mean high-density lipoprotein (HDL) was 35.44 (SD±12.64), mean waist circumference was 102.44 (SD±10.68), mean body mass index (BMI) was 29.85 (SD±4.65), mean fatty liver grade on ultrasonography was 0.81 (SD±0.92), mean Shear wave elastography stiffness was 9.31 (SD±4.55) and mean NAFLD Fibrosis score was -0.46 (SD±1.83). [**Table 1**]

Table 1: The mean and standard deviation of numerical variable in metabolic syndrome patients

Parameter	Mean	± SD
Age	55.8	15.34
Systolic blood pressure (SBP)	150.15	21.65
Diastolic blood pressure (DBP)	91.64	11.93
Fasting blood sugar (FBS)	160.72	54.96
Post-prandial blood sugar (PPBS)	235.03	89.31
Glycosylated Hb (HbA1c)	7.06	1.72
Total cholesterol (CHO)	154.87	46.67
Triglycerides (TRG)	152.56	62.38
High density lipoprotein (HDL)	35.44	12.64
Body mass index (BMI)	29.85	4.65
Waist circumference (WC)	102.44	10.68
Fatty liver grade on ultrasonography (FL-USG)	0.81	0.92
Shear wave elastography stiffness (SWE)	9.31	4.55
NAFLD Fibrosis score (NFS)	-0.46	1.83

Here out of the 10 subjects who had elasticity <4.6kPa (F0, no fibrosis) 10 (100.0%) subjects had 3 components of MetS, none had 4 components of MetS and none had 5 components of MetS. Out of the 41 subjects who had elasticity 4.6-5.6kPa (F1, Mild fibrosis), 18 (43.9%) subjects had 3 components of MetS, 18 (43.9%) subjects had 4 components of MetS and 5 (12.2%) subjects had 5 components of MetS. Out of the 11 subjects who had elasticity 5.7-7.0kPa (F2, Severe fibrosis), 3 (27.3%) subjects had 3 components of MetS, 8 (72.7%) subjects had 4 components of MetS and none had 5 components of MetS. Out of the 25 subjects who had elasticity 7.1-12.0kPa (F3, Significant fibrosis), 4 (16.0%) subjects had 3 components of MetS, 11 (44.0%) subjects had 4 components of MetS and 10 (40.0%) subjects had 5 components of MetS. Out of the 13 subjects who had elasticity >12kPa (F4, Cirrhosis), 8 (61.5%) subjects had 3 components of metabolic syndrome (MetS), 4 (30.8%) subjects had 4 components of MetS and 1 (7.7%) subject had 5 components of MetS. [**Table 2**] [**Figure 1**].

Here out of the 51 subjects who had no fatty liver (Grade 0), 30 (58.8%) subjects had 3 components of MetS, 19 (37.3%) subjects had 4 components of MetS and 2 (3.9%) subjects

had 5 components of MetS. Out of the 19 subjects who had grade 1 fatty liver, 13 (68.4%) subjects had 3 components of MetS, 6 (31.6%) subjects had 4 components of MetS and none had 5 components of MetS. Out of the 14 subjects who had grade 2 fatty liver, none had 3 components of MetS, 7 (50.0%) subjects had 4 components of MetS and 7 (50.0%) subjects had 5 components of MetS. Out of the 16 subjects who had grade 3 fatty liver, none had 3 components of MetS, 9 (56.3%) subjects had 4 components of MetS and 7 (43.8%) subjects had 5 components of MetS. [**Table 2**] [**Figure 2**]

It was observed that out of the 23 subjects who had fibrosis score < - 1.455 (No fibrosis), 15 (65.2%) subjects had 3 components of MetS, 6 (26.1%) subjects had 4 components of MetS and 2 (8.7%) subjects had 5 components of MetS. Out of the 51 subjects who had fibrosis score -1.455 – 0.67 (Indeterminate fibrosis), 16 (31.4%) subjects had 3 components of MetS, 27 (52.9%) subjects had 4 components of MetS and 8 (15.7%) subjects had 5 components of MetS. Out of the 26 subjects who had fibrosis score >0.67 (Fibrosis), 12 (46.2%) subjects had 3 components of MetS, 8(30.8%) subjects had 4 components of MetS and 6 (23.1%) subjects had 5 components of MetS. [**Table 2**] [**Figure 3**]

Table 2: The association between fatty liver on ultrasonography, fibrosis on shear wave elastography and NAFLD fibrosis score and components of MetS scoring in study group.

		Number of MetS components				Sign. (Spearman rank correl.)
Modality	Parameter	3	4	5	Total	
NAFLD on SWE	<4.6kPa (F0, No fibrosis)	10 (100.0%)	0	0	10 (10%)	*r=0.447; p<0.001*
	4.6-5.6kPa (F1, Mild fibrosis)	18 (43.9%)	18 (43.9%)	5 (12.2%)	41 (41%)	
	5.7-7.0kPa (F2, Severe fibrosis)	3 (27.3%)	8 (72.7%)	0	11 (11%)	
	7.1-12.0kPa (F3, Significant fibrosis)	4 (16.0%)	11 (44.0%)	10 (40.0%)	25 (25%)	
	>12kPa (F4, Cirrhosis)	8 (61.5%)	4 (30.8%)	1 (7.7%)	13 (13%)	
NAFLD on conventional USG	No fatty liver	30 (58.8%)	19 (37.3%)	2 (3.9%)	51 (51%)	*r=0.529; p<0.001*
	Grade 1 fatty liver	13 (68.4%)	6 (31.6%)	0	19 (19%)	
	Grade 2 fatty liver	0	7 (50.0%)	7 (50.0%)	14 (14%)	
	Grade 3 fatty liver	0	9 (56.3%)	7 (43.8%)	16 (16%)	
NAFLD-fibrosis score	< - 1.455 (No fibrosis)[F0-2]	15 (65.2%)	6 (26.1%)	2 (8.7%)	23 (23%)	*r=0.148; p=0.141*
	-1.455 – 0.67 (Indeterminate fibrosis)	16 (31.4%)	27 (52.9%)	8 (15.7%)	51 (51%)	
	>0.67 (Fibrosis)[F3-4]	12 (46.2%)	8 (30.8%)	6 (23.1%)	26 (26%)	

Figure 1: Association between Liver fibrosis grade by SWE and components of MetS in study group

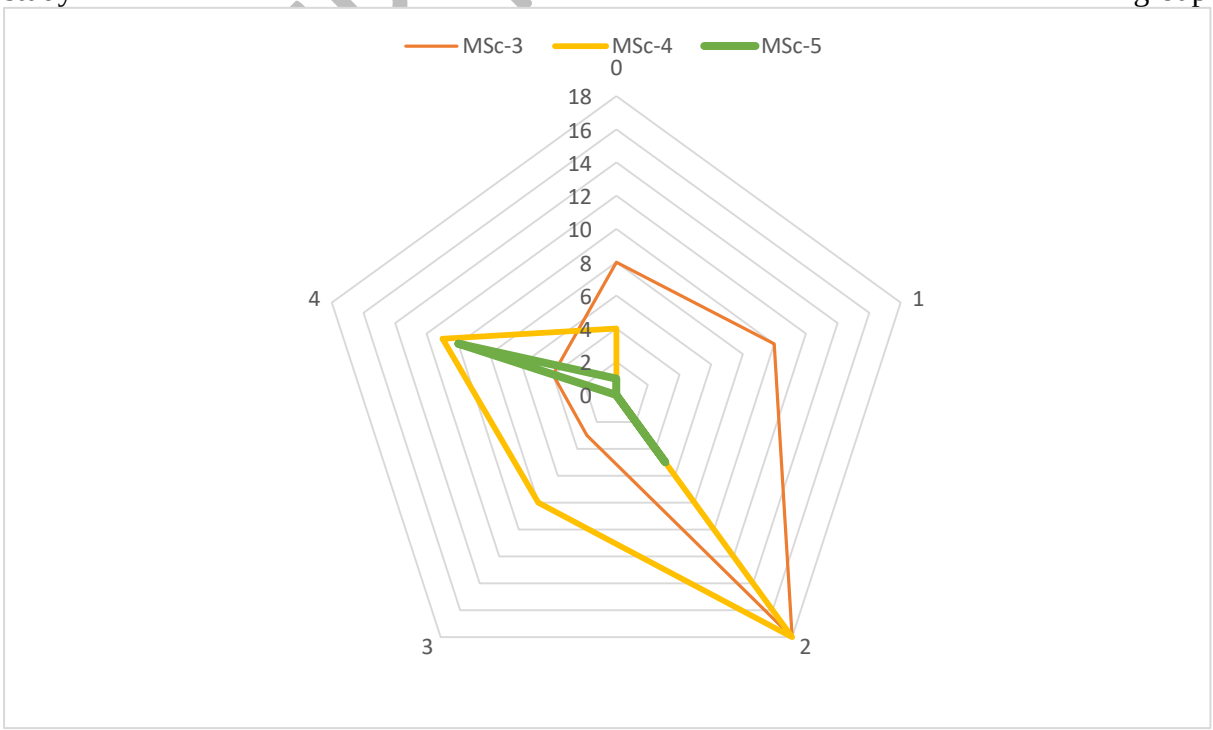


Figure 2: Association between NAFLD on conventional USG and components of MetS scoring in study group

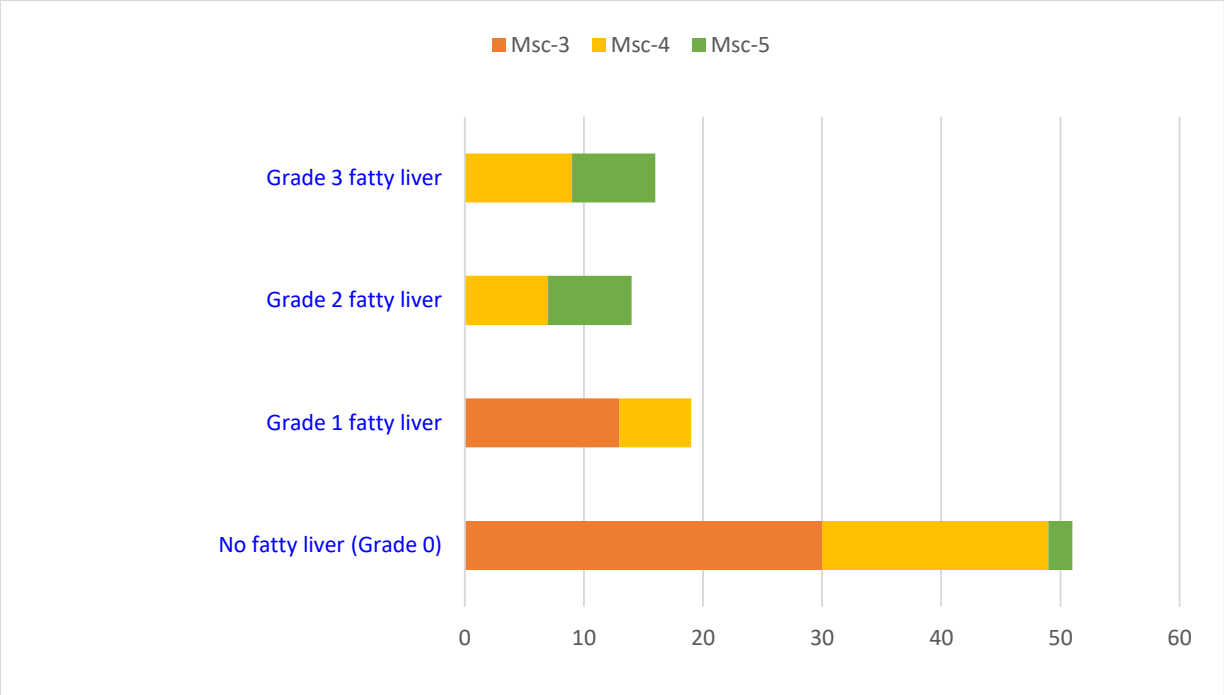
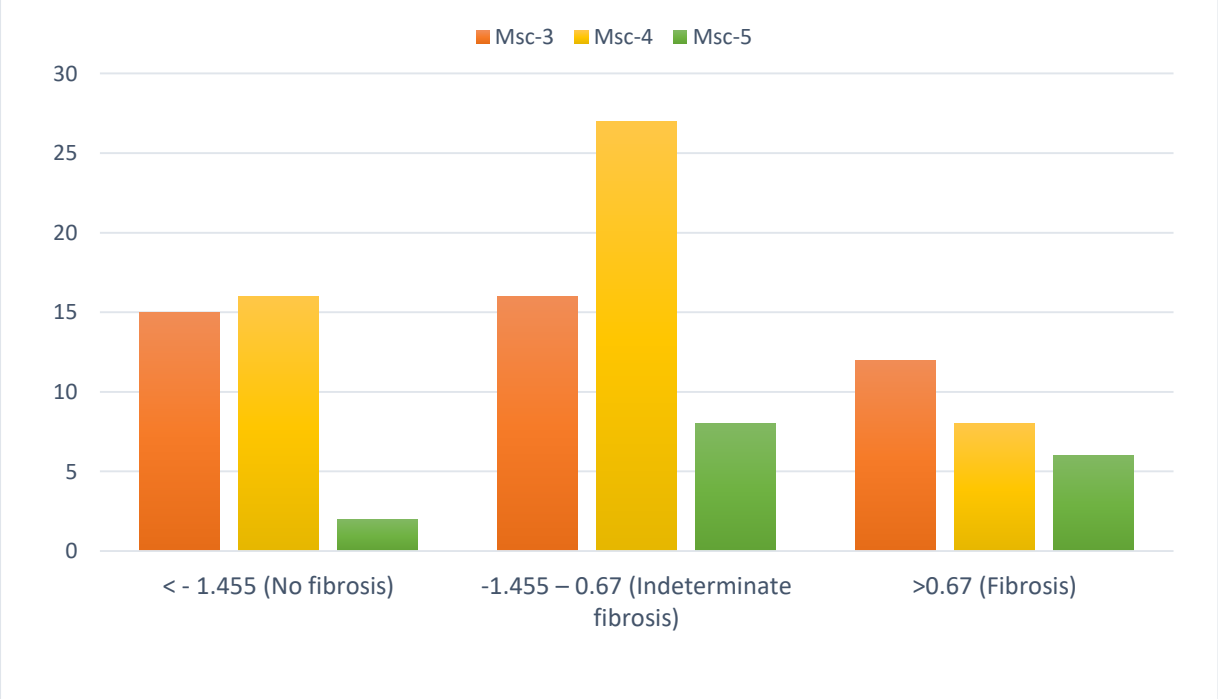


Figure 3: Association between NAFLD-fibrosis scoring and components of MetS scoring in study group



Discussion:

In the present study, the majority of the were in the age group of 51-65 years (33 %) followed by 36-50 years (30%) with the mean age of 55.80 (SD ± 15.347). The distribution according to the gender showed that majority of subjects were males 68 (68%) and females were 32 (32%). The findings were similar to other studies such as *Krishnamoorthy Y et al* (2020, n=133,926) where the major age group was 50-59 years at 50%, however, the gender

distribution was different with females having a higher prevalence at 63.6% in comparison to 36.4 % in males.[9] However in contrast to the findings in this study population *Kuk J et al* reported the majority population in an older age group of >65 years with the majority (54.2%) being females and the remaining (45.8%) as males.[10] Studies like *Vishram et al* reported the majority age to lie in the age group of 60-78 years (37.6%) with majority being males (56%) and the remaining as females (44%) similar to the present study.[11] The variation amongst various studies can be attributed to the regional, cultural and ethnic differences in the study population taken in the studies. In the present study it was noted that majority of the population had a body mass index (BMI) of 30 kg/m^2 and above (obese) (46%) followed a BMI of 25 – 29.99 kg/m^2 (38%) (Overweight) and minority of the population had a BMI less than 25 (16%). The findings were similar to studies such as *He Y et al* reported similar findings where a majority of the subjects had a body mass index 24.0–27.9 kg/m^2 (49.68%) followed by ≥28.0 kg/m^2 (30.89%) and a minority of those with a body mass index between 18.6–23.9 kg/m^2 (19.4%).[12] *Meigs et al* reported majority of those with metabolic syndrome (MetS) had a body mass index 30kg/m^2 or above (50%) and only 9.3% of them had a body mass index under 25kg/m^2.[13] *Ärnlöv J et al* reported a majority of the population was overweight (49.01%) followed by those who were obese (25.8%).[14] *Marchesini et al* reported that the presence of the MetS had increased with the increasing body mass index, from 18% in those with normal-weight to 67% in obesity.[15] *Lizardi-Cervera J et al* reported that overweight was present in 46.79% and obesity in 36.49% of subjects.[16] *Uchil D et al* reported that in the NAFLD group normal body mass index (BMI) was present in only 20% of the subjects whereas 52.8% were overweight and 24.8% were found to be obese. The variation amongst various studies can be attributed to the regional, cultural and ethnic differences in the study population taken in the studies.[17] [**Table 3**]

Table 3: Comparison of body Mass Index wise distribution of subjects in study group with other similar studies

Author	Type of study	Sample size (n)	BMI		
			Under 25.0 (normal)	25.0-29.9 (over-weight)	30 and above (obesity)
Present study	Cross-sectional	100	16 (16%)	38 (38%)	46 (46%)
Meigs et al	Prospective cohort	804	75 (9.3%)	327 (40.6%)	402 (50%)
Ärnlöv J et al	Retrospective cohort	255	64 (25.09%)	125 (49.01%)	66 (25.8%)
He Y et al	Cross-sectional	1,256	244 (19.4%)	624 (49.68%)	388 (30.89%)
Marchesini et al	Cross-sectional	78	14 (18%)	12 (15%)	52 (67%)
Lizardi-Cervera J et al	Cross-sectional	359	60 (16.72%)	168 (46.79%)	131 (36.49%)
Uchil D et al	Cross-sectional	106	21 (20%)	56 (52.8%)	29 (24.8%)

In the present study, it was noted that, majority of those with non-alcoholic fatty liver disease (NAFLD) had 4 components (44.89%) of MetS and the minority were those with 3 components (26.5%). It was also observed that there is a significant correlation with increased grade of fatty liver with the number of MetS components *($r = 0.529$ (Spearman's rho); $p<0.001$)* these findings were similar to the study by *Jinjuvadia R et al* found that the presence of NAFLD on conventional ultrasonography among subjects with MetS increased with the number of metabolic abnormalities (37%, 49% and 67% for those with 3, 4, and 5 components respectively.[18] *Jinjuvadia R et al* also reported that prevalence of NAFLD and the presence of advanced fibrosis according to NAFLD fibrosis score increased substantially

with the increase in the number of metabolic abnormalities. The findings were also similar to a study by *Petrović G et al* reported that there was the association between the MetS components and the ultrasonography degree of fatty liver infiltration. In those patients with ultrasonography finding of fatty liver grade 2 and 3, there were significantly higher number of patients with either four or five MetS components.[19] *PK Agrawal et al* reported that majority had 3 components (67.9%) of MetS and the minority were those with 5 components (5.6%).[20] [**Table 4**] Similar findings were observed in a study by *Paudel et al* reported that at least one component of MetS was present in 352 (91.4%) subjects and that five components of MetS were found in 41 (10.64%) subjects suggesting an association between MetS components and NAFLD on conventional ultrasonography.[21] Similar findings were observed by *Shen HS et al* reported that MetS (yes Vs no, OR 1.53, 95% CI 1.08–2.17) was significantly related to mild severity of NAFLD. MetS (1–2 metabolic factors Vs none, OR 4.36, 95% CI 1.75–10.84; ≥3 metabolic factors Vs none, OR 14.84, 95% CI 5.96–36.93) were significantly associated to moderate severity NAFLD.[22]

Table 4: Association between NAFLD on conventional USG and components of MetS scoring

Study	**Type of study**	**Grade of fatty liver (FL)**	**Components of MetS**			
			3	**4**	**5**	**Total**
Present study (n=100)	Cross-sectional	Grade 1	13 (68.4%)	6 (31.6%)	0	19 (19%)
		Grade 2	0	7 (50.0%)	7 (50.0%)	14 (14%)
		Grade 3	0	9 (56.3%)	7 (43.8%)	16 (16%)
		Total	13 (26.5%)	22 (44.89%)	14 (28.57%)	49
PK Agrawal et al (n=53)	Cross-sectional	FL present	36 (67.9%)	14 (26.4%)	3 (5.6%)	53
Jinjuvadia R et al (n=2817)	Cohort study	FL present	37.3% with MetS-3 had Fatty Liver	48.5% with MetS-4 had Fatty Liver	67.3% with MetS-5 had Fatty Liver	
Petrović G et al (n=48)	Cross-sectional	Grade 1	3	1	2	6 (12.5%)
		Grade 2	6	9	5	20 (41.6%)
		Grade 3	7	6	9	22 (45.8%)
		Total	16 (33.3%)	16 (33.3%)	16 (33.3%)	48

In the present study we compared the association between NAFLD-fibrosis scoring and components of MetS scoring in study group to a similar study by *Jinjuvadia R et al.*[18] and divided No fibrosis (< - 1.455), Indeterminate fibrosis (-1.455 – 0.67) and Fibrosis (>0.67). The results were as follows: [**Table 5**]

Table 5: Comparison of association between NAFLD-fibrosis scoring and components of MetS scoring

NAFLD fibrosis score	Number of components of MetS							
	Present study				*Jinjuvadia R et al*			
	3	4	5	Total	3	4	5	Total
No fibrosis	15 (65.2%)	6 (26.1%)	2 (8.7%)	23 (23%)	195 (56.5%)	125 (36.2)	25 (7.2%)	345 (42.9%)
Indeterminate fibrosis	16 (31.4%)	27 (52.9%)	8 (15.7%)	51 (51%)	153 (41.4%)	141 (38.21%)	75 (20.3%)	369 (45.8%)
Fibrosis	12 (46.2%)	8 (30.8%)	6 (23.1%)	26 (26%)	25 (27.7%)	21 (23.3%)	44 (48.8%)	90 (11.1%)
Total	43	41	16	100	373	287	144	804

Positive correlation was observed between the NAFLD fibrosis score and the number of components of MetS *(r= 0.148 (Spearman's rho); p=0.141)*, however this correlation was not statistically significant. Positive correlation was observed between NAFLD on conventional USG and liver fibrosis by SWE amongst those with MetS *(r= 0.248 (Spearman's rho); p=0.013)* in subjects with MetS which was statistically significant. These findings were similar to the study by *Koc et al* who reported that the presence of liver steatosis (mild or moderate-severe), waist circumference and hypertension were independent predictors of the liver fibrosis. Presence of mild or moderate-severe liver steatosis, hypertension, waist circumference (each 1-cm increment) were associated with a 2.78-fold, 7.16 times greater likelihood of liver fibrosis, respectively.[23] In contrast to the present study, in a study done by *Suh CH et al*, it was observed that hepatic steatosis which has been suggested to influence ultrasound elastography measurements, demonstrated negligible effects on the normal reference range of liver elasticity, however it must be noted that this study was not done specifically on those subjects with MetS.[24] Binomial logistic regression analysis was performed with the two possible outcomes based on the grade by SWE as those having F0-F2(no, mild and severe fibrosis) and those having F3-F4(significant fibrosis and cirrhosis). After adjusting for age and gender, grade 3 fatty liver (steatosis) on ultrasonography had 3.39 times more chance of having significant fibrosis or cirrhosis(F3-F4) by SWE over those who do not have fatty liver (steatosis) on USG independently (OR: 3.39, 95% C.I.: 1.03–11.09, p = 0.043). Significant associations could not be appreciated with lower grades of fatty liver. After adjusting for age, gender and of fatty liver (steatosis) on USG, those with 4 components of MetS had 6 times (OR: 6.04, 95% C.I.: 1,86–19.58, p = 0.003) and those with 5 components of MetS had 13.7 (OR: 13.768, 95% C.I.: 2.86–66.28, p = 0.001) times more chance of having significant fibrosis or cirrhosis(F3-F4) by SWE over those who have 3 components of MetS independently. The findings of present study were found to be similar to a study by *Mohan V et al* which stated that after adjusting for gender, age and waist circumference, NAFLD was found to be associated with MetS (OR: 2.0, 95% C.I.: 1.3–3.1, p < 0.001).[25] Similarly, *McPherson S et al* quoted that blood glucose was found to be an independent variable of severe fibrosis and advanced NAFLD status.[26] *Keshani P et al* conducted a cohort study on those having NAFLD and they quoted that changes in waist-circumference, fasting blood sugar, triglycerides and low-density lipoprotein were significantly lower in regressed than that of progressed groups which show a strong association between the NAFLD with imaging evidence and components of MetS.[27] *Marchesini et al* quoted that in particular, metabolic syndrome was associated with high risk of severe fibrosis of the liver.[15]

Conclusion:

Metabolic syndrome (MetS) continues to have an association with non-alcoholic fatty liver disease (NAFLD) and its complications. Shear-wave elastography (SWE) has been established as a reliable tool to assess the level of fibrosis. In the present study we evaluated the association between fibrosis by SWE and various factors such as components of MetS, steatosis on ultrasonography (USG), NAFLD fibrosis score and other routine laboratory parameters. Greater number of components of MetS were present in subjects with higher grades of fibrosis in comparison to those with lower grades of fibrosis by SWE even after adjusting for age, gender and steatosis on USG. Greater number of components of MetS were present in subjects with higher grades of steatosis on USG. Also, fibrosis by SWE had a positive correlation with serum triglycerides.

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