Research

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Decoding PNPLA3: Genetic Drivers Of Quality Of Life In Metabolic Associated Fatty Liver Disease Subjects Patients

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1. Abstract

1.1. Objective: To evaluate the association between PNPLA3 polymorphisms (rs738408 and rs738409) and quality of life, measured by SF 36, in patients with metabolic dysfunction associated fatty liver disease (MAFLD).

1.2. Methodology: A cross sectional study was conducted at Aziz Fatimah Hospital with collaboration of Universiti Sains Malaysia, Malaysia between 2022- 2024.Total 158 subjects, 81 MAFLD patients and 77 healthy controls were enrolled by convenient sampling technique following the inclusion and exclusion criteria. DNA was extracted using 5mL of blood followed by genotyping of PNPLA3 variants using PCR. Sanger sequence was used to confirm the single nucleotide polymorphism. Quality of life was assessed using SF-36 form. Physical and mental component summary scores derived from physical and mental component of SF36 questionnaire were compared among MAFLD and control groups. Quality of life categorized as poor and good based of MCS scores (cut off point at 50) were compared across CC, CT/CG, and TT/GG genotypes in control and MAFLD groups.

1.3. Results: PCS scores were less than 50 in MAFLD patients and Control subjects indicating poor quality of life in both groups. However, these scores were statistically significantly lower in the MAFLD subjects than control (P<0.001). Concerning MCS scores, MAFLD group has significantly less MCS scores than control group (P<0.001).

Based on MCS scores, good quality of life was noticed among majority of CC carriers of rs 738408 and rs 738409. CT/TT and CG/GG genotypes showed higher representation among poor quality of life, indicating a gradient effect of risk genotypes on quality of life.

1.4. Conclusion: MAFLD subjects showed poorer quality of life than controls.

CC carriers of PNPLA3 rs738408 and rs738409 had better quality of life, while CT and TT genotypes had poorer quality of life.

2. Keywords: PNPLA3, rs738408, rs738409, MAFLD, SF 36, MCS, quality of life.

3. Introduction

Metabolic dysfunction associated fatty liver disease (MAFLD) has recently replaced the term non alcoholic fatty liver disease (NAFLD) to better reflect its close association with metabolic syndrome and related comorbidities. [1] It is now recognized as the most prevalent chronic liver disease globally, affecting nearly one quarter of the adult popu-lation. [1] This redefinition underscores the metabolic drivers of hepatic steatosis, including obesity, insulin resistance, dyslipidemia, and hypertension, and highlights its systemic impact beyond the liver. Importantly, MAFLD is not only a hepatic disorder but also a major contributor to cardiovascular morbidity, diabetes, and impaired health related quality of life (HRQoL). [2]

Genetic predisposition plays a crucial role in the susceptibility and progression of MAFLD. Among the identified genetic variants, patatin like phospholipase domain containing 3 (PNPLA3 I148M),) polymorphisms, particularly rs738408 (C>G) and rs738409 have been consistently associated with hepatic fat accumulation, inflammation, and fibrosis. [3] These variants impair triglyceride hydrolysis, leading to lipid retention within hepatocytes and acceler-ating disease progression. Recent evidence suggests that carriers of risk alleles not only demonstrate more severe hepatic injury but also experience greater impairment in HRQoL, reflecting the broader impact of genetic suscepti-bility on patient well being. [4]

HRQoL assessment has become an essential dimension in the management of chronic liver disease. Beyond bio-chemical and histological markers, HRQoL provides a patient centered measure of disease burden, encompassing physical, psychological, and social domains. Studies have shown that MAFLD patients with

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PNPLA3 risk alleles report poorer HRQoL scores, particularly in domains related to fatigue, emotional well being, and social function-ing. [5] This dual impact accelerated hepatic injury and diminished quality of life underscores the importance of inte-grating genetic and patient reported outcomes in clinical practice.

In Pakistan, where metabolic disorders are rapidly increasing, the exploration of PNPLA3 variants in relation to MAFLD progression has gained momentum. A recent study conducted in Punjab Pakistan, demonstrated that rs738408 and rs738409 polymorphisms are significant predictors of MAFLD severity, underscoring their relevance in local populations. [6] However, limited data exist on how these variants influence HRQoL outcomes, particularly in South Asian cohorts, where cultural, dietary, and socioeconomic factors may further modulate disease expression.

The rationale for the present study lies in bridging this critical knowledge gap. While genetic associations with dis-ease progression are well documented, their correlation with HRQoL impairment remains underexplored. Under-standing this relationship is essential for holistic patient care, as it integrates molecular insights with patient centered outcomes. Moreover, identifying genetic determinants of HRQoL impairment may pave the way for precision med-icine approaches, ensuring that therapeutic strategies address not only hepatic pathology but also the lived experi-ences of patients. Hence, our aim is to evaluate the association between PNPLA3 polymorphisms (rs738408 and rs738409) and quality of life, measured by SF-36, in patients with metabolic

4. Methodology

This cross-sectional study, conducted after obtaining ethical approval from Universiti Sains Malaysia (USM/JEPeM/21090631) and the Institutional Ethics Committee of Aziz Fatimah Medical and Dental College, Faisalabad (Ref. No: IEC/122-21), recruited 81 patients diagnosed with metabolic dysfunction-associated fatty liver disease (MAFLD) and 77 healthy controls from Aziz Fatimah Hospital, Faisalabad, Pakistan, between 2022 and 2024. Participants were selected via non-probability purposive sampling based on predefined inclusion and exclusion criteria.

4.1. Inclusion criteria: Inclusion criteria encompassed patients aged ≥18 years with confirmed MAFLD upon the presence of two or more of these conditions: (1) Waist circumference >95th percentile for age and gender, (2) Blood pressure >95th for age, gender, and height. Triglycerides >150 mg/dL, (4) HDL < 40 mg/dl, (5) C-reactive protein (CRP) levels>2 mg/L. All non-diabetic subjects determined by blood glucose level ≤ 126 mg/dL, age-matched normotensive and healthy non-diabetic normal weight individuals without fatty liver as subjects in control groups. [7] And who provided written informed consent for participation, genetic testing, and quality of life assessment were enrolled in the study

4.2. Exclusion criteria: exclusion criteria ruled out significant alcohol intake, viral hepatitis (HBV or HCV), auto-immune liver disease, drug-induced liver injury, pregnancy, malignancy, and chronic systemic or psychiatric illness-es that could independently affect health-related quality of life.

4.3. Research design: A cross-sectional design with convenience sampling method was used due to its feasibility in hospital setting. Although, this design limits the causal inference and sampling method may introduce selection bias and limit the generalizability of findings to other populations, this study provides valuable baseline into dietary pat-terns and glycemic control among patients in real world clinical context and provide insights to guide future longitu-dinal research.

This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cross-sectional studies. [8]

4.4. Efforts to Minimize Bias

In order to minimize information bias, validated SF36questionnaire was used with cronbach Alpha 80%. Partici-pants were encouraged to recall what they really experience in their daily routine of life concerning physical and mental well-being to reduce recall bias.

4.5. Sample size calculation: The sample size was calculated using Ps software. Sample size was calculated by PS software. The study was conducted with a predetermined Type I error probability (α) of 5% (0.05) and a statis-tical power of 80% (0.8) across all parameters. Drawing upon prior literature, the estimated mean differences (δ) between the two groups for serum AST, ALT, and TG were 6.0, 9.0, and 45, respectively, with corresponding with-in group standard deviations (σ) of 11.7, 19.11, and 97.94. The allocation ratio between the control and experi-mental groups (m) was fixed at 1:1. The maximum calculated sample size was 75 participants. After adjusting for an anticipated 15% attrition rate, the required sample size per group was increased to 86. Ultimately, following ex-clusions due to drop outs, the final sample comprised 77 participants in the control group and 81 in the MAFLD group, yielding a total study population of 158 individuals. [9]

4.6. Data collection tool

MAFLD was diagnosed using ultrasonography (GE Logiq P7, USA) showing fatty liver alongside metabolic dys-function, such as overweight/obesity, type 2 diabetes mellitus, or other metabolic abnormalities, per international criteria.

Following DNA extraction (Thermo Fisher Scientific, K0722) per the manufacturer's protocol from the participants blood, PNPLA3 SNPs were amplified using forward and reverse primers via conventional PCR, with the expected 333 bp amplicon visualized on agarose gel electrophoresis; Sanger sequencing (Macrogen, Korea) confirmed the genotyping results and identified true SNPs. Health-related quality of life (HRQoL) was assessed using the validated 36-Item Short Form Health Survey (SF-36) questionnaire, with a Cronbach alpha of 80%, ensuring reliability and construct validity across diverse cultural and clinical settings. The SF-36 comprised of eight domain; physical func-tioning,

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role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health.

Scores for each domain were calculated according to standard SF-36 scoring guidelines, with higher scores indicat-ing better perceived health status. Each domain score was transformed to a scale ranging from 0 to 100, with higher scores indicating better health-related quality of life, according to standard SF-36 scoring guidelines. The PCS and MCS scores were calculated using validated algorithms derived from the individual domain scores. PCS was calculated using Physical Functioning (PF; 10 items on limitations in daily activities like walking or self-care), Role-Physical (RP; 4 items on role limitations due to physical health), Bodily Pain (BP; 2 items on pain interference), and General Health (GH; 5 items on perceived health) while MCS included include Vitality (VT; 4 items on energy/fatigue), Social Functioning (SF; 2 items on social activity limits), Role Emotional (RE; 3 items on role limits due to emotions), and Mental Health (MH; 5 items on psychological distress Quality of life was measured in our popu-lation with MCS . pcs was not measure because all the enrolled subjects had cutoff value less than 50 and was not categorized into good and poor Quality of life. [10] Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were derived. HRQoL im-pairment was defined as lower domain and component scores relative to population-based reference values. Partic-ipants with PCS and/or MCS scores below the normative reference mean were categorized as having impaired HRQoL. Lower scores across individual SF-36 domains were interpreted as greater functional limitation and poorer perceived health status.

5. Statistical Analysis

Statistical analysis was carried out using SPSS version 27. Continuous variables were expressed as mean ± stand-ard deviation (SD). Categorical variables such as quality of life (good and poor) were presented as frequencies and percentages among genotypes of rs738408 and rs738409. Comparisons of SF-36 domain mean scores was done with independent sample t-tests among MAFLD and control groups. A p-value <0.05 was considered statistically significant.

6. Results

Baseline Demographic Characteristics

A total of 158 participants were included in the study, comprising 77 individuals in the control group and 81 pa-tients with MAFLD. The median age of participants in the control group was 50.0 years (IQR: 19.5), while the MAFLD group had a median age of 49.0 years (IQR: 11.82). There was no statistically significant difference in age distribution between the two groups (p = 0.554).

Age stratification revealed that the majority of participants in both groups belonged to the 40–49 and 50–59 year age categories. Comparison of age ranges between the control and MAFLD groups showed no statistically signifi-cant difference (p = 0.889).

With respect to gender distribution, males constituted 44.2% of the control group and 43.2% of the MAFLD group, while females accounted for 55.8% and 56.8%, respectively. A statistically significant difference was observed in overall gender distribution between the two groups (p = 0.014). However, when age distribution was analyzed sepa-rately within male and female subgroups, no statistically significant differences were found between controls and MAFLD patients (male: p = 0.66; female: p = 0.19). (Table 1)

Table 1: Demographic parameters of participants (comparison of age and gender between Control group and MAFLD group)

Parameters	Median(IQR)	Control group	MAFLD group	p value
Age (years)	49.5(18.00)	50.00(19.50)a	49.00(11.82) a	0.554 a
Age range (years)	n(f)	(n=77)	(n=81)	
30-39	38(24.1)	17(22.1)	21(25.9)	
40-49 50-59	41(25.9)	20(26.0)	21(25.9)	
60-69	42(26.6)	20(26.0)	22(27.2)	0.889b
70-75	24(15.2)	12(15.6)	12(14.8)	
	13(8.2)	8(10.4)	5(6.2)	
Gender				
Male	69(43.7)	34(44.2)	35(43.2)	0.014 b
Female	89(56.3)	43(55.8)	46(56.8)	0.101
Age range based on gender				
MALE (years)		MALE n=34	MALE n=35	
30-39	17(24.6)	9(26.4)	8(22.8)	
40-49	14(20.3)	8(23.5)	6(17.1)	
50-59	20(29.0)	9(26.4)	11(31.4)	0.66 b
60-69	13(18.8)	7(38.2)	6(17.1)	
70-75	5(7.2)	1(2.94)	4(11.4)	
FEMALE (years)		FEMALE n=43	FEMALE n=46	
30-39	21(23.6)	8(18.6)	13(28.2)	
40-49	27(30.3)	12(27.9)	15(32.6)	
50-59	22(24.7)	11(25.5)	11(23.9)	
60-69	11(12.4)	5(11.6)	6(13.0)	0.19 b
70-75	8(9.0)	7(16.2)	1(2.17)	

Age in years is presented as median (interquartile range) aMann-Whitney U test; Data for age range and gender are presented as frequency (%); b Chi-square, p value ≤0.05 was taken as statistically significant

Analysis of the SF-36 questionnaire in the overall study population (n = 158) demonstrated reduced scores across several health domains. The lowest mean score was observed for physical functioning (38.07 ± 11.90), followed by role limitation due to

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physical health (44.62 ± 38.52) and role limitation due to emotional health (46.20 ± 37.83). Higher mean scores were noted for social functioning (64.42 ± 21.53) and mental health (63.70 ± 18.66).
The mean Physical Component Summary (PCS) score was 34.31 ± 6.28, whereas the mean Mental Component Summary (MCS) score was 47.17 ± 10.17, indicating greater impairment in the physical component of health-related quality of life compared to the mental component (Table 2).

Table 2: Domain Analysis of SF-36 survey in studied population (n=158)

Domain	Mean	Std. Deviation	Lower interval	Upper Interval
Physical functioning	38.07	11.9	36.2	39.94
Role limitation due to physical health	44.62	38.52	38.57	50.67
Role limitation due to emotional health	46.2	37.83	40.26	52.15
Social functioning	64.42	21.53	61.04	67.81
Bodily Pain	50.95	15.07	48.58	53.32
General health perception	52.03	24.44	48.18	55.87
Vitality	55.16	23.23	51.51	58.81
Mental health	63.7	18.66	60.76	66.63
PCS	34.31	6.28	33.32	35.3
MCS	47.17	10.17	45.57	48.77

P value <0.05 was taken as significant

Table 3 shows comparison of SF-36 domain scores between the control group (n = 77) and the MAFLD group (n = 81) revealed statistically significant differences across all domains.
Patients with MAFLD demonstrated significantly lower mean scores for physical functioning compared to controls (34.01 ± 11.52 vs 42.34 ± 10.81; p < 0.001). Similarly, role limitation due to physical health was markedly re-duced in the MAFLD group (27.47 ± 35.27) relative to the control group (62.66 ± 33.35; p < 0.001).
A significant reduction was also observed in role limitation due to emotional health, with MAFLD patients show-ing lower scores compared to controls (30.83 ± 33.71 vs 62.38 ± 35.26; p < 0.001). Social functioning scores were significantly lower among MAFLD patients (58.37 ± 18.28) than controls (70.79 ± 22.93; p < 0.001).
Similarly, MAFLD patients reported significantly poorer scores for bodily pain, general health perception, vitality, and mental health compared to the control group (all p < 0.001).
The mean PCS score was significantly lower in the MAFLD group than in controls (31.47 ± 6.42 vs 37.29 ± 4.53; p < 0.001). Likewise, the MCS score was significantly reduced among MAFLD patients compared to the control group (42.31 ± 8.33 vs 52.28 ± 9.43; p < 0.001). (Table 3)

Table 3: Domain Analysis of SF36 in Control group and MAFLD group (n=158)

	Control group (n=77)				**MAFLD group (n=81)**				p value
Domain	Mean	SD	Lower interval	Upper Interval	Mean	SD	Lower interval	Upper Interval	
Physical functioning	42.34	10.81	39.88	44.79	34.01	11.52	31.46	36.56	<0.001
Role limitation due to physical health	62.66	33.35	55.09	70.23	27.47	35.27	19.67	35.27	<0.001
Role limitation due to emotional health	62.38	35.26	54.37	70.38	30.83	33.71	23.37	38.28	<0.001
Social functioning	70.79	22.93	65.59	7 6	58.37	18.28	54.33	62.41	<0.001
Bodily Pain	51.29	13.42	48.24	54.33	50.63	16.56	46.97	54.29	<0.001
General health	67.6	19.73	63.12	72.08	37.22	18.64	33.1	41.34	<0.001
Vitality	67.66	18.74	63.41	71.91	43.27	20.78	38.68	47.87	<0.001
Mental health	71.38	16.24	67.69	75.06	56.4	17.95	52.43	60.36	<0.001
PCS	37.29	4.53	36.26	38.32	31.47	6.42	30.05	32.89	<0.001
MCS	52.28	9.43	50.14	54.42	42.31	8.33	40.47	44.15	<0.001

P value <0.05 was taken as significant

Comparison of Health related quality of life among genotypes of PNPLA3 rs738408 shown in table 4 Among the cc genotype of PNPLA3 rs 738408 majority of the CC carrier of PNPLA3 had good quality of life having MCS scores greater than 50 whereas poor quality of life was predominantly found among the CT and TT genotypes carriers having MCS score less than 50
Shown table 5 showing that ;among the cc genotype of PNPLA3 rs 738409 majority of the CC carrier of PNPLA3 had good quality of life having MCS scores greater than 50 whereas poor quality of life was predom-inantly found among the CG and GG genotypes carriers having MCS score less than 50

Table 4: Comparison of Health related quality of life among genotypes of PNPLA3 rs738408

Genotypes PNPLA3 738408	Good Quality of Life (MCS≥50)		poor Quality of Life (MCS<50)	
	Frequency(n)	Percentage (%)	Frequency (n)	Percentage (%)
CC	70	71.4	40	66.7
CT	23	23.5	15	25
TT	5	5.1	5	8.3

Quality of life was categorized based on MCS score cutoff points 50

Table 5 Comparison of Health related quality of life among

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genotypes of PNPLA3 rs738408

Genotypes PNPLA3 738409	Good Quality of Life (MCS≥50)		poor Quality of Life (MCS<50)	
	Frequency(n)	Percentage (%)	Frequency (n)	Percentage (%)
CC	68	69.4	42	70.0
CG	21	21.4	13	21.7
GG	9	9.2	5	8.3

7. Discussion

The present study showed that majority of the MAFLD patients were from the age 40-59 years while least number of patients were found in the age between 60-75years. This is been justified with the study stating that the increasing age has the negative association with MAFLD. The study additionally found an age-based decreasing prevalence of MAFLD, from 45% in ages 65–70 years to 31.8% in ages >80 years (p=0.01). Furthermore, age was found to be negatively associated with fatty liver in the logistic regression analysis in the older adults

(Tanaka et al., 2020)

As present study evaluated the impact of metabolic dysfunction-associated fatty liver disease (MAFLD) and PNPLA3 genetic polymorphisms on health-related quality of life (HRQoL) using the SF-36 questionnaire. The find-ings demonstrated that patients with MAFLD experienced significantly impaired HRQoL compared with healthy controls across all SF-36 domains. Statistically significant reductions were observed in physical functioning ($p<0.001$), role limitation due to physical health ($p<0.001$), role limitation due to emotional health ($p<0.001$), social functioning ($p<0.001$), bodily pain ($p<0.001$), general health ($p<0.001$), vitality ($p<0.001$), and mental health ($p<0.001$). Moreover, both the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were significantly lower in MAFLD patients compared with controls (PCS: 31.47±6.42 vs 37.29±4.53; $p<0.001$; MCS: 42.31±8.33 vs 52.28±9.43; $p<0.001$). The greater decline observed in PCS compared with MCS indicates that MAFLD predominantly affects the physical aspects of quality of life, although mental health im-pairment is also evident.

The deterioration in HRQoL observed in this study reflects the multisystem nature of MAFLD, which is closely as-sociated with metabolic syndrome, insulin resistance, chronic inflammation, and fatigue. [11] These pathophysiologi-cal mechanisms can significantly affect daily functioning and overall health perception. Recent studies have simi-larly demonstrated that individuals with MAFLD exhibit significantly reduced SF-36 scores compared with healthy populations ($p<0.01$), particularly in domains related to physical functioning, vitality, and general health percep-tion.[12, 13] These findings reinforce the concept that MAFLD imposes a considerable burden not only on hepatic health but also on patients' functional and psychosocial well-being.

At the national level, limited studies from Pakistan have examined HRQoL in patients with metabolic liver disease. However, research conducted in Pakistani populations with metabolic disorders has reported significant impairment in physical functioning and vitality scores compared with controls ($p<0.05$). [14,15] The results of the present study are consistent with these findings, as MAFLD patients demonstrated markedly lower general health (37.22±18.64 vs 67.60±19.73; $p<0.001$) and vitality scores (43.27±20.78 vs 67.66±18.74; $p<0.001$) than controls. The similarity between the present results and national observations may reflect the increasing prevalence of metabolic risk fac-tors in Pakistan, including obesity, type 2 diabetes mellitus, and sedentary lifestyle, which contribute to both disease progression and compromised quality of life.

The findings of the present study are also consistent with international evidence. Several recent international inves-tigations have reported significantly lower HRQoL scores among patients with MAFLD compared with healthy in-dividuals, particularly in physical functioning and vitality domains ($p<0.001$).[16-18] Studies conducted in European and Asian populations have demonstrated that individuals with hepatic steatosis frequently report lower PCS scores and impaired general health perception, reflecting the chronic fatigue and metabolic burden associated with the disease.[16] These international observations align closely with the present findings, further supporting the notion that HRQoL impairment is a universal feature of MAFLD across different populations.

In addition to evaluating HRQoL differences between MAFLD patients and controls, the present study also investi-gated the relationship between PNPLA3 polymorphisms and quality-of-life outcomes. The results demonstrated that individuals carrying the CC genotype of PNPLA3 rs738408 and rs738409 were more likely to have better qual-ity of life (MCS ≥50), whereas variant genotype carriers (CT/TT for rs738408 and CG/GG for rs738409) were more frequently represented among individuals with poorer mental health scores (MCS <50). These findings suggest that genetic susceptibility may influence patient-perceived disease burden, particularly with respect to mental health components of HRQoL.

Although limited national data are available regarding the association between PNPLA3 polymorphisms and HRQoL, studies conducted in Pakistani populations have reported significant associations between PNPLA3 vari-ants and susceptibility to fatty liver disease ($p<0.05$).[19,20] The presence of these polymorphisms has been linked with increased hepatic fat accumulation and metabolic dysregulation, which may indirectly contribute to reduced quali-ty of life due to worsening disease severity and metabolic complications.

Internationally, the PNPLA3 rs738409 polymorphism is widely recognized as one of the strongest genetic determi-nants of MAFLD susceptibility and progression.[21-23] Recent genomic studies have demonstrated that carriers of the risk allele exhibit significantly higher hepatic fat content and increased risk of

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disease progression ($p<0.001$).[21] These pathological alterations may lead to fatigue, reduced physical capacity, and increased metabolic burden, thereby influencing patients' perception of health and emotional well-being. Consequently, the poorer HRQoL observed among variant genotype carriers in the present study may reflect the broader systemic consequences of genetically mediated metabolic liver disease.

The strengths of the present study include the use of a validated SF-36 instrument for HRQoL assessment and the simultaneous evaluation of PNPLA3 polymorphisms within a Pakistani MAFLD cohort. However, certain limita-tions should be acknowledged. The cross-sectional study design limits causal inference, and the single-center sample may restrict generalizability to wider populations.

Despite these limitations, the present study highlights that MAFLD significantly impairs health-related quality of life, particularly within the physical health domains. Furthermore, the observed association between PNPLA3 genet-ic variants and poorer mental health scores suggests that genetic susceptibility may influence the subjective disease burden experienced by patients. These findings emphasize the importance of incorporating patient-reported out-comes and genetic risk assessment into the comprehensive evaluation and management of MAFLD.

8. Conclusion

Quality of life was found poor in MAFLD subjects than control. CC carriers of PNPLA3 rs 738408 and rs 738409 in MAFLD had good quality of life while CT and TT genotypes of rs 738408 and rs 738409 had poor quality of life.

9. Strength

To best of our knowledge, this study is the first to report association between PNPLA3 polymorphisms (rs738408 and rs738409) and quality of life, measured by SF 36, in patients with metabolic dysfunction associated fatty liver disease (MAFLD).

10. Limitations

Since this is a cross sectional study and can only show association between variables without proving cause and effect therefore lack of longitudinal data may limit the changes over time.

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