

Review began 09/24/2026
Review ended 10/12/2026
Published 10/25/2026

© Copyright 2026
Raina et al. This is an open access article distributed under the terms of the Creative Commons Attribution License CC-BY 4.0., which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

DOI: 10.7759/cureus.118545

Serum DsbA-L Levels and DsbA-L rs1917760 Polymorphism in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A Hospital-Based Case-Control Study

Manzoor A. Raina ¹, Karanpreet Bhutani ¹, Gowhar Rashid ², Mushtaq A. Khan ³, Mudassar Syed ²

1. Biochemistry, M.M. Institute of Medical Sciences and Research, Maharishi Markandeshwar (Deemed to be University), Mullana, IND 2. Clinical Biochemistry, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, IND 3. Gastroenterology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar, IND

Corresponding author: Mudassar Syed, syed.mudassar@skims.ac.in

Abstract

Background

Metabolic dysfunction-associated steatotic liver disease (MASLD) is a common chronic liver disease associated with obesity, insulin resistance, dyslipidemia, oxidative stress, and chronic low-grade inflammation. Various proteins and gene variants are involved in the pathogenesis of MASLD; however, evidence regarding the role of DsbA-L in this disease is still limited. Therefore, this study evaluated the possible role of DsbA-L and its polymorphism at rs1917760 (-1308 G/T) in the pathogenesis of MASLD and attempted to address critical knowledge gaps regarding MASLD in the Indian population.

Methods

This was a hospital-based case-control study comprising 100 patients with MASLD and 100 healthy controls. Hepatic steatosis was assessed by abdominal USG. Blood samples were collected from the subjects, and serum was separated. Serum DsbA-L levels were quantified using a commercially available research-grade ELISA kit. DNA from MASLD cases was extracted using the QIAamp DNA Blood Mini Kit, whereas DNA from healthy controls was extracted using the phenol-chloroform method. DsbA-L rs1917760 was amplified using conventional PCR. All statistical analyses were conducted using R software and GraphPad Prism.

Results

The mean DsbA-L level among cases was 130.86 ± 59.89 ng/mL, whereas that in the control group was 168.89 ± 60.84 ng/mL. The difference between these groups was statistically significant ($p < 0.0001$). Receiver operating characteristic (ROC) analysis indicated a modest discriminatory ability of DsbA-L (area under the curve (AUC) = 0.69). In univariable analysis, DsbA-L was significantly inversely associated with disease status; however, this association was no longer significant after adjusting for age, sex, and BMI (adjusted OR = 0.997, 95% CI: 0.991-1.003; $p = 0.389$). BMI remained independently associated with case status (adjusted OR = 1.761, 95% CI: 1.496-2.073; $p < 0.001$). The scatter plot demonstrated a statistically significant moderate inverse association between BMI and serum DsbA-L levels (Spearman's $r = -0.43$, $p < 0.001$). This indicates that individuals with higher BMI tended to have lower serum DsbA-L concentrations. The DsbA-L rs1917760 polymorphism exhibited the wild-type genotype (GG) in all subjects.

Conclusion

Serum DsbA-L levels were significantly lower in patients with MASLD and were inversely associated with BMI, suggesting a possible relationship between DsbA-L and MASLD. However, serum DsbA-L was not independently associated with the disease after adjustment for potential confounding factors. Furthermore, the DsbA-L rs1917760 polymorphism was monomorphic in our study population.

Categories: Internal Medicine, Endocrinology/Diabetes/Metabolism, Gastroenterology

Keywords: case-control, dsba-l, hgstk1, masld, polymorphism

Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), one of the most common chronic liver diseases, is associated with obesity, insulin resistance, dyslipidemia, oxidative stress, and chronic low-grade inflammation [1]. The pathogenesis of MASLD is complex and multifactorial [2]. Various proteins and genetic variants are known to be involved in the pathogenesis of MASLD [3]. There is growing evidence that disulfide-bond A oxidoreductase-like protein (DsbA-L), also known as hGSTK1, plays an important role in metabolic diseases by regulating various cell signaling pathways and adiponectin multimerization and secretion [4]. This protein belongs to the superfamily of enzymes known as glutathione S-transferases

How to cite this article

Raina M A, Bhutani K, Rashid G, et al. (October 25, 2026) Serum DsbA-L Levels and DsbA-L rs1917760 Polymorphism in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A Hospital-Based Case-Control Study. Cureus 18(10): e118545. DOI 10.7759/cureus.118545

(GSTs). Cellular detoxification is mainly carried out by GSTs. The human DsbA-L gene maps to the long arm of chromosome 7 at 7q34, contains 8 exons and 7 introns, and spans 5.68 kb [5]. The gene encodes a chaperone protein known as DsbA-L that plays a vital role in various physiological processes in metabolic tissues, which are essential for insulin sensitivity, fat metabolism, and inflammatory responses. The DsbA-L protein has a well-defined structure that is essential for its proper functioning and integrity. The molecular weight of the DsbA-L protein is approximately 25 kDa, and it has a dimeric structure. It adopts a thioredoxin-like fold, with a highly conserved structure essential for disulfide bond formation and reducing properties. It possesses two domains: a thioredoxin-like domain core, which helps in its oxidoreductase activity, and a helical domain [4,5]. DsbA-L is expressed in various tissues, but its expression level is highest in adipose tissue [6]. Numerous studies have found that overexpression of the DsbA-L gene can enhance insulin sensitivity, reduce body fat, and alleviate symptoms of metabolic diseases [7].

Studies focusing on the DsbA-L gene suggest that genetic variability may play a role in the development of MASLD and other metabolic disorders [8]. Polymorphisms within the DsbA-L gene, such as the rs1917760 variant, have been associated with risk profiles for metabolic diseases, potentially through cytokine and adipokine dynamics and other cellular processes [9]. In the context of MASLD, these polymorphisms could potentially affect the levels of different inflammatory cytokines and adipokines, such as adiponectin.

Despite many advances in understanding MASLD, there remains a need for reliable biomarkers that better explain the underlying metabolic and inflammatory disturbances associated with disease pathogenesis. Considering the important role of DsbA-L, investigating its circulating levels and genetic variation may provide valuable insights into disease development and biomarker development.

Therefore, this hospital-based case-control study was undertaken to evaluate DsbA-L protein levels and the rs1917760 polymorphism in the DsbA-L gene to investigate their potential roles in the pathogenesis of MASLD.

Materials And Methods

Study design

The study was conducted at the Department of Clinical Biochemistry and Gastroenterology, Sher-i-Kashmir Institute of Medical Sciences (SKIMS), Soura, and was conceptualized at Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), Ambala, Haryana. Ethical approval for the study was obtained from the Institutional Ethics Committee of SKIMS (approval no. SIMS 131/IEC-SKIMS/2025-189). Written informed consent was obtained from the subjects prior to enrolment.

The study employed a hospital-based case-control design in which 100 MASLD cases and 100 healthy controls were enrolled. Cases and controls were matched for age (± 5 years), sex, and residence. Cases were recruited from the Gastroenterology OPD, SKIMS, Soura. However, controls were recruited from health check-up camps and among patient attendants.

To confirm the presence of MASLD in subjects, abdominal USG was performed on two separate occasions by an experienced radiologist.

The predefined inclusion and exclusion criteria were taken into consideration when selecting subjects. Cases were selected according to internationally accepted diagnostic criteria that required the presence of hepatic steatosis along with at least one cardiometabolic risk factor (type 2 diabetes, dyslipidemia, hypertension, or obesity) [10]. Controls had no liver disease or metabolic disorder, as confirmed by USG and baseline investigations.

Individuals with significant alcohol consumption (≥ 20 g/day for females and ≥ 30 g/day for males), substance or drug abuse, or use of drugs known to contribute to hepatic steatosis, including anabolic steroids, amiodarone, methotrexate, and tamoxifen, were excluded. Individuals with chronic conditions such as tuberculosis or hepatitis B or C, pregnant women, and participants younger than 18 years were also excluded.

Sample collection and processing

Venous blood samples (4–5 mL) were collected from all recruited subjects using a standard phlebotomy procedure into plain red-top (for serum) and ethylenediaminetetraacetic acid (EDTA) Vacutainer tubes (for DNA). Serum was separated by centrifugation at $1,006 \times g$ for 10 minutes within 30 minutes of collection. Serum was stored at -20°C until analysis. Serum samples were appropriately thawed at room temperature before DsbA-L estimation and were not subjected to repeated freeze-thaw cycles.

Serum DsbA-L estimation

Serum DsbA-L levels were quantified using a commercially available research-grade human DsbA-L ELISA kit (Qayee Bio-Technology Co., Ltd., Shanghai, China; cat. no. QY-E0 5978), based on a double-antibody

sandwich enzyme-linked immunosorbent one-step process. The assay was performed according to the manufacturer’s guidelines.

The analytical assay range was 12.5-800 ng/mL. All samples were analyzed in duplicate to ensure assay precision and reproducibility.

DNA extraction

DNA was isolated from blood collected in EDTA tubes using different extraction methods for the two study groups. DNA from MASLD cases was extracted using the QIAamp DNA Blood Mini Kit (QIAGEN, Hilden, Germany; cat. no. 51104), whereas DNA from healthy controls was extracted using the phenol-chloroform method. The quality of the genomic DNA obtained from the blood samples was analyzed using a 0.8% agarose gel.

PCR amplification of rs1917760

A fragment of the DsbA-L gene encompassing the rs1917760 (-1308 G/T) variant was amplified by PCR using primers specific to this region, designed to flank the target region (Table 1).

Reference SNP ID	SNP name	Primer sequence	Annealing temperature	Amplicon size
rs1917760	DsbA-L (-1308 G/T)	F: 5'-TCAGAGAGGTCAAGTGGCTCAC-3'	62.5 °C	230 bp
		R: 5'-TGGTCTCCTGTTTAGCTGGCTC-3'		

TABLE 1: Primer sequences for amplification of the DsbA-L gene (rs1917760).

DsbA-L: Disulfide-bond A oxidoreductase-like protein; SNP: Single-nucleotide polymorphism; ID: Identification; F: Forward primer; R: Reverse primer; bp: Base pairs; G/T: Guanine-to-thymine nucleotide substitution; °C: Degrees Celsius; 5': 5-prime end; 3': 3-prime end.

PCR-restriction fragment length polymorphism (PCR-RFLP) analysis of PCR products

The PCR products were digested using the restriction enzyme RsaI under the following conditions, as shown in Table 2.

Gene name	Amplicon (bp)	Restriction enzyme used	Incubation	Digestion products (bp)
DsbA-L (-1308 G/T)	230	RsaI	37 °C for 16 hours	GG: 230 bp (wild-type)
				GT: 230 bp, 130 bp, 100 bp (heterozygous)
				TT: 130 bp, 100 bp (homozygous variant)

TABLE 2: Primers, PCR-RFLP conditions, restriction enzyme, and restriction digestion fragments of the DsbA-L gene (-1308 G/T, rs1917760).

DsbA-L: Disulfide-bond A oxidoreductase-like protein; RFLP: Restriction fragment length polymorphism; SNP: Single-nucleotide polymorphism; bp: Base pairs; RsaI: Restriction endonuclease RsaI; GG: Wild-type genotype; GT: Heterozygous genotype; TT: Homozygous variant genotype; G/T: Guanine/thymine nucleotide variant; °C: Degrees Celsius.

Sequencing

PCR-RFLP results were validated by Sanger sequencing of 5% of randomly selected samples to determine the nucleotide present at the rs1917760 locus. For sequencing, unpurified PCR products were sent to a commercial sequencing facility. Sequencing chromatograms were analyzed using appropriate sequence scanner software, and the obtained sequences were compared with the reference DsbA-L gene sequence for genotype identification and polymorphism analysis.

Statistical analysis

The sample size was calculated using Cochran’s formula. Based on this formula, the required sample size was estimated, and 100 patients with MASLD and 100 controls were included in the study. The normality of the

data was assessed using the Shapiro-Wilk test. Categorical variables were analyzed using the chi-square test, and continuous variables were analyzed using Student's t-test. Receiver operating characteristic (ROC) curve analysis was performed to assess the diagnostic performance of the studied variables. Multivariable logistic regression analysis was performed to identify the independent factors associated with MASLD. Spearman's correlation analysis was performed to assess the associations. Statistical analyses were performed using R version 4.6.1 (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism version 8 (GraphPad Software, LLC, San Diego, CA, USA). A p-value < 0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

The study recruited 100 MASLD cases and 100 healthy controls. Among the patients with MASLD, 38.0% had Grade I steatosis, 57.0% had Grade II steatosis, and 5.0% had Grade III steatosis (Figure 1).

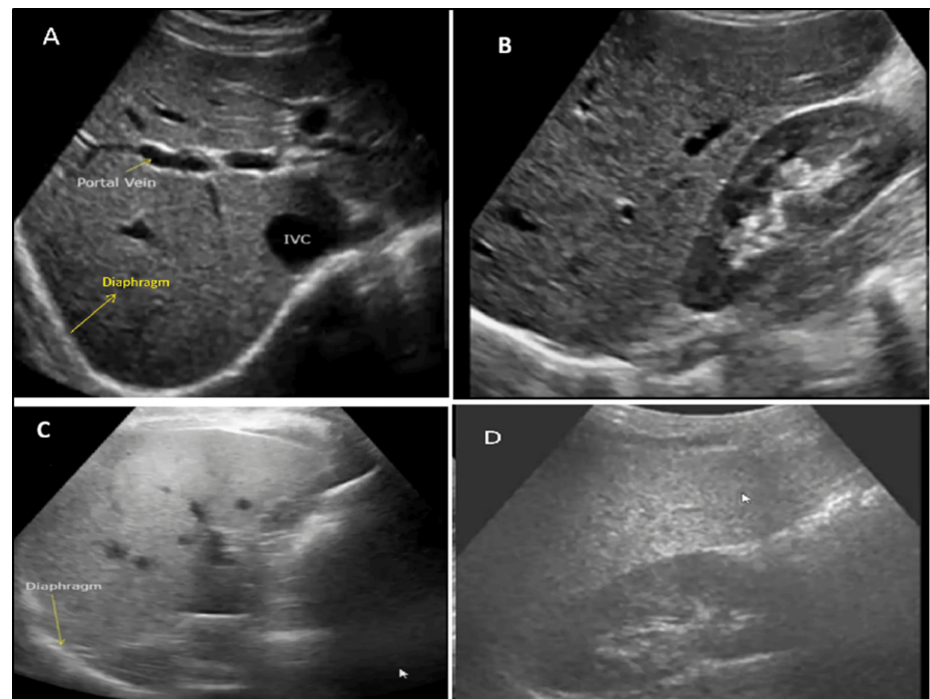


FIGURE 1: Representative ultrasonographic images of different grades of hepatic steatosis.

A: Normal liver: Homogeneous parenchymal echotexture with echogenicity equal to or slightly less than that of the right renal cortex; sharp, well-defined visualisation of the diaphragm and portal vein walls; clear depiction of intrahepatic vessels and the posterior right hepatic lobe; and normal posterior acoustic enhancement.

B: Grade I (mild steatosis): Mildly increased hepatic echogenicity with preserved visualisation of the diaphragm and portal vein walls.

C: Grade II (moderate steatosis): Moderately increased hepatic echogenicity accompanied by partial obscuration of the portal vein walls and diaphragm.

D: Grade III (severe steatosis): Markedly increased hepatic echogenicity resulting in poor or absent delineation of the portal vein walls, diaphragm, and posterior segment of the right hepatic lobe.

IVC: Inferior vena cava.

The mean age of the MASLD group was 42.25 ± 9.97 years, while that of the control group was 40.19 ± 9.99 years, with no statistically significant difference ($p = 0.146$). The distributions of sex and residence were matched, with males (47%) and females (53%) in each group, while 38% of participants belonged to urban areas and 62% to rural areas in both groups.

A significant difference was found in educational status, with a higher proportion of MASLD cases having primary education or less compared with the control group (40% vs. 18%; $p < 0.05$). Smoking status also differed significantly, with a higher percentage of smokers in the MASLD group compared with controls (8%

vs. 1%; p < 0.05). Dietary habits were comparable and did not differ significantly, with the majority of participants being non-vegetarian (82% in the MASLD group vs. 79% in controls; p = 0.601).

A significant difference in the proportion of participants with BMI ≥25 kg/m² was observed (75% in the MASLD group vs. 12% in controls). For blood pressure parameters, significant differences were observed (p < 0.05): a greater proportion of patients with MASLD had systolic blood pressure ≥130 mmHg compared with controls (55% vs. 6%) and diastolic blood pressure ≥85 mmHg (46% vs. 11%).

Serum DsbA-L levels in MASLD and controls

The mean DsbA-L level among cases was 130.86 ± 59.89 ng/mL, whereas that in the control group was 168.89 ± 60.84 ng/mL. The difference between these groups was statistically significant (p < 0.0001), as shown in Table 3.

Table with 4 columns: Parameter, MASLD cases (n = 100), Controls (n = 100), p-value. Row 1: DsbA-L (ng/mL), 130.86 ± 59.89, 168.89 ± 60.84, <0.0001.

TABLE 3: Comparison of serum DsbA-L levels between MASLD cases and healthy controls.

Values are expressed as mean ± SD.
MASLD: Metabolic dysfunction-associated steatotic liver disease.

Receiver operating characteristic (ROC) curve analysis of DsbA-L levels

To evaluate the discriminatory ability of serum DsbA-L levels between patients with MASLD and controls, receiver operating characteristic (ROC) curve analysis was performed. With controls coded as 0 and patients with MASLD as 1, the area under the curve (AUC) was 0.69 (95% CI: 0.617-0.764), indicating modest discriminatory ability. These findings suggest that serum DsbA-L levels alone have limited ability to discriminate between patients with MASLD and controls (Figure 2).

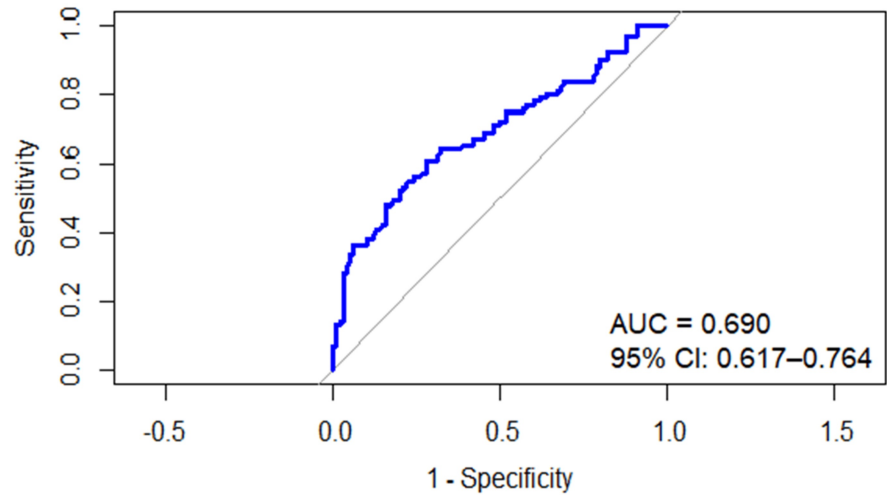


FIGURE 2: ROC curve analysis of DsbA-L levels.

ROC: Receiver operating characteristic; AUC: Area under the curve.

Logistic regression analysis of factors associated with MASLD

In univariable analysis, DsbA-L was significantly inversely associated with case status (OR = 0.990, 95% CI: 0.985-0.995; p < 0.001). However, after adjustment for age, sex, and BMI, the association between DsbA-L and case status was no longer statistically significant (adjusted OR = 0.997, 95% CI: 0.991-1.003; p = 0.389). In the multivariable model, BMI remained significantly associated with case status (adjusted OR = 1.761, 95% CI: 1.496-2.073; p < 0.001), whereas age was not significantly associated with case status (adjusted OR =

1.005, 95% CI: 0.966-1.044; p = 0.816). Sex was also significantly associated with case status (adjusted OR = 0.452, 95% CI: 0.207-0.990; p = 0.047) (Table 4).

Variable	Univariable OR	95% CI	p-value	Adjusted OR	95% CI	p-value
DsbA-L	0.99	0.985-0.995	<0.001	0.997	0.991-1.003	0.389
Age	-	-	-	1.005	0.966-1.044	0.816
Sex	-	-	-	0.452	0.207-0.990	0.047
BMI	-	-	-	1.761	1.496-2.073	<0.001

TABLE 4: Univariable and multivariable logistic regression analysis of factors associated with case status.

Adjusted ORs were obtained from multivariable logistic regression analysis.

Association between BMI and DsbA-L levels

The scatter plot (Figure 3) showed a moderate, statistically significant inverse association between BMI and serum DsbA-L levels (Spearman’s r = -0.43, p < 0.001). This indicates that individuals with higher BMI tended to have lower serum DsbA-L concentrations.

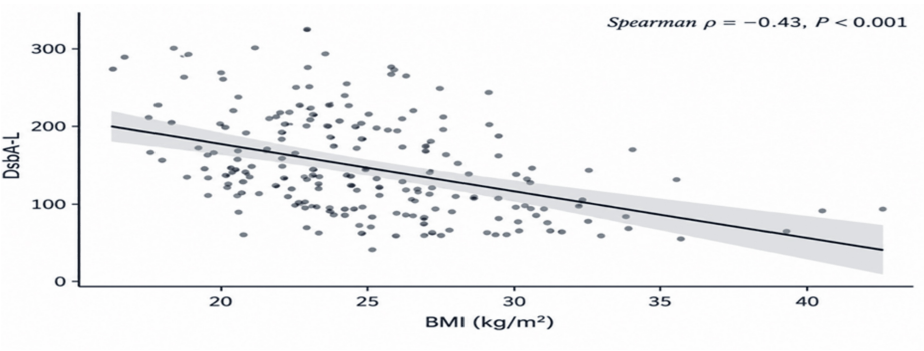


FIGURE 3: Scatter plot depicting the association between BMI and DsbA-L levels.

DsbA-L: Disulfide-bond A oxidoreductase-like protein; r: Spearman’s rank correlation coefficient; p: P-value.

Genotypic analysis

Polymorphism of DsbA-L (rs1917760)

A representative gel image showing the PCR-amplified fragment of DsbA-L (rs1917760) is presented in Figure 4.

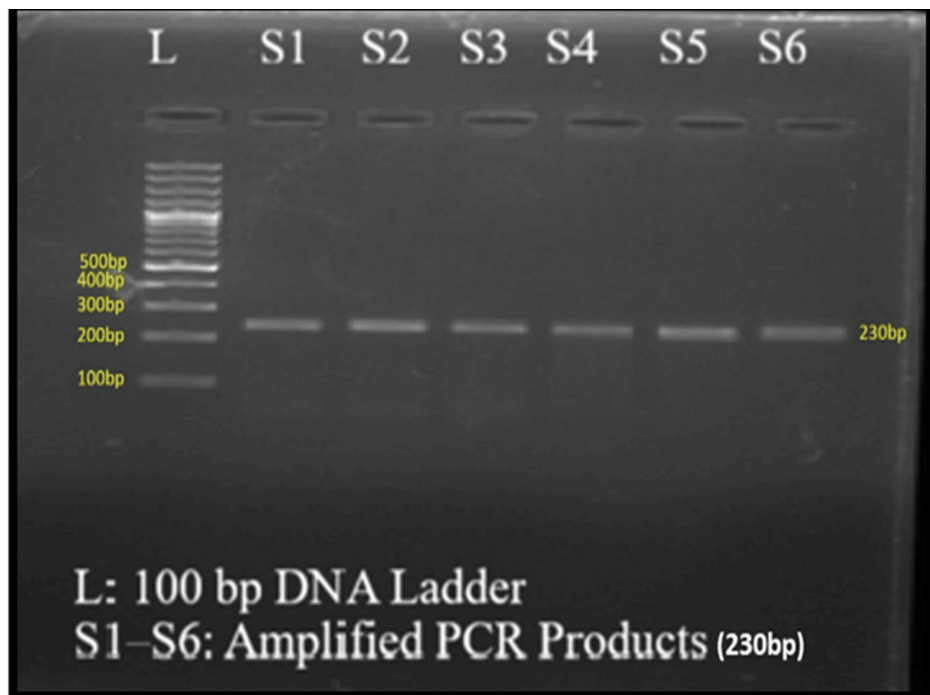


FIGURE 4: Representative gel image of the PCR-amplified fragment of DsbA-L (rs1917760).

L represents the 100 bp DNA ladder; S1–S6 represent amplified PCR products corresponding to 230 bp.

DsbA-L: Disulfide-bond A oxidoreductase-like protein; bp: Base pairs.

RFLP Genotypic Analysis

All subjects, including 100 cases and 100 controls, had the wild-type (GG) genotype of the DsbA-L gene (rs1917760). A representative gel image showing the PCR-RFLP results for DsbA-L (rs1917760) is presented in Figure 5, and the sequencing chromatogram used to validate the results is shown in Figure 6.

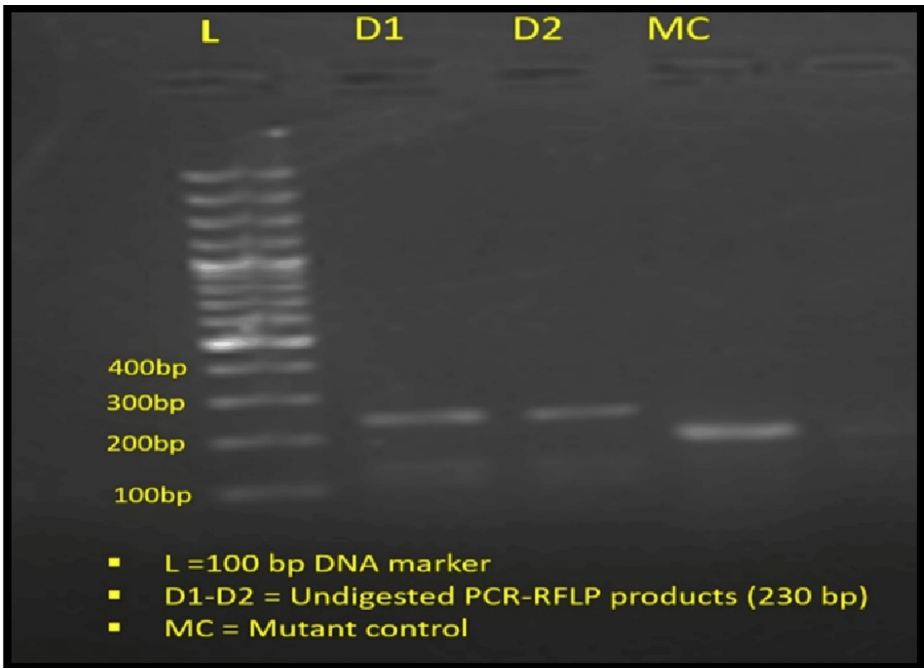


FIGURE 5: Representative gel image of PCR-RFLP products of DsbA-L (rs1917760).

L represents the 100 bp DNA ladder; D1-D2 represent undigested PCR-RFLP products corresponding to 230 bp; MC represents the mutant control.

DsbA-L: Disulfide-bond A oxidoreductase-like protein; rs: Reference SNP cluster ID; SNP: Single-nucleotide polymorphism; RFLP: Restriction fragment length polymorphism; bp: Base pairs.

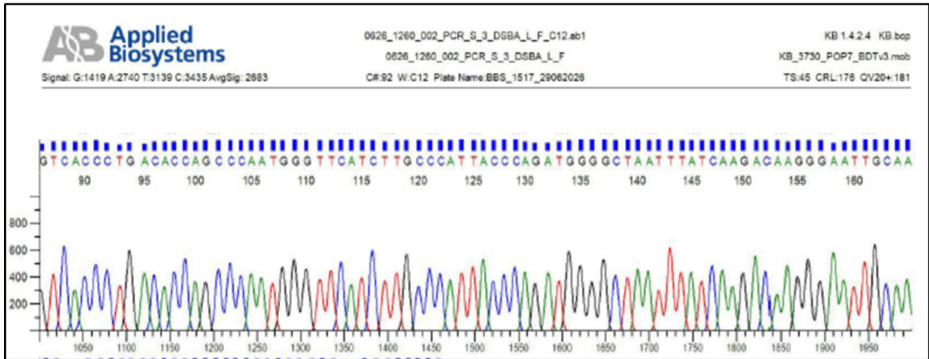


FIGURE 6: Representative sequencing chromatogram demonstrating the DsbA-L rs1917760 G/G genotype.

The chromatogram shows the nucleotide sequence surrounding the -1308 position of the DsbA-L gene. A single, well-resolved guanine (G) peak is present at the polymorphic site, with no thymine (T) peak detected, confirming homozygosity for the reference G allele in the representative sample.

DsbA-L: Disulfide-bond A oxidoreductase-like protein; rs: Reference SNP cluster ID; SNP: Single-nucleotide polymorphism; G: Guanine; T: Thymine.

Discussion

This hospital-based case-control study comprised 100 patients with MASLD and 100 healthy controls, whose demographic characteristics, such as age, sex, and area of residence, were comparable and did not differ significantly, in agreement with several prior studies [11]. Among the patients with MASLD, grade II steatosis was the most common ultrasonographic category (57%), followed by grade I (38%) and grade III (5%), indicating that moderate hepatic steatosis predominated in the study population. However, educational attainment and smoking status differed significantly between the two groups. Lower

educational status was more prevalent among patients with MASLD, and most smokers were in this group [12,13]. These findings suggest that differences in socioeconomic and lifestyle factors may potentially contribute to the pathogenesis of MASLD.

Furthermore, obesity was substantially more prevalent in the MASLD group, with a statistically significant difference between the groups. These findings are consistent with numerous studies that demonstrate a close association between MASLD and excess adiposity [14-16].

Systolic and diastolic blood pressure were significantly elevated among cases, demonstrating the clustering of cardiometabolic risk factors in MASLD, consistent with a previous study [17].

One of the most important findings of this study was that serum DsbA-L levels differed significantly between cases and controls (131 vs. 169 ng/mL; $p < 0.0001$). This suggests that lower levels of DsbA-L are associated with the presence of MASLD. The findings of this study also demonstrate that metabolic and adipose tissue dysfunction may influence serum DsbA-L levels, although this requires further validation [18].

ROC curve analysis showed an AUC of 0.690 (95% CI: 0.617-0.764), indicating modest discriminatory ability. Thus, although DsbA-L alone does not demonstrate strong diagnostic performance, its lower levels may have potential value as part of a panel of metabolic or biochemical markers for identifying individuals with MASLD [6].

The logistic regression analysis provided further insights into this association. In univariable analysis, DsbA-L was significantly inversely associated with case status (OR = 0.990, 95% CI: 0.985-0.995; $p < 0.001$), indicating that higher DsbA-L levels were associated with lower odds of having MASLD [19]. However, after adjustment for age, sex, and BMI, this association was attenuated and was no longer statistically significant (adjusted OR = 0.997, 95% CI: 0.991-1.003; $p = 0.389$). In contrast, BMI remained independently associated with case status (adjusted OR = 1.761, 95% CI: 1.496-2.073; $p < 0.001$). These findings suggest that the apparent association between DsbA-L and MASLD may be substantially influenced by adiposity, particularly BMI, which is consistent with numerous studies [20]. Therefore, the lower DsbA-L levels observed among patients with MASLD should not be interpreted as evidence that DsbA-L is an independent predictor of MASLD after accounting for BMI.

A moderate, statistically significant inverse association was observed between BMI and serum DsbA-L levels (Spearman's $r = -0.43$, $p < 0.001$). This finding indicates that individuals with higher BMI had lower serum DsbA-L concentrations. The inverse relationship suggests that increasing adiposity is associated with reduced circulating DsbA-L levels, potentially reflecting alterations in adipose tissue function and mitochondrial homeostasis. Given the proposed role of DsbA-L in adipocyte biology and mitochondrial function, reduced DsbA-L levels with increasing BMI may indicate a link between obesity-related metabolic disturbances and impaired DsbA-L expression or secretion. However, the cross-sectional nature of the present study does not permit causal inference.

In the present study, genotyping of the DsbA-L (rs1917760) polymorphism revealed monomorphic results in both the 100 patients with MASLD and the 100 healthy controls, with all subjects carrying the wild-type (GG) genotype for this SNP. No variant genotype was detected in either group. Consequently, no association between the DsbA-L (rs1917760) polymorphism and MASLD could be evaluated in the present study [21]. The absence of genetic variation at this locus may indicate a low frequency of the variant allele in the study population; however, this finding should be interpreted cautiously given the relatively modest sample size and the possibility that rare variants may not be captured in a cohort of this size. The PCR-RFLP findings were further validated by sequencing, supporting the reliability of the genotyping results.

Several limitations should be considered when interpreting the results of this study, such as the relatively small sample size of Grade III MASLD patients, assessment of hepatic steatosis based on ultrasonography grading rather than liver biopsy (the gold standard) or other high-end imaging tools, which could have provided additional information. Furthermore, DsbA-L is primarily an intracellular protein, and circulating levels may reflect tissue release or leakage rather than classical secretion [4], which may limit direct biological interpretation, although many research-grade ELISA kits are available. For these reasons, DsbA-L protein levels should be considered an exploratory marker. Therefore, it is pertinent to include larger cohorts involving diverse populations to determine the role of DsbA-L protein levels and its genotypic variations in order to clarify its possible role in the development and progression of MASLD.

Conclusions

Serum DsbA-L concentrations were significantly lower in participants with MASLD and were inversely correlated with BMI; however, DsbA-L was not independently associated with MASLD after adjustment for potential confounders, indicating that the observed reduction may be attributable, at least in part, to coexisting metabolic characteristics such as adiposity. The DsbA-L rs1917760 (-1308G>T) locus was monomorphic in this cohort, with all participants carrying the reference G/G genotype, precluding genotype-phenotype analysis. The lack of observed genotypic variation may be related to the sample size

and allele distribution in the study population and should not be interpreted as evidence that this polymorphism lacks relevance in other populations. Circulating DsbA-L is not a validated marker for MASLD and should be regarded as an exploratory research marker. Because DsbA-L is predominantly an intracellular protein localized to mitochondria and peroxisomes rather than a well-established secreted protein, serum concentrations may not directly reflect tissue expression or functional activity. Although research-grade ELISA kits are available for DsbA-L, further analytical and clinical validation is required before serum DsbA-L can be considered for any clinical application.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Mudassar Syed, Mushtaq A. Khan, Karanpreet Bhutani

Critical review of the manuscript for important intellectual content: Mudassar Syed, Mushtaq A. Khan, Karanpreet Bhutani

Supervision: Mudassar Syed

Acquisition, analysis, or interpretation of data: Manzoor A. Raina, Gowhar Rashid

Drafting of the manuscript: Manzoor A. Raina, Gowhar Rashid

Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. IEC Sher-i-Kashmir Institute of Medical Sciences issued approval SIMS 131/IEC-SKIMS/2025-189. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

References

1. Miller DM, McCauley KF, Dunham-Snary KJ: Metabolic dysfunction-associated steatotic liver disease (MASLD): mechanisms, clinical implications and therapeutic advances. *Endocrinol Diabetes Metab*. 2025, 8:e70132. [10.1002/edm2.70132](https://doi.org/10.1002/edm2.70132)
2. Yang Z, Zhao J, Xie K, Tang C, Gan C, Gao J: MASLD development: from molecular pathogenesis toward therapeutic strategies. *Chin Med J (Engl)*. 2025, 138:1807-1824. [10.1097/CM9.00000000000003629](https://doi.org/10.1097/CM9.00000000000003629)
3. Kuchay MS, Choudhary NS, Ramos-Molina B: Pathophysiological underpinnings of metabolic dysfunction-associated steatotic liver disease. *Am J Physiol Cell Physiol*. 2025, 328:C1637-C1666. [10.1152/ajpcell.00951.2024](https://doi.org/10.1152/ajpcell.00951.2024)
4. Li S, Wan J, Peng Z, Huang Q, He B: New insights of DsbA-L in the pathogenesis of metabolic diseases. *Mol Cell Biochem*. 2024, 479:3293-3303. [10.1007/s11010-024-04964-8](https://doi.org/10.1007/s11010-024-04964-8)
5. Shield AJ, Murray TP, Cappello JY, Coggan M, Board PG: Polymorphisms in the human glutathione transferase Kappa (GSTK1) promoter alter gene expression. *Genomics*. 2010, 95:299-305. [10.1016/j.ygeno.2010.02.007](https://doi.org/10.1016/j.ygeno.2010.02.007)
6. Deng Y, Yan L, Liu X, Xiao T, Meng W: The DsbA-L paradox in protective and pathogenic stress adaptation. *iScience*. 2026, 29:117449. [10.1016/j.isci.2026.117449](https://doi.org/10.1016/j.isci.2026.117449)
7. Liu M, Xiang R, Wilk SA, et al.: Fat-specific DsbA-L overexpression promotes adiponectin multimerization and protects mice from diet-induced obesity and insulin resistance. *Diabetes*. 2012, 61:2776-2786. [10.2337/db12-0169](https://doi.org/10.2337/db12-0169)
8. Yang M, Luo S, Yang J, et al.: DsbA-L: a promising therapeutic target for metabolic diseases. *Curr Med Chem*. 2025, 32:982-991. [10.2174/0109298673252630231018044159](https://doi.org/10.2174/0109298673252630231018044159)
9. Gao F, Fang Q, Zhang R, et al.: Polymorphism of DsbA-L gene associates with insulin secretion and body fat distribution in Chinese population. *Endocr J*. 2009, 56:487-494. [10.1507/endocrj.k08e-322](https://doi.org/10.1507/endocrj.k08e-322)
10. Kaylan KB, Paul S: NAFLD no more: a review of current guidelines in the diagnosis and evaluation of metabolic dysfunction-associated steatotic liver disease (MASLD). *Curr Diab Rep*. 2024, 25:5. [10.1007/s11892-024-01558-y](https://doi.org/10.1007/s11892-024-01558-y)
11. Corrao S, Scibetta S, Scardina S, Granà W, Bongiorno B, Calvo L, Volpato S: Prevalence and association of metabolism-associated steatotic liver disease across age groups and gender. *Nutr Metab Cardiovasc Dis*. 2025, 35:103926. [10.1016/j.numecd.2025.103926](https://doi.org/10.1016/j.numecd.2025.103926)
12. Wiering L, Demir M: Socioeconomic factors and their role in metabolic dysfunction-associated steatotic liver disease: a comprehensive review. *Liver Int*. 2026, 46:e70731. [10.1111/liv.70731](https://doi.org/10.1111/liv.70731)

13. El-Azab G, Elkhoully E, Abouyoussef R, Nagdy H: Smoking and liver diseases: an updated review of pathogenesis, progression, and therapeutic implications. *Clin Exp Med*. 2025, 26:51. [10.1007/s10238-025-01922-6](https://doi.org/10.1007/s10238-025-01922-6)
14. Romanos M, Garcia Cordova JM, Villamarin J, Pazmino Zurita JD, Acosta A: Obesity and metabolic dysfunction-associated steatotic liver disease (MASLD): a literature review on pathophysiology and treatment. *Diabetes Obes Metab*. 2026, 28:19-30. [10.1111/dom.70659](https://doi.org/10.1111/dom.70659)
15. Koliaki C, Dalamaga M, Kakounis K, Liatis S: Metabolically healthy obesity and metabolic dysfunction-associated steatotic liver disease (MASLD): navigating the controversies in disease development and progression. *Curr Obes Rep*. 2025, 14:46. [10.1007/s13679-025-00637-9](https://doi.org/10.1007/s13679-025-00637-9)
16. Rinella ME, Sanyal AJ, Loomba R, Noureddin M, Bansal MB, Newsome PN, Ratzliff V: MASLD as a complication of obesity must include liver risk stratification. *Nat Med*. 2026, 32:18-19. [10.1038/s41591-025-04130-7](https://doi.org/10.1038/s41591-025-04130-7)
17. Yang T, Yin J, Li J, Wang Q: The influence of different combinations of cardiometabolic risk factors on the prevalence of MASLD and risk of advanced fibrosis deserves attention. *J Hepatol*. 2024, 80:e82-e85. [10.1016/j.jhep.2023.09.030](https://doi.org/10.1016/j.jhep.2023.09.030)
18. Bai J, Cervantes C, Liu J, et al.: DsbA-L prevents obesity-induced inflammation and insulin resistance by suppressing the mtDNA release-activated cGAS-cGAMP-STING pathway. *Proc Natl Acad Sci U S A*. 2017, 114:12196-12201. [10.1073/pnas.1708744114](https://doi.org/10.1073/pnas.1708744114)
19. Zargar AH, Bhansali A, Majumdar A, et al.: Management of metabolic dysfunction-associated steatotic liver disease (MASLD)-an expert consensus statement from Indian diabetologists' perspective. *Diabetes Obes Metab*. 2025, 27:3-20. [10.1111/dom.16496](https://doi.org/10.1111/dom.16496)
20. Lee WH, Kipp ZA, Bates EA, Pauss SN, Martinez GJ, Hinds TD Jr: The physiology of MASLD: molecular pathways between liver and adipose tissues. *Clin Sci (Lond)*. 2025, 139:1015-1046. [10.1042/CS20257571](https://doi.org/10.1042/CS20257571)
21. Oniki K, Watanabe T, Kudo M, et al.: Modeling of the weight status and risk of nonalcoholic fatty liver disease in elderly individuals: the potential impact of the disulfide bond-forming oxidoreductase A-like protein (DsbA-L) polymorphism on the weight status. *CPT Pharmacometrics Syst Pharmacol*. 2018, 7:384-393. [10.1002/psp4.12292](https://doi.org/10.1002/psp4.12292)