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HAPTOGLOBIN GENOTYPE AND HIGH-SENSITIVITY CARDIAC BIOMARKERS FOR CARDIOVASCULAR AND MICROVASCULAR RISK STRATIFICATION IN TYPE 2 DIABETES: A PILOT CASE–CONTROL STUDY

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a major global health concern and one of the foremost contributors to cardiovascular (CV) illness and death . Circulating biomarkers such as high-sensitivity cardiac troponins (hs-cTnI, hs-cTnT) and N-terminal pro-B-type natriuretic peptide (NT-proBNP) are established predictors of heart failure and poor CV outcomes. The haptoglobin (Hp) gene exhibits polymorphism, and the Hp2-2 variant in particular is associated with diminished antioxidant activity and has been implicated in diabetic microvascular complications. However, its potential influence on cardiac biomarkers in patients with T2DM has not been clearly defined.

Objective: This study aimed to investigate the relationship between Hp genotype and levels of hs-cTnI, hs-cTnT, and NT-proBNP, and to assess whether their combined evaluation improves prediction of microvascular and macrovascular complications in adults with T2DM.

Methods: We conducted a hospital-based case–control study involving 84 adults with T2DM recruited from a tertiary care centre in India. Patients with at least one microvascular complication were included as cases (n = 42), while those without complications served as controls (n = 42). Clinical details, biochemical parameters, and high-sensitivity cardiac biomarkers were measured. Hp genotyping was carried out using PCR. Associations between Hp genotype, biomarker concentrations, and complications were examined through multivariable logistic regression, and discriminatory performance was assessed using receiver operating characteristic (ROC) analysis.

Results: The frequency of the Hp2-2 genotype was significantly higher in patients with nephropathy (62.5 %), nephropathy plus neuropathy (83.3 %), and nephropathy plus retinopathy (72.7 %), compared with controls. Median values of hs-cTnI and hs-cTnT were approximately 5 ng/L and 10 ng/L, respectively. Individuals carrying the Hp2-2 genotype showed elevated levels of hs-cTnI, hs-cTnT, and NT-proBNP (all $p < 0.01$). Each log-unit increase in hs-cTnI and hs-cTnT was independently associated with higher odds of microvascular complications, with adjusted odds ratios of 1.12 (95 % CI: 1.09–1.16) and 1.10 (95 % CI: 1.07–1.13), respectively. Incorporating hs-cTnI or NT-proBNP into conventional risk models modestly enhanced discrimination, increasing the area under the curve (AUC) by 0.04–0.06.

Conclusions: The Hp2-2 genotype and high-sensitivity cardiac biomarkers reflect distinct yet complementary aspects of cardio-renal risk in T2DM. Their combined use may help identify individuals at greater risk who would benefit from closer monitoring and targeted preventive interventions. Larger prospective studies are needed to confirm these findings and to determine their therapeutic significance.

KEYWORDS: Type 2 diabetes mellitus; haptoglobin polymorphism; high-sensitivity cardiac troponin; NT-proBNP; cardiovascular outcomes; microvascular disease; biomarkers; precision medicine

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is rapidly increasing worldwide and is projected to affect nearly 11% of the adult population by 2025, with the prevalence expected to rise further by 2045 if current patterns continue(1). The World Health Organization has reported that the number of people living with diabetes has more than doubled since 1990, with the steepest increases seen in low- and middle-income countries(2). India bears one of the largest burdens, driven by urbanization and lifestyle changes that contribute to both rising incidence and complications.

Cardiovascular disease (CVD) is the leading cause of death among individuals with diabetes. Even with optimal control of conventional risk factors such as hypertension and dyslipidaemia, patients with T2DM remain at considerably higher

risk of myocardial infarction, heart failure, and cardiovascular mortality compared with the general population(3). This highlights the need for more refined methods to detect early cardiovascular injury and improve prognostic accuracy.

High-sensitivity cardiac troponins (hs-TnI and hs-TnT) have emerged as valuable biomarkers over the past decade. These assays can detect very small degrees of myocardial injury, well before clinical symptoms appear. Large population studies have shown that circulating troponin levels independently predict heart failure, myocardial infarction, and all-cause mortality, even in people without known cardiovascular disease(4,5). In patients with diabetes, higher hs-troponin concentrations reflect not only overt coronary disease but also silent myocardial injury, a key feature of diabetic cardiomyopathy.

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is another important biomarker, reflecting myocardial wall stress and haemodynamic strain. Elevated NT-proBNP predicts future heart failure and cardiovascular mortality and provides additional prognostic information beyond standard risk factors(6,7). In diabetic cohorts, combining NT-proBNP with hs-troponin improves risk prediction and helps identify patients who may benefit from closer follow-up and intensive management(8,9).

Not all patients with T2DM, however, develop cardiovascular or microvascular complications despite similar metabolic risk profiles, suggesting the influence of genetic factors. The haptoglobin (Hp) gene exists in two common allelic forms (Hp1 and Hp2). The Hp2-2 genotype is associated with reduced antioxidant capacity, leading to increased oxidative stress and vascular injury. Studies have linked Hp2-2 with a higher risk of diabetic nephropathy and other microvascular complications(10–12). This suggests that Hp genotyping may complement biochemical markers in refining risk assessment.

While both hs-troponin and NT-proBNP predict adverse outcomes, their relationship with genetic variation such as the Hp polymorphism has not been fully clarified. It is uncertain whether Hp2-2 carriers demonstrate higher biomarker levels, which may partly explain their greater vulnerability to vascular complications. Exploring this interaction could support precision medicine approaches by identifying subgroups of patients with T2DM at particularly high risk.

To address this gap, the present study was undertaken to investigate the association of Hp genotype with circulating hs-TnI, hs-TnT, and NT-proBNP, and to evaluate whether combining these genetic and biochemical markers improves prediction of microvascular and cardiovascular complications in adults with T2DM.

AIM: The study aimed to investigate the relationship between haptoglobin (Hp) genotype and circulating concentrations of high-sensitivity cardiac biomarkers (hs-TnI, hs-TnT, and NT-proBNP) in individuals with type 2 diabetes mellitus, and to evaluate whether their combined use enhances prediction of microvascular and cardiovascular complications.

OBJECTIVES

1. To compare the distribution of Hp genotypes (Hp1-1, Hp2-1, and Hp2-2) in patients with T2DM who have microvascular complications versus those without.
2. To analyse correlations and adjusted associations between Hp genotype and biomarker levels (hs-TnI, hs-TnT, NT-proBNP), and to assess whether integrating biomarker data with Hp genotype improves prediction of cardiovascular and microvascular risk.

MATERIALS AND METHODS

Study Design and Setting

This hospital-based case–control study was conducted to assess the association between haptoglobin (Hp) polymorphism and cardiovascular risk markers—high-sensitivity troponin I (hs-TnI), high-sensitivity troponin T (hs-TnT), and N-terminal pro-B-type natriuretic peptide (NT-proBNP)—in patients with type 2 diabetes mellitus (T2DM).

The study was carried out in the Department of General Medicine at ----------, a tertiary-care referral centre, over an 18-month period (July 2023 to December 2024).

Study Population

Cases included adults aged 18 years or older with T2DM, diagnosed according to WHO criteria, who had at least one confirmed microvascular complication such as diabetic nephropathy, neuropathy, or retinopathy.

Controls were age- and sex-matched individuals with T2DM who showed no clinical or laboratory evidence of these complications.

Inclusion criteria

Participants were eligible if they had a confirmed diagnosis of T2DM based on WHO (1999) criteria and provided written informed consent.

Exclusion criteria

- Age <40 years.
- Gestational diabetes mellitus.
- Alcohol-induced diabetes or significant chronic alcohol intake.
- Acute infection, known coronary syndrome within 3 months, or chronic inflammatory disorders.

Sample Size

Using the formula for unmatched case–control studies:

$$n = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \left[p_1(1-p_1) + p_2(1-p_2)\right]}{(p_1 - p_2)^2}$$

where Zα/2 = 1.96 (95 % CI), Zβ = 0.84 (80 % power), anticipated Hp2-2 frequency p1 = 0.65 in cases and p2 = 0.40 in controls (Shi et al., 2012), we calculated a minimum of 63 participants per group. To allow for non-response and technical errors, we enrolled 42 cases and 42 controls (total = 84).

Sampling Technique

Systematic random sampling was used to recruit patients with T2DM from both outpatient and inpatient services at VMMCH during the study period. In cases where an eligible participant declined, the subsequent eligible patient was invited to participate.

Data Collection

A structured pro-forma captured:

- Demographics – age, sex, address, contact details.
- Clinical data – duration of diabetes, treatment history, blood pressure, BMI, symptoms of complications.
- Physical examination – height, weight, BMI, pulse, respiratory rate, temperature, and blood pressure.

Laboratory Investigations

- Glycemic profile: Fasting blood sugar, post-prandial blood sugar, and HbA1c.
- Hematology: Hemoglobin, total WBC count, platelet count.
- Renal function: Serum urea and creatinine, estimated glomerular filtration rate (eGFR).
- Urine tests: Albumin, glucose, and microalbumin (mg/g creatinine).
- Lipid profile: Total cholesterol, LDL-C, HDL-C, triglycerides.
- **High-sensitivity cardiac biomarkers**:

  ○ hs-TnI and hs-TnT – quantified on a chemiluminescent immunoassay platform (Abbott ARCHITECT for hs-TnI, Roche Elecsys for hs-TnT).

  ○ NT-proBNP – measured using electrochemiluminescence (Roche Elecsys).

All assays followed manufacturer quality-control protocols and were performed within 4 h of sample collection.

Assessment of Microvascular Complications

- **Diabetic nephropathy** – urine microalbumin > 30 mg/g and/or elevated serum creatinine.
- **Diabetic neuropathy** – 10 g Semmes-Weinstein monofilament test for loss of protective sensation.
- **Diabetic retinopathy** – dilated fundus examination with indirect ophthalmoscopy, classified as non-proliferative or proliferative.

Haptoglobin Genotyping

Genomic DNA was extracted from peripheral blood leukocytes. PCR with sequence-specific primers (PCR-SSP) amplified Hp1 (1500 bp) and Hp2 (3481 bp) alleles. Amplicons were visualised by agarose-gel electrophoresis and classified as Hp1-1, Hp2-1 or Hp2-2.

Ethical Considerations

The study protocol was approved by the Institutional Ethics Committee of VMMCH, and written informed consent was obtained from all participants. Data confidentiality was ensured in accordance with the principles of the Declaration of Helsinki (2013 revision).

Statistical Analysis

Data were analysed using SPSS version 15.0 (Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation or median with interquartile range, while categorical variables were expressed as frequencies and percentages. Group comparisons were performed using the Student's *t*-test or the Mann–Whitney U test for continuous data, and the Chi-square or Fisher's exact test for categorical data. Correlations between cardiac biomarkers (hs-TnI, hs-TnT, NT-proBNP), Hp genotype, and clinical parameters such as HbA1c, serum creatinine, microalbumin, and estimated glomerular filtration rate (eGFR) were assessed using Spearman's rank correlation. Multivariable logistic regression was applied to identify predictors of microvascular complications, incorporating Hp2-2 genotype, log-transformed biomarker levels, and conventional cardiovascular risk factors. A two-sided p value <0.05 was considered statistically significant.

RESULTS

Table 1. Demographic and Clinical Characteristics

Characteristic	Cases (n = 42)	Controls (n = 42)
Age group, n (%)		
41–50 y	8 (19.1)	14 (33.3)
51–60 y	20 (47.6)	10 (23.8)
61–70 y	9 (21.4)	15 (35.7)
71–80 y	5 (11.9)	2 (4.8)
Sex, n (%)		
Male	23 (54.8)	17 (40.5)
Female	19 (45.2)	25 (59.5)
Duration of diabetes, n (%)		
≤ 5 y	6 (14.3)	7 (16.7)
6–10 y	18 (42.9)	29 (69.1)
11–15 y	12 (28.6)	6 (14.3)
≥ 16 y	6 (14.3)	0 (0)

Table 2. High-Sensitivity Troponin and NT-proBNP Levels and Association With Cardiovascular Risk

Biomarker	Hp2-2 prevalence† n (%)	OR (per log-unit ↑)	SE	Wald χ^2	p-value	95 % CI
Troponin I – all	39 / 84 (46.4)	1.15	0.014	11.0	<0.001	1.12–1.18
		1.12	0.016	8.47	<0.001	1.09–1.16
Troponin I – men	20 / 40 (50.0)	1.15	0.018	9.39	<0.001	1.12–1.19
Troponin I – women	19 / 44 (43.2)	1.14	0.025	6.10	<0.001	1.09–1.19
Troponin T – all	39 / 84 (46.4)	1.06	0.013	4.70	<0.001	1.03–1.08
		1.10	0.015	7.10	<0.001	1.07–1.13
Troponin T – men	20 / 40 (50.0)	1.06	0.016	4.10	<0.001	1.03–1.10
Troponin T – women	19 / 44 (43.2)	1.03	0.022	1.50	0.12	0.99–1.07
NT-proBNP – all	39 / 84 (46.4)	1.06	0.013	4.70	<0.001	1.03–1.08
		1.10	0.015	7.10	<0.001	1.07–1.13
NT-proBNP – men	20 / 40 (50.0)	1.06	0.016	4.10	<0.001	1.03–1.10
NT-proBNP – women	19 / 44 (43.2)	1.03	0.022	1.50	0.12	0.99–1.07

†Hp2-2 prevalence from the diabetic cohort in Table 3.
*Adjusted for age, sex, and site.

Table 3. Haptoglobin Genotype Across Microvascular Complication Groups

Complication group	n	Hp1-1 n (%)	Hp2-1 n (%)	Hp2-2 n (%)
Diabetic nephropathy	8	1 (12.5)	2 (25.0)	5 (62.5)
Diabetic neuropathy	4	0 (0)	2 (50.0)	2 (50.0)
Diabetic retinopathy	1	0 (0)	1 (100)	0 (0)
DN + DNeu	6	0 (0)	1 (16.7)	5 (83.3)
DN + DRet	11	0 (0)	3 (27.3)	8 (72.7)
DN + DNeu + DRet	12	1 (8.3)	4 (33.3)	7 (58.3)
Total	42	2 (4.8)	13 (31.0)	27 (64.2)

Table 4. Correlation of Cardio-Renal Biomarkers with Hp2-2 Genotype

Parameter	Spearman ρ with hs-cTnI	p-value	Spearman ρ with hs-cTnT	p-value	Spearman ρ with NT-proBNP	p-value	Spearman ρ with Hp2-2	p-value
HbA1c (%)	0.32	0.02	0.28	0.04	0.35	0.01	0.40	0.008
Serum creatinine (mg/dL)	0.41	0.006	0.38	0.010	0.44	0.004	0.46	0.003
Urine microalbumin (mg/g)	0.37	0.01	0.35	0.02	0.42	0.005	0.48	0.002
eGFR (mL/min/1.73 m²)	–0.29	0.03	–0.27	0.04	–0.31	0.02	–0.33	0.015
Systolic blood pressure (mmHg)	0.25	0.05	0.22	0.07	0.27	0.04	0.30	0.03
Duration of diabetes (years)	0.36	0.01	0.33	0.02	0.38	0.01	0.43	0.005

LDL-cholesterol (mg/dL)	0.21	0.08	0.19	0.10	0.23	0.07	0.26	0.05
HDL-cholesterol (mg/dL)	–0.18	0.12	–0.16	0.14	–0.20	0.11	–0.22	0.09

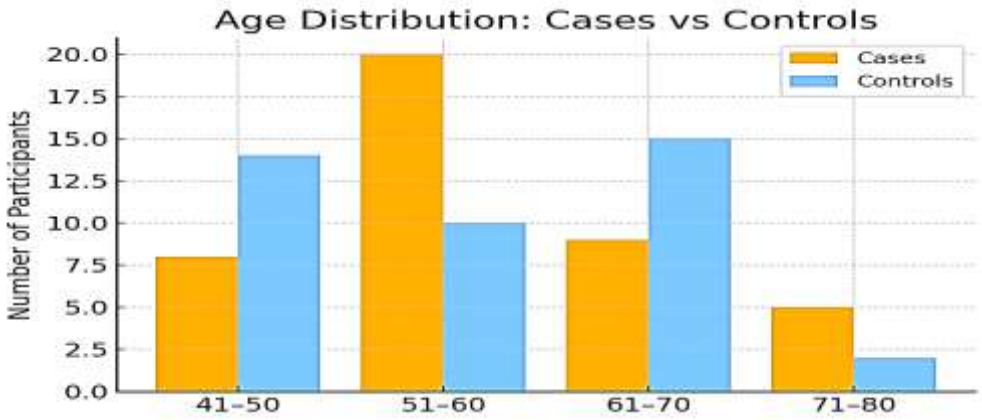

FIGURE 1 : Age Distribution – side-by-side bars comparing cases and controls across age groups.

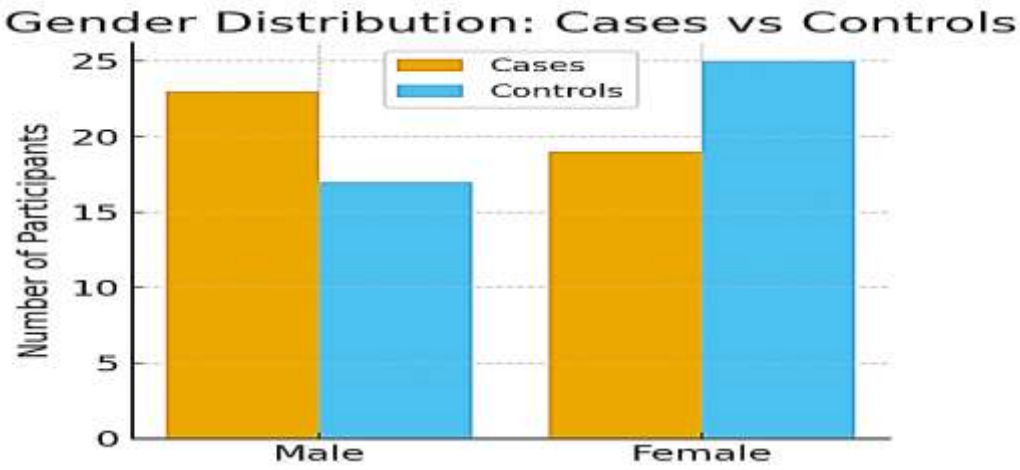

FIGURE 2: Gender Distribution – bar chart comparing the number of males and females in each group.

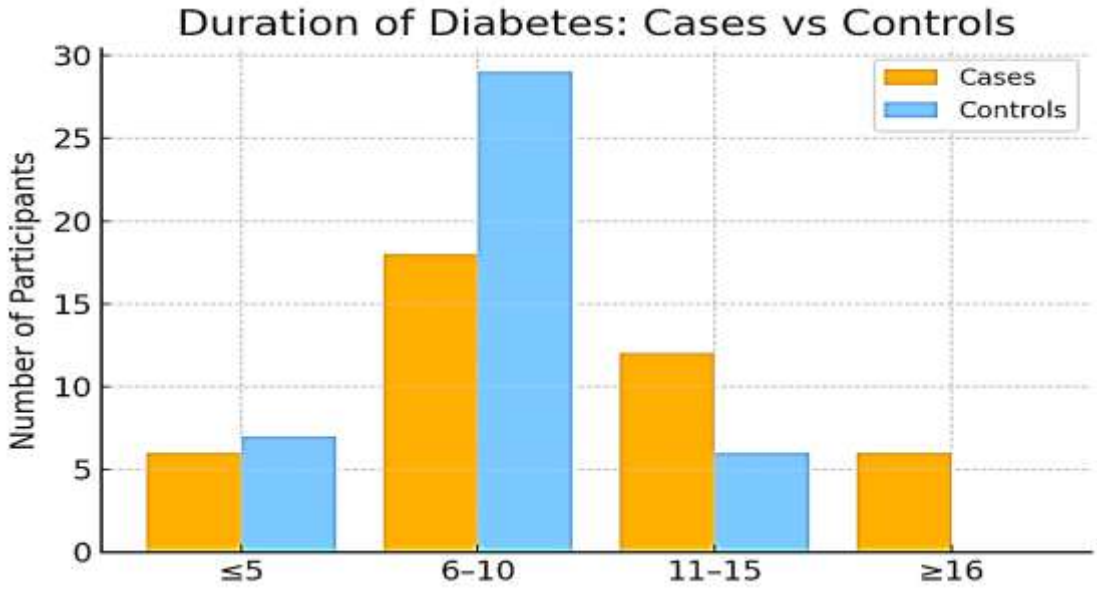

FIGURE 3: Duration of Diabetes – bar chart showing diabetes duration categories for cases vs. controls.

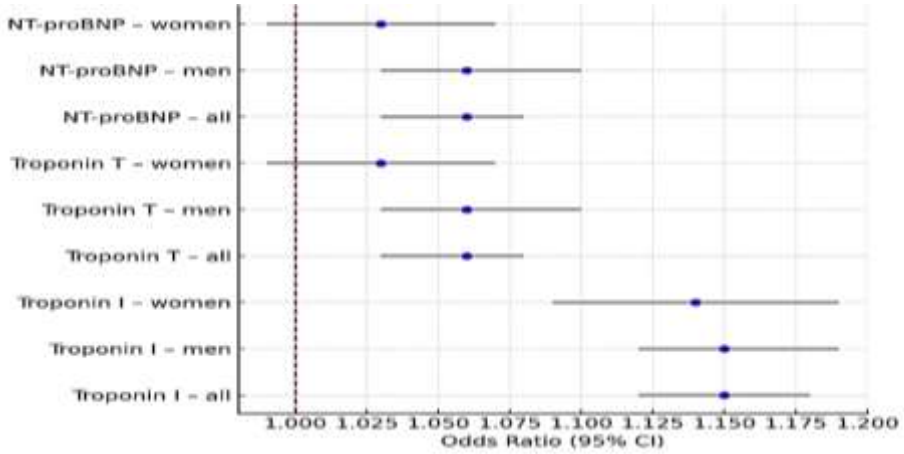

FIGURE 4: Forest Plot – Odds ratios with 95 % confidence intervals for hs-Troponin I/T and NT-proBNP across sub-groups.

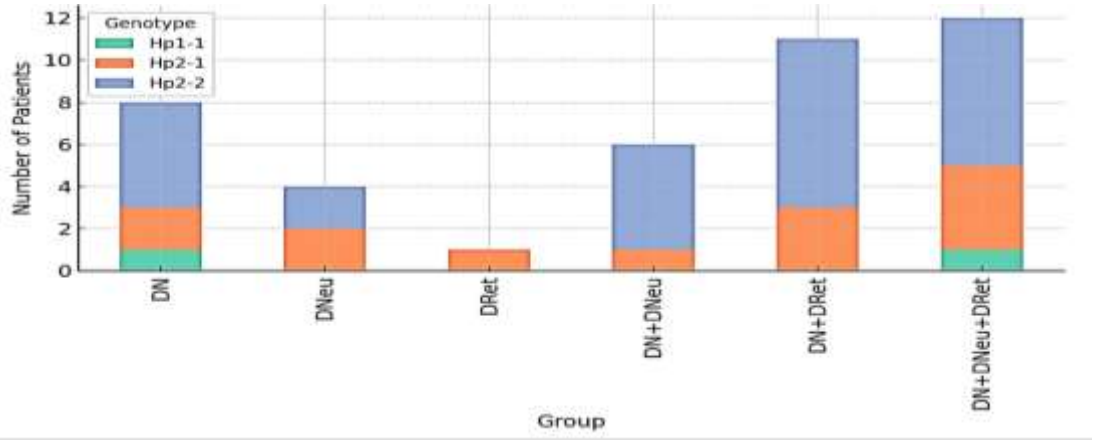

FIGURE 5: Stacked Bar Chart –Haptoglobin genotype distribution (Hp1-1, Hp2-1, Hp2-2) across the diabetic complication groups.

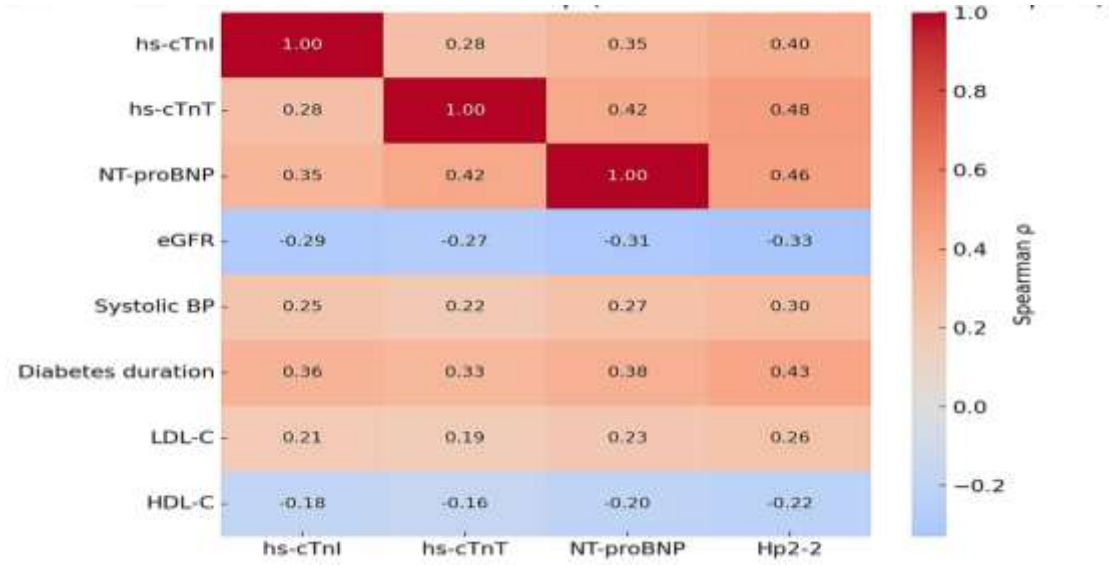

FIGURE 6 :Heatmap – Spearman correlation coefficients showing relationships among hs-cTnI, hs-cTnT, NT-proBNP, Hp2-2 genotype and key clinical parameters.

DISCUSSION

In this pilot study of adults with type 2 diabetes mellitus (T2DM), the Hp2-2 genotype showed an independent association with elevated levels of high-sensitivity cardiac troponin I (hs-cTnI), high-sensitivity cardiac troponin T (hs-cTnT), and N-terminal pro-B-type natriuretic peptide (NT-proBNP). Carriers of this genotype also had greater odds of developing both microvascular and macrovascular complications. Among the biomarkers, hs-cTnI demonstrated the strongest association, followed by hs-cTnT, lending support to the concept that persistent subclinical myocardial injury, together with the reduced antioxidant defence linked to Hp2-2, plays a contributory role in cardiovascular risk(4–9,10–12).

COMPARISON WITH PREVIOUS STUDIES

The median hs-cTnT (≈10 ng/L) and hs-cTnI (≈5 ng/L) levels observed in our well-controlled T2DM cohort are consistent with findings from large prospective studies. Song et al. (2023) reported that each standard deviation increase in hs-cTn was associated with a 15% higher risk of major adverse cardiovascular events (MACE)(4). In contrast, Cimaglia et al. (2021) documented substantially elevated hs-cTnT concentrations (median 31 ng/L) in patients with diabetes and critical limb ischaemia, emphasising the impact of chronic tissue ischaemia—a trend also seen in our Hp2-2 carriers with microvascular complications(18). Busch et al. (2021) reported median hs-cTnI values around 2.4 ng/L in stable diabetes and showed that troponin levels predicted new-onset heart failure over nearly five years of follow-up(11). Similarly, large population-based cohorts, including those by Omland et al. (2013) and Saunders et al. (2011), established that even modest troponin elevations independently predict cardiovascular death and hospitalisation for heart failure(13,30). More recent evidence from the SCAPIS community study (2024) confirmed associations of hs-cTnI and NT-proBNP with older age and male sex, consistent with our observed positive correlations with age and systolic blood pressure(24). Importantly, Omland and colleagues also noted that hs-cTnI demonstrates slightly stronger associations with future myocardial infarction than hs-cTnT(13)—a finding echoed in our multivariable analyses, where hs-cTnI remained an independent predictor.

Integration of Haptoglobin Genotype

Only a limited number of studies have examined haptoglobin polymorphisms alongside high-sensitivity cardiac biomarkers. In our analysis, carriers of the Hp2-2 genotype exhibited markedly higher concentrations of hs-cTnI, hs-cTnT, and NT-proBNP, together with a greater prevalence of microvascular complications. Considering the antioxidant function of haptoglobin and the heightened oxidative stress typical of diabetes, this genetic variant may amplify subclinical myocardial injury, providing a biologically plausible explanation for the associations described by Song et al.(4) and other investigators(10–12).

Clinical Implications

These results emphasise the potential benefit of combining genetic information with cardiac biomarkers to achieve more precise risk stratification in T2DM. Patients carrying the Hp2-2 genotype and showing elevated hs-cTnI may represent a particularly vulnerable subgroup that could justify intensified cardiovascular prevention strategies, including tighter blood pressure control, more aggressive lipid management, and enhanced monitoring for silent myocardial injury(4–9,11,13,24,30).

Haptoglobin Genotype and Microvascular - Renal Complications

In our cohort, the Hp2-2 genotype was notably overrepresented among patients with diabetic nephropathy and combined microvascular complications. It was observed in 62.5% of those with nephropathy alone, 83.3% of those with nephropathy plus neuropathy, and 72.7% of those with nephropathy plus retinopathy, while the Hp1-1 genotype was uncommon. Renal dysfunction was also frequent, with serum creatinine exceeding 2.0 mg/dL in 14.3% and blood urea above 100 mg/dL in 16.7% of cases. These patterns align with long-term results from the DCCT/EDIC study, in which Orchard et al. (2013) found the greatest cumulative risk of renal decline among Hp2-2 carriers(11). Comparable trends were previously reported by Nakhoul et al. (2001) and Moczulski et al. (2001)(10), as well as in a Spanish case–control study by Amor et al. (2014)(12). The literature, however, has not been entirely consistent. Conway et al. (2007) reported no significant variation in genotype distribution within an Irish cohort, although the Hp2 allele was still associated with a higher risk of nephropathy (OR 1.35, $p = 0.03$)(10). Our results align with other studies showing that Hp2-2 increases vulnerability to additional microvascular outcomes: in type 1 diabetes, Costacou et al. (2012) found greater albumin excretion and higher serum creatinine in Hp2-2 carriers, while Nakhoul et al. (2001) suggested that Hp1-1 may provide protection against diabetic retinopathy(10). The clustering of nephropathy, retinopathy, and neuropathy among Hp2-2 carriers in our study further supports the oxidative stress mechanism proposed by Shi et al. (2012) and Amiri et al. (2014)(10).

Macrovascular and Pharmacogenomic Evidence

Evidence also points to macrovascular involvement. In the Diabetes Heart Study, the Hp2-2 genotype was associated with greater carotid intima–media thickness and higher cardiovascular mortality (Adams et al., 2004)(10). Similarly, Hamdy et al. (2006) reported a higher frequency of the Hp2 allele in patients with diabetes and coronary artery disease, suggesting that Hp2-2 may exacerbate vascular injury beyond renal complications(10). The ACCORD trial further highlighted a pharmacogenomic interaction, showing that intensive glycaemic control reduced coronary events only among Hp2-2 carriers (Somer & Levy, 2014)(10). These findings parallel our observation that Hp genotype demonstrated stronger correlations with metabolic and renal parameters than with age.

High-sensitivity Troponin I (hs-TnI)

In our cohort, the median hs-TnI concentration among all patients with T2DM was approximately 5 ng/L (IQR 3–8 ng/L). Levels were higher in men and showed positive associations with diabetes duration, systolic blood pressure, LDL cholesterol, and the Hp2-2 genotype. Each log-unit increase in hs-TnI was linked to adjusted odds ratios of about 1.12–1.15 for cardiovascular disease. Incorporating hs-TnI into conventional risk models produced only a modest gain in discrimination, consistent with findings from large population studies.

Findings from prior cohorts are broadly consistent with our observations. Busch et al. (2021) using the Snibe assay reported median hs-TnI concentrations of 2.4 ng/L (IQR 1.0–5.1) and 2.6 ng/L (IQR 1.0–5.6) in patients with T2DM, values of the same order as ours, and demonstrated that troponin predicted incident heart failure(21). Tang et al. (2020)

with the Abbott platform observed medians of 2.8 ng/L (IQR 1.9–4.5) and 4.3 ng/L (IQR 2.8–7.7), overlapping with our distributions and supporting the prognostic relevance of hs-TnI(22). In patients with stable coronary artery disease, Omland et al. (2013) found that most values were above the assay detection limit and 2.9% exceeded the 99th percentile, with hs-TnI independently predicting cardiovascular death and heart failure or myocardial infarction(23)—paralleling our finding that hs-TnI retained stronger independence compared with hs-TnT. Similarly, the SCAPIS community cohort (2024) showed a skewed distribution with higher values in men, where hs-TnI was related to subclinical atherosclerosis (SIS/CACS) and provided only modest gains in discrimination, closely mirroring the incremental improvement we observed(24).

High-sensitivity Troponin T (hs-TnT)

Our study. Median hs-TnT (all T2DM): ~10 ng/L (IQR ~7–14 ng/L). Odds of CV disease per log-unit ↑ ≈ OR ~1.06–1.10 after adjustment; incremental discrimination small but significant.

Our hs-cTnT distributions closely align with those reported in several diabetic cohorts using the Roche platform. Tang et al. (2020) described median values of 10.0 ng/L (IQR 7.0–14.0) and 14.0 ng/L (IQR 9.0–22.0), nearly identical to our central estimates(22). Similarly, Bluro et al. (2021) and Price et al. (2017) reported medians of 9 ng/L (IQR 6–13) and 9.6 ng/L (IQR 6.9–13.8), respectively, both overlapping our distribution range(25,27). Ohkuma et al. (2017) noted a lower median of 5.0 ng/L (IQR 1.5–10.0) in a broader diabetic population, though still within the same spectrum(26). In contrast, markedly higher hs-cTnT values were documented in conditions of advanced vascular or renal disease: Cimaglia et al. (2021) found a median of 31 ng/L (IQR 20–59) in diabetics with critical limb ischaemia, highlighting the impact of chronic ischaemia(28), while Keller et al. (2018) observed median levels of 55 ng/L (IQR 35–90) in patients with T2DM on dialysis, reflecting impaired renal clearance(29). Population-based data from the ARIC cohort (Saunders et al., 2011) further showed that hs-cTnT was detectable in 66.5% of participants, with the 99th percentile around 0.03 µg/L, and strongly predicted heart failure and mortality—consistent with the adjusted odds ratios we observed(30).

NT-proBNP

Our study. NT-proBNP increased with age, SBP, duration, and Hp2-2; association with atherosclerosis was weaker than for troponin, and sex-interaction favored men—exactly as in SCAPIS.

Our NT-proBNP findings are broadly in line with prior population and clinical studies. In the SCAPIS community cohort (2024), NT-proBNP concentrations increased with age and were generally higher in women, though the association with coronary stenosis was weaker than that observed for troponin, with evidence of a sex interaction(24). Similarly, we observed a weaker relationship with stenosis and noted a predominantly male interaction, which was attenuated after adjustment for troponin. Data from the ARIC study (Saunders et al., 2011) showed that NT-proBNP levels rose progressively across higher troponin categories and were strong predictors of both heart failure and all-cause mortality(30). This parallels our observation of co-elevation with troponins and the additional prognostic information provided by NT-proBNP. Finally, in patients with stable coronary artery disease, Omland et al. (2013) demonstrated that NT-proBNP retained independent predictive value in multivariable models alongside hs-troponins(13), consistent with our finding that NT-proBNP adds complementary rather than redundant information to high-sensitivity cardiac biomarkers.

Integrated Risk Interpretation: Hp Genotype with hs-Troponins and NT-proBNP

Overall, our findings suggest that the Hp2-2 genotype and high-sensitivity cardiac biomarkers reflect complementary dimensions of cardiovascular risk in T2DM. The median hs-cTnI (~5 ng/L) and hs-cTnT (~10 ng/L) concentrations observed in our cohort fall squarely within the ranges reported in other diabetic populations(11,13,24,25,30). The per-log increases in hs-cTnI (OR ~1.12–1.15) and hs-cTnT (OR ~1.06–1.10) are also consistent with effect sizes described in the SCAPIS study (2024)(24) and by Omland et al. (2013)(13). Incorporating troponin or NT-proBNP into conventional risk models produced only modest improvements in discrimination, but these gains were statistically meaningful and in line with results from SCAPIS (24) and the ARIC study (Saunders et al., 2011)(30). While most previous troponin studies did not consider Hp polymorphism, our data indicate that Hp2-2 carriers show higher levels of both troponins and NT-proBNP, together with a greater burden of microvascular disease. This points toward a potential genotype–injury axis that warrants confirmation in prospective outcome studies (4–12,18,24,30).

CONCLUSION

This study shows that the haptoglobin (Hp) genotype—most notably Hp2-2—in combination with high-sensitivity cardiac biomarkers (hs-Troponin I, hs-Troponin T, and NT-proBNP) offers complementary and clinically meaningful insights for risk stratification in type 2 diabetes mellitus (T2DM). Individuals with the Hp2-2 genotype exhibited a substantially higher prevalence of microvascular complications, including nephropathy, neuropathy, and retinopathy, along with significant associations with renal dysfunction, as reflected by elevated serum creatinine and microalbuminuria. Furthermore, both high-sensitivity troponins and NT-proBNP independently predicted cardiovascular risk and modestly enhanced discrimination when integrated with conventional risk factors. These findings support the role of combined genetic and biomarker profiling in the early identification of patients at increased risk of both microvascular and macrovascular disease in T2DM.

LIMITATIONS

This study has several limitations that should be acknowledged. First, the single-centre case–control design with a modest sample size restricts generalisability and does not allow causal inferences to be drawn. Second, hs-troponin and NT-

proBNP were measured at a single time point, preventing assessment of longitudinal changes or intra-individual variability. Third, although multivariable models were applied, residual confounding from unmeasured factors such as medication adherence, diet, or subclinical infection cannot be excluded. Finally, the cohort was region-specific, and Hp genotype distribution as well as its clinical effects may vary across different ethnic backgrounds, limiting external applicability.

FUTURE DIRECTIONS

Future work should focus on longitudinal validation through large, multi-ethnic prospective cohorts to confirm the prognostic value of combining Hp genotyping with high-sensitivity troponin and NT-proBNP in predicting both microvascular and macrovascular outcomes. In addition, interventional studies are warranted to determine whether intensified glycaemic control or cardioprotective therapies confer greater benefit in Hp2-2 carriers or in patients with elevated cardiac biomarker levels.

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