Research Article

Plasma Gasdermin D as a Biomarker for Pyroptosis in Early Detection of Newly Diagnosed Type 2 Diabetes Mellitus

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Article Info

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Keywords

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Abstract

Pyroptosis, a caspase-mediated inflammatory cell death pathway driven by Gasdermin D (GSDMD), has emerged as a potential mechanistic link between metabolic stress, β-cell injury, and chronic inflammation in Type 2 diabetes mellitus (T2DM). This study evaluated plasma GSDMD as a biomarker for newly diagnosed T2DM and explored its metabolic and inflammatory correlates. In a hospital-based case–control study, 130 newly diagnosed T2DM patients and 130 age- and sex-matched normoglycemic controls were recruited. Anthropometric indices, glycemic parameters, βFins, HOMA-IR, HOMA-β, lipid profile, and hs-CRP were measured using standard methods. Plasma GSDMD, IL-18, and IL-1β were quantified by ELISA. Group differences, correlations, multivariable logistic regression, and receiver operating characteristic (ROC) analyses were performed. T2DM patients exhibited higher BMI, adverse lipid profile, increased hs-CRP, and marked elevation of GSDMD, IL-18, and IL-1β compared with controls (all $p<0.0001$). Plasma GSDMD correlated positively with FBS, HbA1c, HOMA-IR, IL-18, IL-1β, and hs-CRP, and negatively with HOMA-β, indicating close links to hyperglycemia, insulin resistance, β-cell dysfunction, and systemic inflammation. In adjusted models, GSDMD remained an independent predictor of T2DM (OR 1.18 per 10 pg/mL, 95% CI 1.09–1.29), alongside IL-18, hs-CRP, higher BMI, and lower HDL-C. ROC analysis showed excellent diagnostic performance for GSDMD (AUC 0.98, 95% CI 0.96–0.99; cutoff 17.5 pg/mL; sensitivity 93.0%; specificity 97.0), superior to IL-18, IL-1β, and hs-CRP. Plasma GSDMD is markedly elevated in T2DM and integrates metabolic and inflammatory information, functioning as an independent risk factor and highly accurate diagnostic biomarker. These findings support GSDMD-mediated pyroptosis as a promising target for early diagnosis and risk stratification in T2DM.

Introduction

The International Diabetes Federation projects 693 million diabetes cases among adults aged 18 and older by 2045 [1]. This chronic metabolic-inflammatory disease arises from deficient insulin secretion or resistance, disrupting anabolic-catabolic equilibrium and elevating blood glucose [2]. Type 2 diabetes mellitus (T2DM) features insulin shortfall and target-cell resistance alongside β-cell impairment, predisposing to complications like cardiomyopathy, nephropathy, and atherosclerosis [3].

Microvascular progression involves interconnected pathways including amplified polyol/hexosamine activity, advanced glycation end-products (AGEs), protein kinase C isoforms, oxidative stress, and diminished antioxidant defences [4]. T2DM commonly presents mixed dyslipidemia with raised triglycerides, lowered HDL-C, and small dense atherogenic LDL-C particles. Chronic sterile inflammation - elevated IL-6 and IL-1β - critically drives disease onset and advancement [5].

Pyroptosis, an inflammatory programmed cell death first identified in Salmonella-infected macrophages, activates via caspase-1/4/5/11 responding to damage- or pathogen-associated molecular patterns, triggering IL-1β/IL-18 release. Gasdermin D (GSDMD), cleaved by these caspases, produces an N-terminal fragment that forms plasma membrane pores, facilitating cytokine efflux and pyroptotic lysis. GSDMD regulates immune cell death and proinflammatory mediator release, accelerating conditions like T2DM [6,7].

Chronic hyperglycemia and inflammation induce insulin resistance in T2DM. High-glucose/fat milieus elevate ROS, activating NLRP3 inflammasomes and caspase-1 to cleave GSDMD, promoting pyroptosis. This intensifies islet inflammation, β-cell loss, and structural damage through cytokine amplification [8].

As per the above content, this study evaluates plasma GSDMD differences across glucose metabolism states, its correlations with disease severity, independent risk for T2DM onset, and diagnostic value via ROC analysis to enable early screening.

Methdology

Study Setting and Design

This hospital-based case–control study was conducted in the Department of Biochemistry in collaboration with the Department of General Medicine at Integral Institute of Medical Sciences & Research, Integral University, Lucknow, Uttar Pradesh, India, a tertiary care teaching hospital. A total of 260 subjects were enrolled, including 130 newly diagnosed Type 2 diabetes mellitus (T2DM) patients and 130 age- and gender-matched normoglycemic controls with no history of T2DM diagnosed as T2DM as per ADA guideline considered as cases and Non-T2DM patients were considered as control.

Diagnostic Criteria

T2DM was diagnosed according to the American Diabetes Association (ADA) criteria: fasting blood glucose (FBG) ≥7.0 mmol/L (126 mg/dL) and/or glycated hemoglobin (HbA1c) ≥6.5%. Normoglycemic controls had FBG <5.6 mmol/L and HbA1c <5.7% and didn't meet any diagnostic criteria for T2DM [9,10].

Inclusion and Exclusion Criteria

The study enrolled participants aged 18–55 years who were either newly diagnosed with Type 2 Diabetes Mellitus (T2DM) according to ADA 2020 criteria or were normoglycemic.

To ensure a controlled cohort, individuals were excluded if they had other forms of diabetes (Type 1, gestational, or secondary), active infections, or recent acute cardiovascular or cerebrovascular events. Furthermore, the study barred those with malignant tumors, heart failure, or severe hepatic or renal dysfunction, as well as anyone with a history of diabetic ketoacidosis or hyperosmolar hyperglycemic states. Finally, patients currently using systemic corticosteroids, immunosuppressants, or lipid-lowering medications were disqualified from participation.

Ethical consideration

Ethics approval was granted by the Institutional Ethics Committee of Integral Institute of Medical Sciences & Research, Integral University, Lucknow approval number: IEC/IIMSR/2025/79, dated 11/07/2025.

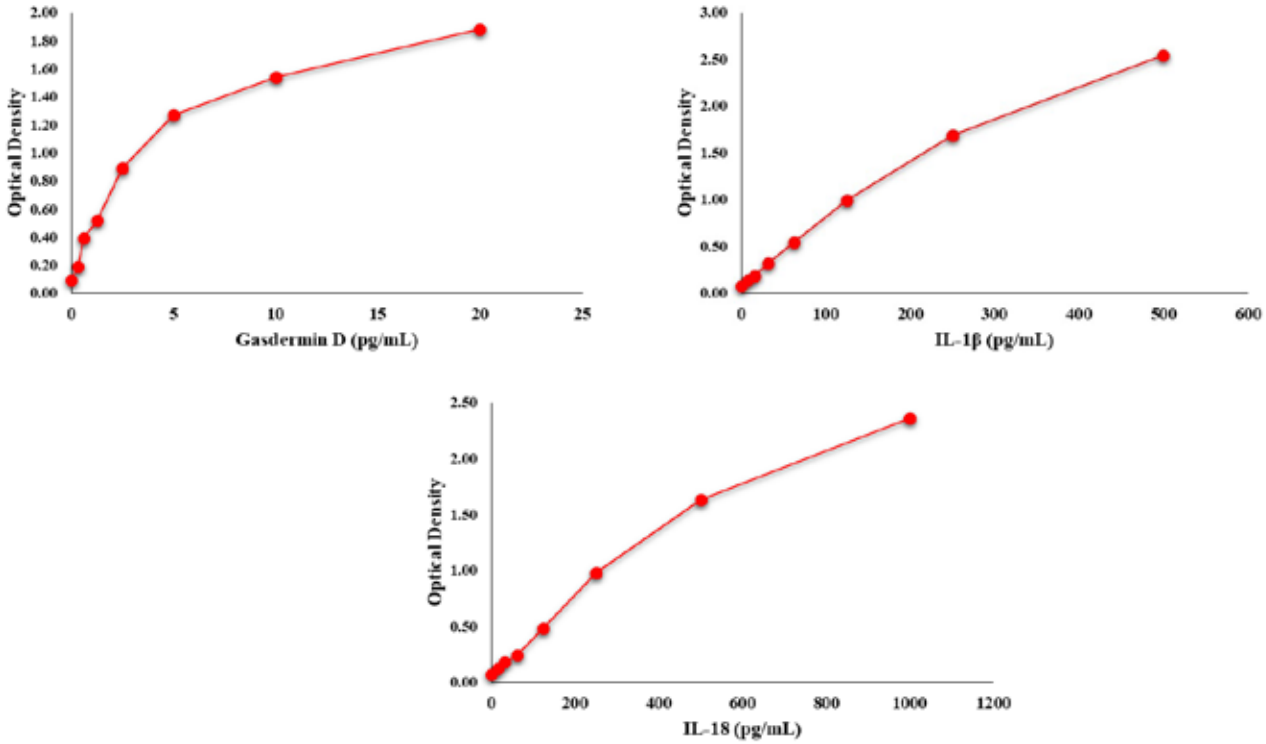
Clinical Data Collection

Demographic, anthropometric, Fasting Insulin (Fins), FBS, HbA1c, high-sensitivity C-reactive protein (hs-CRP), and lipid profile were recorded from patient sheet were recorded. The homeostasis model assessment indices were calculated as follows: HOMA-β = 20 × Fins (μIU/mL) / [FBG (mmol/L) − 3.5] and HOMA-IR = FBG (mmol/L) × Fins (μIU/mL) / 22.5.

Sample Collection and Biomarker Assays

All participants had an overnight fast of at least 8 hours. On the following morning, 5 mL of venous blood was collected in EDTA vial and centrifuged at 3500 rpm for 15 minutes. Plasma was used to do ELISA experiment. Plasma Gasdermin D (GSDMD) (ELK Biotechnology; Catalog no. ELK-5357), interleukin-18 (IL-18) (Elabscience ; Catalog no. E-EL-H0253), and interleukin-1β (IL-1β) (Elabscience ; Catalog no. E-EL-H0149) were quantified using an ELISA-based platform , with all calibration, quality-control, and validation procedures performed as per the kit manuals (Figure 1).

Figure 1: Calibration Graphs on ELISA.



Statistical Analysis

Data is presented as mean ± standard deviation. Between-group comparisons (T2DM vs. controls) was performed using the independent student t-test for distributed variables and categorical variables were compared using the chi-square test. Pearson correlation analysis was applied to assess associations between plasma GSDMD levels and clinical parameters such as FBG, HbA1c, HOMA-IR, HOMA-β, IL-18, IL-1β, lipids, and hs-CRP. Multiple logistic regression was used to evaluate GSDMD and other variables as independent risk factors for the presence of T2DM. The diagnostic performance of plasma GSDMD was determined using receiver operating characteristic (ROC) curve analysis, with calculation of the area under the curve (AUC), optimal cutoff value, sensitivity, and specificity. All statistical tests were two-tailed, with a significance threshold of $p< 0.05$, and analyses was carried out using SPSS version 24.0 (IBM Corp., Armonk, NY, USA).

Result

Table 1 shows that, compared with normoglycemic controls, patients with T2DM had significantly higher BMI, fasting blood glucose, HbA1c, fasting insulin, HOMA-IR, total cholesterol, triglycerides, LDL-C, and hs-CRP, and significantly lower HOMA-β and HDL-C (all $p< 0.001$). Age and sex distribution did not differ between groups ($p>0.05$), indicating that the two groups were well matched demographically. These findings suggest that the T2DM group exhibited a more adverse metabolic and inflammatory profile, with marked insulin resistance, β-cell dysfunction, atherogenic dyslipidemia, and systemic low-grade inflammation compared with controls.

Table 1: Baseline clinical and biochemical characteristics of study participants.

Variable	T2DM (n=130) mean ± SD	Control (n=130) mean ± SD	p-value
Age (years)	48.5 ± 7.8	47.9 ± 8.1	0.52
Male/Female n (%)	66/64	64/66	0.79
BMI (kg/m²)	26.2 ± 3.4	24.8 ± 3.1	0.001
FBG (mmol/L)	8.7 ± 7.9	5.1 ± 4.8	<0.001
HbA1c (%)	8.4 ± 5.3	5.6 ± 2.4	<0.001
Fins (μIU/mL)	16.8 ± 14.5	9.6 ± 7.8	<0.001
HOMA-IR	6.4 ± 5.3	2.1 ± 1.7	<0.001
HOMA-β	68.0 ± 22.0	132.0 ± 45.0	<0.001
TC (mmol/L)	5.3 ± 0.8	4.5 ± 0.7	<0.001
TG (mmol/L)	1.7± 1.2	1.0 ± 0.8	<0.001
LDL-C (mmol/L)	3.3 ± 0.7	2.7 ± 0.6	<0.001
HDL-C (mmol/L)	1.02 ± 0.21	1.30 ± 0.24	<0.001
hs-CRP (mg/L)	4.8 ± 3.2	1.9 ± 1.0	<0.001

Values are presented as mean ± standard deviation (SD) for normally distributed. BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Fins: Fasting Insulin; hs-CRP, high-sensitivity C-reactive protein. Student t-test and chi-square test were used to calculate the p-value. $p<0.05$ considered significant.

Plasma levels of GSDMD and inflammatory cytokines were markedly higher in T2DM patients than in controls. Median GSDMD was 70.5 (40–110) pg/mL in the T2DM group versus 6.0 (3.5–8.5) pg/mL in controls ($p< 0.001$), indicating a pronounced activation of pyroptosis in diabetes. Similarly, IL-18 and IL-1β were significantly elevated in T2DM [12.0 (9.5–15.2) vs 3.5 (2.5–4.8) pg/mL and 2.4 (1.6–3.8) vs 0.9 (0.5–1.4) pg/mL, respectively; both $p< 0.001$], reflecting an enhanced systemic inflammatory state in diabetic subjects compared with normoglycemic individuals (Table 2).

Table 2: Comparison of plasma GSDMD and inflammatory markers between T2DM patients and controls.

Marker	T2DM (n=130) median (IQR)	Control (n=130) median (IQR)	p-value
GSDMD (pg/mL)	70.5 (40–110)	6.0 (3.5–8.5)	<0.001
IL-18 (pg/mL)	12.0 (9.5–15.2)	3.5 (2.5–4.8)	<0.001
IL-1β (pg/mL)	2.4 (1.6–3.8)	0.9 (0.5–1.4)	<0.001

Abbreviation: GSDMD: Gasdermin D, IL-18: Interleukin-18, IL-1β: Interleukin 1 beta. Mann-Whitney test used to calculate the p-value. $p<0.05$ considered as statistical significance.

Plasma GSDMD levels showed significant correlations with both glycemic control and inflammatory status. GSDMD was strongly and positively correlated with fasting blood glucose ($r = 0.62$, $p< 0.001$) and HbA1c ($r = 0.58$, $p< 0.001$), indicating that higher GSDMD concentrations are associated with poorer glycemic control. A moderate positive correlation with HOMA-IR ($r = 0.40$, $p<0.001$) and a moderate negative correlation with HOMA-β ($r = −0.36$, $p<0.001$) suggest that elevated GSDMD is linked to greater insulin resistance and impaired β-cell function.

In addition, GSDMD demonstrated significant positive correlations with inflammatory markers IL-18 ($r = 0.46$, $p<0.001$), IL-1β ($r = 0.35$, $p<0.001$), and hs-CRP ($r = 0.24$, $p=0.002$), reflecting that higher pyroptosis activity parallels heightened systemic inflammation. Collectively, these findings imply that plasma GSDMD integrates information on metabolic dysregulation and inflammation and may serve as a composite indicator of T2DM severity.

Table 3: Correlation between plasma GSDMD levels and metabolic/inflammatory parameters in all participants.

Variable vs GSDMD	r value	p-value
FBG	0.62	<0.001
HbA1c	0.58	<0.001
HOMA-IR	0.4	<0.001
HOMA-β	-0.36	<0.001
IL-18	0.46	<0.001
IL-1β	0.35	<0.001
hs-CRP	0.24	0.002

Correlation coefficients (r) were calculated using Pearson's rank correlation. GSDMD, Gasdermin D; FBG, fasting blood glucose; HbA1c, glycated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment of β-cell function; IL-18, interleukin-18; IL-1β, interleukin-1 beta; hs-CRP, high-sensitivity C-reactive protein. $p<0.05$ considered significant.

Multivariable logistic regression analysis identified several variables as independent predictors of T2DM after mutual adjustment. For every 10 pg/mL increase in plasma GSDMD, the odds of having T2DM increased by 18% (adjusted OR 1.18, 95% CI 1.09–1.29, $p<0.001$), indicating a strong association between higher GSDMD levels and diabetes status. IL-18 and hs-CRP were also independently related to T2DM, with each 1 pg/mL rise in IL-18 (OR 1.10, 95% CI 1.03–1.18, $p= 0.004$) and each 1 mg/L rise in hs-CRP (OR 1.12, 95% CI 1.04–1.20, $p=0.002$) conferring higher odds of disease.

Among traditional risk factors, each 1 kg/m² increase in BMI was associated with a 9% increase in T2DM odds (OR 1.09, 95% CI 1.01–1.18, $p=0.03$), whereas higher HDL-C showed a protective effect, with an OR of 0.35 (95% CI 0.18–0.68, $p=0.002$), meaning greater HDL-C levels substantially reduced the likelihood of T2DM. These results suggest that GSDMD, alongside IL-18, hs-CRP, adiposity, and low HDL-C, independently contributes to T2DM risk, highlighting the importance of pyroptosis-related and inflammatory pathways beyond conventional metabolic factors.

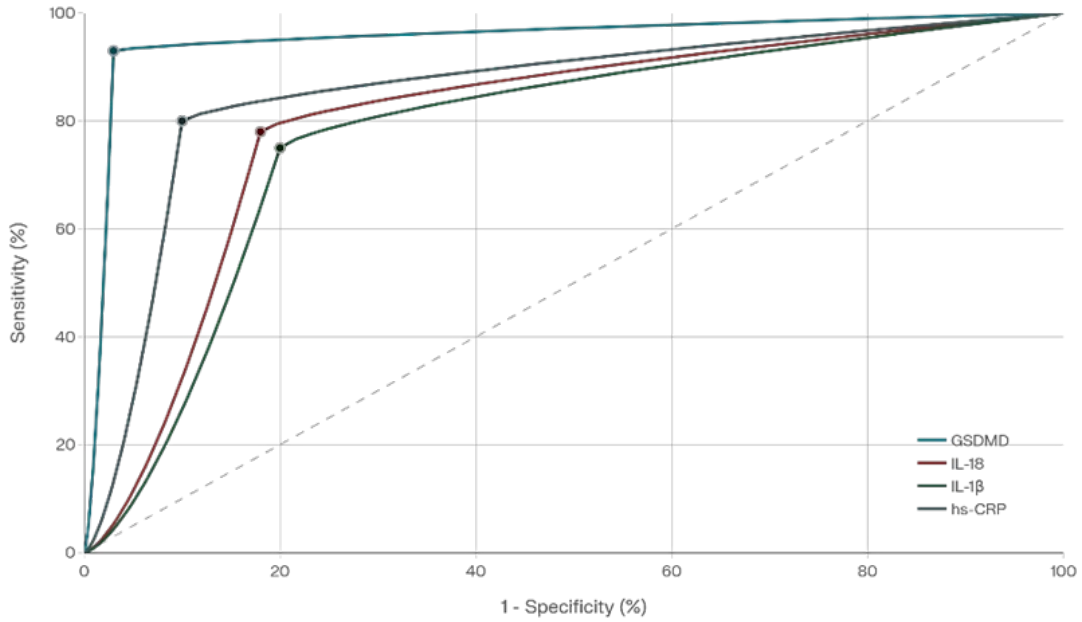
Table 4: Multivariable logistic regression analysis of factors independently associated with T2DM.

Variable	Adjusted OR	95% CI	p-value
GSDMD (per 10 pg/mL)	1.18	1.09–1.29	<0.001
IL-18 (pg/mL)	1.1	1.03–1.18	0.004
hs-CRP (mg/L)	1.12	1.04–1.20	0.002
BMI (kg/m²)	1.09	1.01–1.18	0.03
HDL-C (mmol/L)	0.35	0.18–0.68	0.002

Adjusted odds ratios (ORs) with 95% confidence intervals (CI) are presented for the presence of T2DM (1) vs normoglycemic controls (0). GSDMD, Gasdermin D; IL-18, interleukin-18; hs-CRP, high-sensitivity C-reactive protein; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol.

ROC analysis showed that plasma GSDMD had the highest diagnostic accuracy for distinguishing T2DM patients from controls. With an AUC of 0.98 (95% CI 0.96–0.99), a cutoff value of 17.5 pg/mL provided 93.0% sensitivity and 97.0% specificity, indicating excellent discrimination. IL-18 and IL-1β demonstrated good but lower performance (AUC 0.88 and 0.86, respectively), with optimal cutoffs of 5.0 pg/mL and 1.5 pg/mL yielding sensitivities of 78.0% and 75.0% and specificities of 82.0% and 80.0%. hs-CRP showed an AUC of 0.90 (95% CI 0.86–0.94), with a cutoff of 3.5 mg/L achieving 80.0% sensitivity and 90.0% specificity, but still inferior to GSDMD, underscoring GSDMD as the most powerful single biomarker for T2DM in this cohort (Figure 2).

Figure 2: Receiver operating characteristic (ROC) curves of plasma GSDMD, IL-18, IL-1β, and hs-CRP for discrimination of patients with type 2 diabetes mellitus from controls.



The ROC analysis shows excellent diagnostic performance of GSDMD (AUC 0.98, 95% CI 0.96–0.99; cutoff 17.5 pg/mL; sensitivity 93.0%; specificity 97.0%), with lower but still good accuracy for IL-18 (AUC 0.88, 95% CI 0.83–0.92; cutoff 5.0 pg/mL; sensitivity 78.0%; specificity 82.0%), IL-1β (AUC 0.86, 95% CI 0.81–0.91; cutoff 1.5 pg/mL; sensitivity 75.0%; specificity 80.0%), and hs-CRP (AUC 0.90, 95% CI 0.86–0.94; cutoff 3.5 mg/L; sensitivity 80.0%; specificity 90.0%), highlighting GSDMD as the most accurate biomarker among the tested inflammatory markers for early detection of type 2 diabetes mellitus.

Table 5: Diagnostic performance of plasma GSDMD and related inflammatory markers for T2DM based on ROC curve analysis.

Marker	AUC	95% CI	Cutoff (pg/mL)	Sensitivity (%)	Specificity (%)
GSDMD	0.98	0.96–0.99	17.5	93	97
IL-18	0.88	0.83–0.92	5	78	82
IL-1β	0.86	0.81–0.91	1.5	75	80
hs-CRP	0.9	0.86–0.94	3.5	80	90

AUC, area under the receiver operating characteristic (ROC) curve; CI, confidence interval. Sensitivity and specificity are reported at the optimal cutoff (Youden index) for each marker. GSDMD, Gasdermin D; IL-18, interleukin-18; IL-1β, interleukin-1 beta; hs-CRP, high-sensitivity C-reactive protein.

Discussion

The present study demonstrates that plasma GSDMD is markedly elevated in newly diagnosed T2DM patients compared with age- and sex-matched normoglycemic controls and is strongly linked to both metabolic derangement and systemic inflammation. The two groups were demographically comparable in terms of age and sex, which minimizes confounding from these factors, but the T2DM group exhibited significantly higher BMI, fasting glucose, HbA1c, Fins, HOMA-IR, lipid profile, and hs-CRP, along with lower HOMA-β and HDL-C, confirming a classic picture of insulin resistance, β-cell dysfunction, dyslipidemia, and low-grade inflammation. Against this background, plasma GSDMD, IL-18, and IL-1β were all substantially raised in T2DM, indicating activation of pyroptosis-related inflammatory pathways in diabetic subjects [12-14].

The correlation analysis provides important mechanistic insight into the role of GSDMD in T2DM. GSDMD showed strong positive correlations with FBG and HbA1c, suggesting that higher GSDMD levels parallel worsening short- and long-term glycemic control. Its positive association with HOMA-IR and negative association with HOMA-β indicate that GSDMD tracks both peripheral insulin resistance and impaired β-cell function, consistent with experimental data implicating inflammasome-mediated pyroptosis in β-cell injury and insulin signaling defects. Moreover, GSDMD correlated moderately with IL-18, IL-1β, and hs-CRP, supporting the concept that it integrates information on inflammasome activation and systemic inflammation. Together, these relationships reinforce GSDMD as a central node connecting metabolic stress, innate immune activation, and β-cell failure in T2DM [15,16].

Multivariate logistic regression further highlights the independent contribution of GSDMD to T2DM risk. Even after adjusting for BMI, HDL-C, and other inflammatory markers, GSDMD remained a significant predictor, with an 18% increase in the odds of T2DM for each 10 pg/mL rise in its plasma concentration. IL-18 and hs-CRP were also independently associated with T2DM, reflecting the importance of chronic inflammation; however, the magnitude and robustness of the GSDMD association suggest that pyroptosis may play a more proximate role in disease pathogenesis than generalized inflammation alone. The inverse association of HDL-C and positive association of BMI with T2DM are in line with established cardiometabolic risk patterns, but their coexistence with a strong GSDMD signal indicates that pyroptosis adds explanatory value beyond traditional risk factors [17-19].

From a diagnostic standpoint, GSDMD clearly outperformed other evaluated markers. The ROC analysis showed an AUC of 0.98 for GSDMD, with an optimal cut-off of 17.5 pg/mL achieving 93% sensitivity and 97% specificity for identifying T2DM, which falls in the "excellent" range for biomarker performance. In comparison, IL-18, IL-1β, and hs-CRP yielded lower AUCs (0.88, 0.86, and 0.90, respectively) and less favorable sensitivity–specificity profiles, indicating that they are less accurate if used alone. These findings suggest that plasma GSDMD could serve as a superior diagnostic tool, particularly in settings where early identification of high-risk individuals is critical. Because traditional markers like fasting glucose and HbA1c often fail to capture early-stage or intermittent dysglycemia, integrating GSDMD into diagnostic protocols could improve the identification of metabolically unstable patients. This approach may allow for clinical intervention before these individuals reach a state of overt metabolic decompensation. [19,20]. The primary strengths of this investigation reside in its rigorous case-control design, characterized by stringent age- and sex-matching to minimize potential confounding. Furthermore, the simultaneous quantification of GSDMD alongside a comprehensive panel of metabolic and inflammatory biomarkers allows for a high-resolution analysis of their pathophysiological associations.

Notwithstanding these strengths, several methodological limitations merit further consideration. First, the cross-sectional nature of the data precludes causal inference; it cannot be definitively concluded whether elevated GSDMD precedes the onset of T2DM or mainly reflects established disease. Longitudinal studies following normoglycemic or prediabetic individuals over time was necessary to clarify temporal relationships and assess predictive value for incident diabetes. Second, the sample was drawn from a single tertiary care center, which may limit generalizability to community settings or other ethnic groups. Third, although multiple confounders were adjusted for, residual confounding by unmeasured factors such as diet, physical activity, or subclinical infections cannot be entirely excluded.

Despite these limitations, the present results align closely with emerging international data showing that GSDMD-mediated pyroptosis is central to the inflammatory–metabolic axis in T2DM and extend this evidence to an Indian hospital-based population. The strong independent association with T2DM, robust correlations with glycemic and inflammatory parameters, and excellent diagnostic performance collectively support plasma GSDMD as a promising biomarker and a potential therapeutic target. Future work should focus on validating these

findings in larger, multi-center cohorts, exploring the utility of GSDMD in prediabetes and complication risk stratification, and assessing whether interventions that attenuate inflammasome activation and GSDMD cleavage can improve metabolic outcomes.

Conclusion

Plasma GSDMD levels were markedly elevated in newly diagnosed T2DM patients compared with age- and sex-matched normoglycemic controls and showed strong associations with hyperglycemia, insulin resistance, β-cell dysfunction, and systemic inflammation. In multivariable analysis, GSDMD remained an independent predictor of T2DM, and ROC analysis demonstrated excellent diagnostic accuracy (AUC 0.98) with high sensitivity and specificity at a cut-off of 17.5 pg/mL, outperforming IL-18, IL-1β, and hs-CRP. These findings indicate that plasma GSDMD is a robust, clinically promising biomarker that integrates metabolic and inflammatory information and may be useful for early diagnosis and risk stratification in T2DM, warranting validation in larger, longitudinal and multi-center studies.

Author Contribution

MS: Proposal concept, writing of manuscript, experimental work, Data analysis.
AK: Formal analysis, Manuscript editing.
AG: Clinical sample, Resources.

Declaration of Conflict of interests

The authors of this article declare that there is no conflict of interest with regard to the content of this manuscript.

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Data Availability

The datasets used and/or analysed during the current study are not available because of the Institutional policy.

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