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ORIGINAL ARTICLE

Predictive value of *Lp-PLA2* for coronary artery disease in type 2 diabetes mellitus patients: an observational study

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Abstract

Objective Type 2 diabetes mellitus (T2DM) is a chronic disease characterized by elevated blood glucose levels, which can result in a variety of complications, including coronary artery disease (CAD). Lp-PLA2 is a proinflammatory enzyme associated with low-density lipoprotein (LDL) particles in the circulation and is thought to be a biomarker for CAD risk.

Methods The purpose of this investigation was to evaluate the diagnostic utility of serum lipoprotein-associated phospholipase A2 (Lp-PLA2) levels in type 2 diabetes mellitus (T2DM) patients with and without coronary artery disease (CAD). Utilizing receiver operating characteristic (ROC) curves, the diagnostic efficacy of Lp-PLA2 was evaluated.

Results Lp-PLA2 levels were substantially higher in T2DM patients without cardiovascular disease (146.7 ng/mL 88.4) compared to HC (103.3 ng/mL 21.7) and T2DM + CAD (124.31 ng/mL 11.7). There was no statistically significant correlation between Lp-PLA2 levels and age, Hba1c, LDL, or Lp(a) in T2DM patients without CAD. Lp-PLA2 levels were not significantly associated with age (p = 0.97), HbA1c ($p = 0.41$), LDL ($p = 0.59$), or Lp(a) ($p = 0.56$), as determined by multiple linear regression analysis. The area under the curve (AUC) for Lp-PLA2 in T2DM without CAD was calculated to be 0.76, with a 95% confidence interval (CI). The sensitivity and specificity of a termination point of > 115 ng/mL were 0.70 and 0.68, respectively. For patients with T2DM + CAD, the AUC was 0.73 with a 95% confidence interval, and a threshold point of > 115 ng/mL yielded sensitivity and specificity values of 0.73 and 0.75, respectively.

Conclusions In T2DM patients with or without CAD, serum Lp-PLA2 concentrations may serve as a diagnostic marker. The cutoff value of > 115 ng/mL exhibited excellent sensitivity and specificity, especially in T2DM patients without CAD. This finding suggests the clinical utility of Lp-PLA2 as a diagnostic tool for identifying those at risk for CAD in the context of T2DM.

Keywords Lipoprotein-associated phospholipase A2 · Type 2 diabetes mellitus · Coronary artery disease · Biomarker for CAD risk and ELISA

Introduction

Type 2 diabetes mellitus (T2DM) is characterized by elevated blood glucose levels, with chronic consequences affecting several organ systems and accounting for a significant portion of morbidity and mortality [1]. The increasing prevalence of T2DM is a major concern in global healthcare. T2DM is recognized as a severe public health issue having a substantial impact on human life and health expenditures. Fast economic growth and urbanization have contributed to an increase in the prevalence of diabetes in many regions of the world [2]. The rising prevalence of diabetes has been attributed principally to population aging.

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The International Diabetes Federation (IDF) estimates the global diabetes prevalence in adults at 10.5% [3].

T2DM is associated with vascular changes that result in organ failure and premature mortality. The immense impact of such diabetic complications sparked rigorous experimental and clinical investigations, which have accelerated dramatically over the past few decades as the diabetes epidemic has grown [4]. Patients with T2DM are predisposed to cardiovascular disease and, more importantly, suffer from prone-rupture plague, which results in myocardial infarction. Macrovascular complications are the result of hyperglycemia-induced chronic metabolic abnormalities, with *HbA1C* being the most important measure for diabetes control in relation to the risk of diabetic complications [5].

The early diagnosis of coronary artery disease (CAD) is crucial to preventing future cardiovascular complications. Hence, circulating biomarkers may be crucial diagnostic tools. It is essential for the medical community to prevent CVD in patients with diabetes mellitus (DM) prior to attempting to find a remedy when the condition has become severe [6]. Various biomarkers like low-density lipoprotein-C, C-reactive protein, adenosine deaminase, nitric oxide, interleukin-8, NF-kB, and protein kinase-C are routinely used to predict the CAD prognosis in type 2 diabetes patients (T2DM) associated with the pathogenesis of atherosclerosis [7]. Oxidative stress, progenitor cell dysfunction, micro-vascular dysfunction, and impaired reverse cholesterol transport are well-known pathological mechanisms that play crucial regulatory roles in the development of diabetic cardiovascular disease [8].

Plasma platelet-activating factor acetyl-hydrolase (*Lp-PLA2*) is an enzyme encoded by the *PLA2G7* gene located at chromosome 6p12-21, secreted by macrophages, circulates in the blood as a complex with lipoproteins, and is known to be involved in endothelial dysfunction, inflammation, and the formation of core necrotic plaque at the arterial intima [9]. Recent pieces of evidence suggest that serum levels of *Lp-PLA2* could serve as potential biomarkers for various pathological conditions like macrovascular complications of T2DM [10], diabetic nephropathy [11], renal impairment [12], and oxidative stress [13].

Lp-PLA2 has the ability to produce molecules with pro-inflammatory properties; these inflammatory proteins play a significant role in the development of atherosclerosis by introducing *Lp-PLA2* into the bloodstream where selective attachment of *Lp-PLA2* to lipoprotein particles occur, mostly to low-density lipoproteins (LDL), as well as high-density lipoproteins (HDL) [14]. Diabetes is a known risk factor for cardiovascular disease. However, the interaction between type 2 diabetes and Lp-PLA2 activity in determining cardiovascular risk in humans is understudied. The Adult Treatment Panel III (ATP III) guideline suggests that *Lp-PLA2* is a valuable addition to conventional risk factors for assessing cardiovascular risk [15]. This recommendation is based on the observation that increased levels of *Lp-PLA2* are associated with an increased vulnerability to atherosclerosis. [16]. It has been reported that approximately 60% of the factors modulating plasma *Lp-PLA2* activity are genetic. Genome-wide association studies (GWAS) have identified a number of single-nucleotide polymorphisms (SNPs) that influence the activity or levels of *Lp-PLA2*. These genetic variants have shed light on the complex genetic underpinnings of *Lp-PLA2* regulation and its role in lipid metabolism [17].

It is essential for the medical community to prevent CAD in patients with DM prior to attempting to find a remedy when the condition has become severe. In order to diagnose CAD at an early stage and assess its severity, circulating biomarkers may be crucial diagnostic tools. Given the clinical scenario that *Lp-PLA2* is a crucial circulating biomarker for various pathological conditions, the present study was undertaken to investigate the predictive value of *Lp-PLA2* for CAD in T2DM.

Materials and methods

Study design

The current study was conducted jointly by Departments of Biochemistry, Endocrinology and Cardiology, Nizam's Institute of Medical Sciences, Panjagutta, Hyderabad, India, from August 2021 to August 2022.This cross-sectional case-control study includes a total of 180 subjects consisting of both male and female, categorized into 3 groups: group 1, healthy controls (HC) ($n = 30$); group 2, type 2 diabetes mellitus with coronary artery disease (T2DM + CAD) confirmed by coronary angiography ($n = 71$), and group 3, uncontrolled type 2 diabetes mellitus who have HbA1C > 8% as per ADA guidelines and no history of CAD and were asymptomatic individuals with no previous medical record of CAD. A comprehensive clinical evaluation was performed on the members of this cohort, including a physical examination, review of the patient's medical history, acquisition of a combination of echocardiograms, chest x-rays, resting electrocardiograms, and negative serum biomarkers including cardiac troponins labeled as (T2DM − CAD) ($n = 75$).

Subjects attending Endocrinology & Cardiology outpatient departments diagnosed with T2DM with CAD were recruited in the study as per criteria of American Diabetes Association. Healthy individuals with no history of T2DM or family history of T2DM were included in the study.

Table 1 Baseline and clinical characteristics of the study population

Parameter	Healthy controls ($n = 30$)	T2DM with CAD ($n = 71$)	T2DM without CAD ($n = 75$)
Age (yrs)	52.2 ± 5.64	57.7 ± 8.6[a]	56.6 ± 10.47
HbA1C (%)	5.5 ± 0.25	7.5 ± 1.8[a]	9.5 ± 2.2[b,c]
Total cholesterol (mg/dL)	163 ± 29.3	146 ± 47.7	167 ± 47.2
Triglycerides (mg/dL)	123 ± 53	170.23 ± 129	167 ± 129
HDL-cholesterol (mg/dL)	38.4 ± 7.32	39 ± 7.05	37.92 ± 9.26
LDL-cholesterol (mg/dL)	94.4 ± 22	68.8.4 ± 31.5[a]	100.1 ± 41.5[c]
Lipoprotein(a) (ng/mL)	22.53 ± 20.71	39.95 ± 39.35	25.08 ± 26.17

Data expressed as mean ± SD; *$p < 0.05$ vs controls, [a]$p < 0.05$ vs HC, [b]$p < 0.05$ vs HC, [c]$p < 0.05$ vs T2DM − CAD

Subjects with history of hereditary hypercholesterolemia and currently undergoing treatment for cancer or with any other systemic infections were excluded from the study.

Sample collection

Four milliliters of fasting peripheral venous blood sample was collected in two tubes, one without anti-coagulant and the other one tube with EDTA (for estimation of *HbA1C*). After the collection, tubes without anti-coagulant were centrifuged at 2000 rpm for 10 min and serum was collected, stored at – 80 °C for further evaluation of various biochemical parameters.

Biochemical estimations

Biochemical analysis of various parameters was estimated on Cobas C501, automated analyzer, Roche Diagnostics, Switzerland. The Human Lipoprotein-associated Phospholipase A2, (Lp-PLA2) GENLISA ELISA Kit (KRISHGEN BioSystems, Cat.no.KBH1530) was used for the evaluation of LP-PLA2 levels in serum as per the manufacturer instructions.

Statistical analysis

The descriptive analysis of variables that follow a normal distribution is typically presented in terms of the mean and standard deviation. The statistical analyses were conducted using version 19.0 of the SPSS software (SPSS Inc., Chicago, IL, USA). The independent *t*-test was employed to compare continuous variables, when available. The Kruskal-Wallis (one-way-ANOVA) test was employed to assess the statistical differences among the groups in our ELISA data. Subsequent post hoc analyses were performed using Dunn's test, to determine pairwise group differences. The study employed Spearman's rank correlation coefficient test and multiple linear regression analysis to assess the relationships between variables. All hypothesis testing conducted in this study used a 2-tailed approach, and a significance level of $p < 0.05$ was deemed as the threshold for statistical significance.

Results

Baseline characteristics of study subjects

Table 1 provides a summary of the baseline characteristics of the study population in three groups: individuals with healthy controls (HC), individuals with type 2 diabetes mellitus and coronary artery disease (T2DM + CAD), and individuals with type 2 diabetes mellitus without coronary artery disease (T2DM − CAD). The average age of the study population was determined to be 52.2 years in the group with healthy controls (HC), 57.7 years in the group with type 2 diabetes mellitus and coronary artery disease (T2DM + CAD), and 56.6 years in the group with type 2 diabetes mellitus without coronary artery disease (T2DM w/o CAD). The study findings revealed a significant increase in low-density lipoprotein (LDL) levels among individuals diagnosed with type 2 diabetes mellitus and coronary artery disease (CAD), as seen in Table 1.

No significant differences were observed in the levels of serum total cholesterol, triglycerides, and HDL-C among the three groups in relation to Lp-PLA2 levels. However, it is evident that individuals with T2DM − CAD had higher concentrations of Lp-PLA2 (146.7 ng/mL ± 88.4) compared to the HC group (103.3 ng/mL ± 21.7) and the T2DM + CAD group (124.31 ng/mL ± 21.7) (Fig. 1).

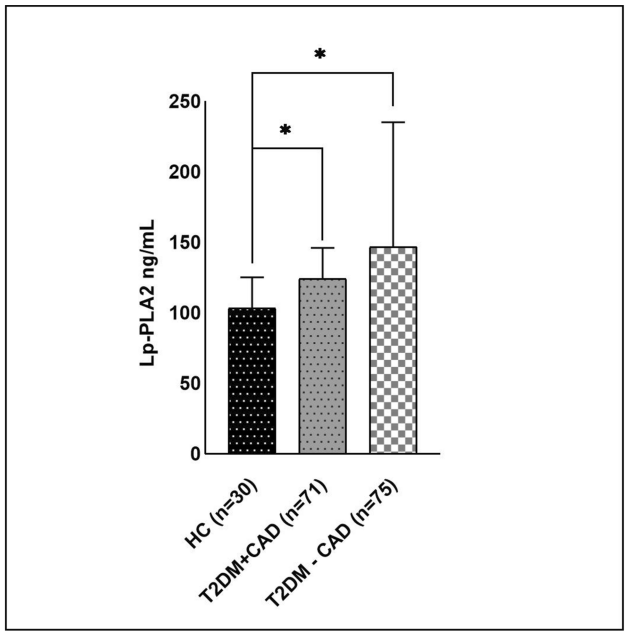

Fig. 1 Serum *Lp-PLA2* levels among the healthy controls, T2DM patients with CAD, and T2DM patients without CAD. *$p < 0.05$ is significant

Association of serum Lp-PLA2 levels with pathological parameters in T2DM patients w/o CAD

Subsequently, we investigated the correlation between serum Lp-PLA2 levels and other clinico-pathological features, specifically age, HbA1C, LDL, and Lp(a), in individuals diagnosed with type 2 diabetes mellitus without coronary artery disease. As depicted in Fig. 2, our study revealed no statistically significant correlation between Lp-PLA2 levels and age, HbA1C, LDL, and Lp(a) in individuals diagnosed with type 2 diabetes mellitus without coronary artery disease. Moreover, a multiple linear regression analysis was conducted to examine the relationship between Lp-PLA2 levels and various clinical parameters in a sample of 75 individuals with type 2 diabetes mellitus (T2DM) but without coronary artery disease (CAD). The results of the research indicated that there was no statistically significant link between *Lp-PLA2* levels and age ($p = 0.97$), HbA1C ($p = 0.41$), LDL ($p = 0.59$), and Lp(a) ($p = 0.56$).

Lp-PLA2 receiver operating characteristic (ROC) curve analysis

The examination of the receiver operating characteristic (ROC) curve for blood Lp-PLA2 in both the control group and patients with type 2 diabetes mellitus (T2DM) without coronary artery disease (CAD) revealed an area under the curve (AUC) of 0.76, with a 95% confidence interval (CI). The serum Lp-PLA2 demonstrated an appropriate cutoff point at a value greater than 115 ng/mL, with corresponding sensitivity and specificity values of 0.70 and 0.68, respectively (Fig. 3a). The study of receiver operating characteristic (ROC) curves was conducted to evaluate the diagnostic performance of serum Lp-PLA2 in patients with both type 2 diabetes mellitus (T2DM) and coronary artery disease (CAD), as well as in patients with T2DM but without CAD. The calculated area under the curve (AUC) for this analysis, along with a 95% confidence interval (CI), was determined to be 0.73. The serum Lp-PLA2 demonstrated an optimum cutoff point of > 115 ng/mL, with corresponding sensitivity and specificity values of 0.73 and 0.75, respectively (Fig. 3b). The flowchart detailing the methods and results of the study is illustrated in Fig. 4.

Discussion

In the current investigation, it was shown that serum levels of Lp-PLA2 were elevated in individuals with diabetes but without coronary artery disease (CAD), as well as in those with diabetes and CAD, in comparison to a control group of healthy volunteers. In comparison to diabetes patients with coronary artery disease (CAD), diabetes patients without CAD had elevated levels of lipoprotein-associated phospholipase A2 (LP-PLA2). In our study, we conducted a correlation analysis to investigate the relationship between HbA1c levels and LP(a), Lp-PLA2, and LDL. A slight positive connection was identified in both groups, namely people without coronary artery disease (CAD) and diabetics with CAD. Nevertheless, no statistically significant correlation was observed between HbA1c levels and the aforementioned factors in either of the diabetes cohorts. Disease progression is influenced by various risk factors, including obesity, a sedentary lifestyle, and smoking. Effective management of these factors has the potential to postpone the onset of life-threatening consequences.

The present study's linear regression analysis indicated that there was no statistically significant connection between Lp-PLA2 and age, HbA1C, LP(a), or LDL. The study of the receiver operating characteristic (ROC) curve reveals that the area under the curve (AUC) for Lp-PLA2 is 0.737. This AUC value, along with a cutoff value of 115 ng/mL, demonstrates a sensitivity of 70% and a specificity of 68% in distinguishing between diabetes without coronary artery disease (CAD) and diabetes with CAD. These findings suggest that Lp-PLA2 moderately predicts the presence of atherosclerosis in individuals with diabetes but without CAD.

Numerous studies have indicated that Lp-PLA2 serves as a biomarker for the assessment of risk associated with

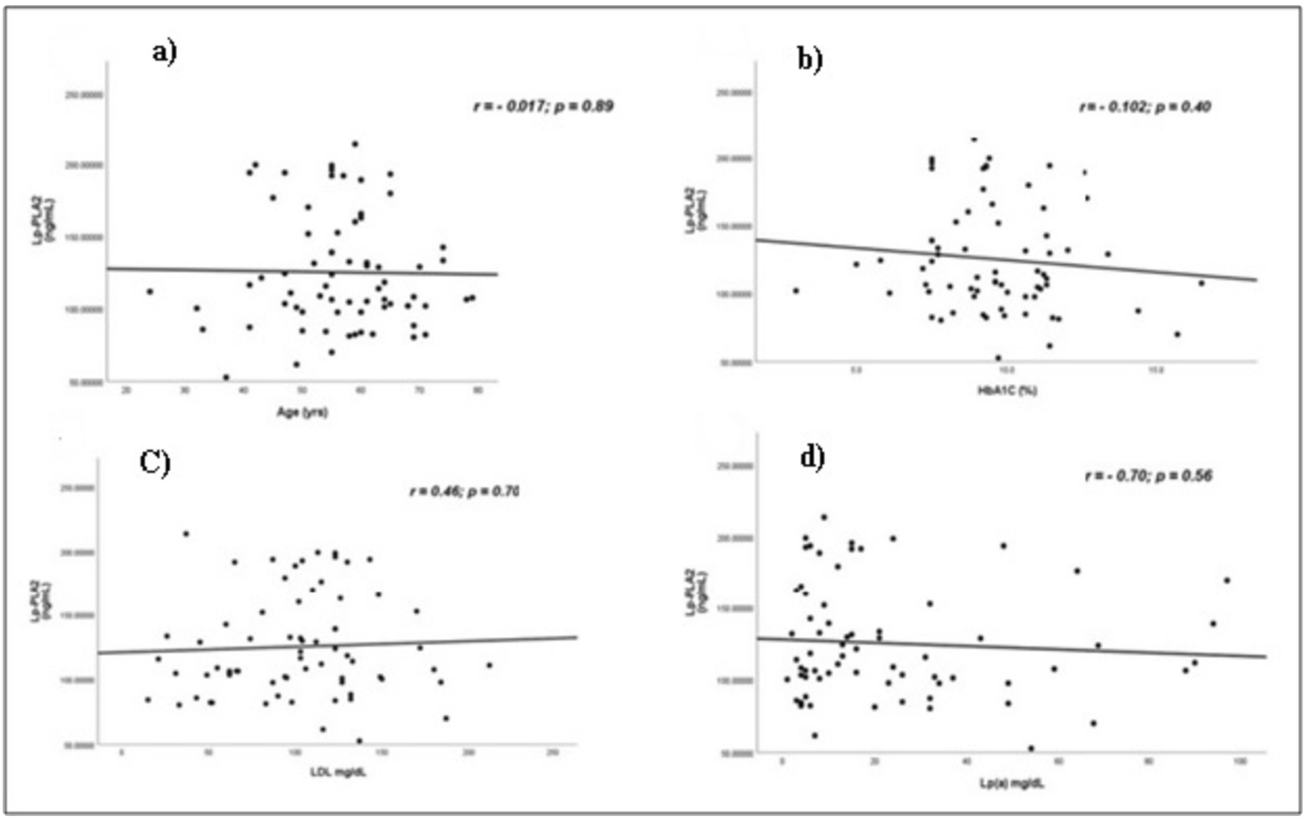

Fig. 2 Association of serum LP-*PLA2* level with clinico-pathological characteristics: **a** age ; **b** *HbA1C%*; **c** LDL; and **d** Lp(a) in patients with T2DMCAD. Data was statistically analyzed using Spearman's rank correlation coefficient test

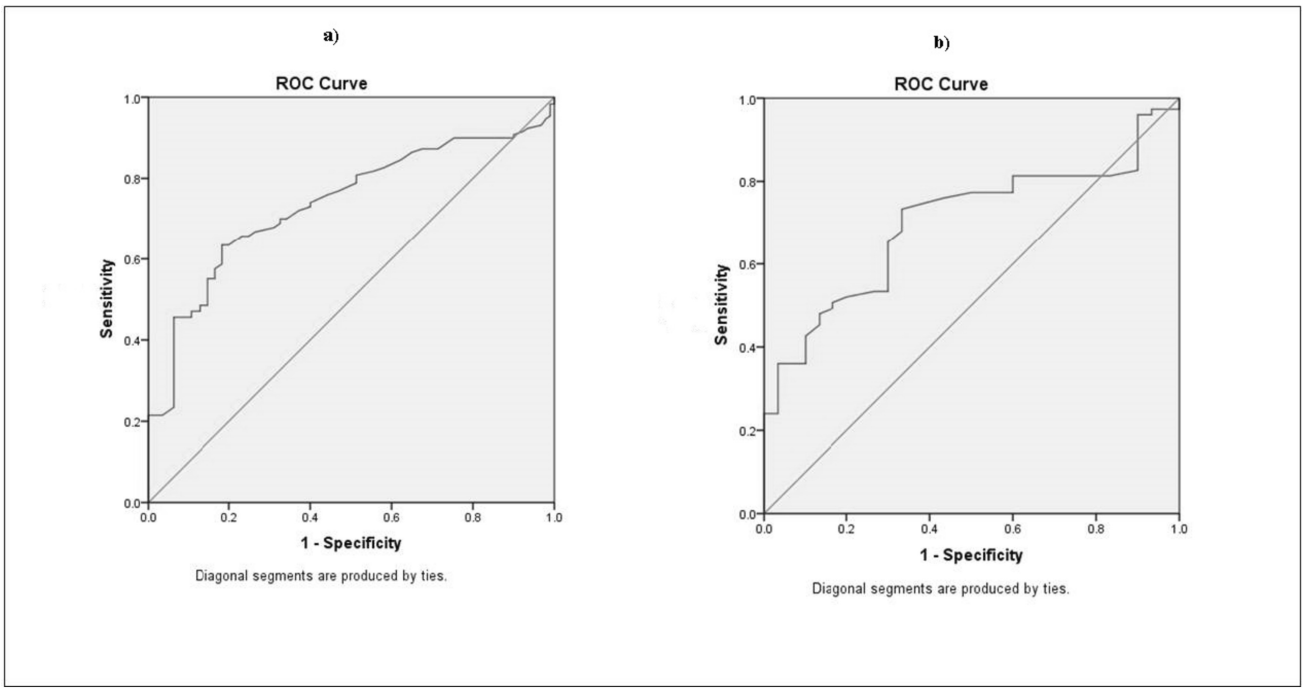

Fig. 3 Receiver operating characteristic (ROC) curve analysis for the **a** *Lp-PLA2* serum circulating levels in controls and T2DM − CAD patients; **b** T2DM + CAD patients and patients with T2DM − CAD

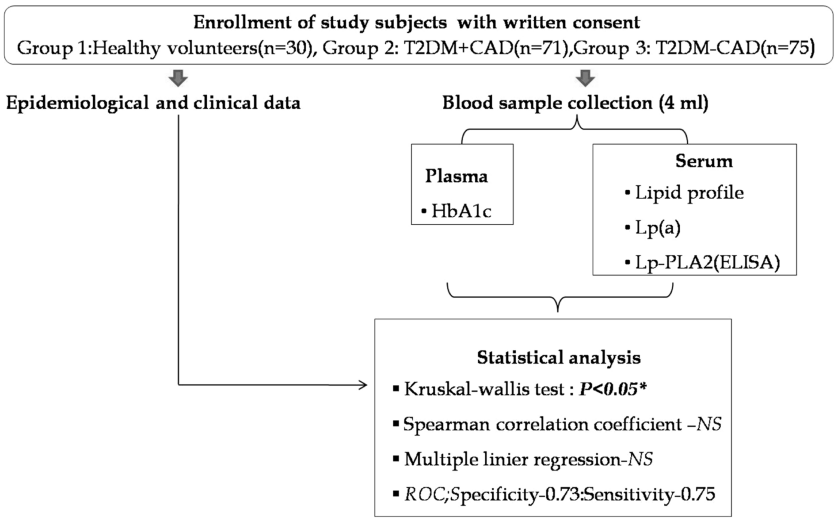

Fig. 4 Flowchart detailing the methods and results of the study. $p < 0.05$* is significant; NS, not significant

cardiovascular disease (CVD). In a study conducted by Thompson et al. (2010), a meta-analysis was performed using data from 32 prospective studies. The findings of this research indicated that Lp-PLA2 serves as a noteworthy prognostic indicator for future mortality risk, irrespective of conventional risk variables [18]. The link between Lp-PLA2 and coronary heart disease (CHD) was observed to be more robust compared to its association with stroke. In a comprehensive study and meta-analysis conducted by O'Donoghue et al. (2019), it was found that there exists a significant association between Lp-PLA2 and an increased occurrence of coronary artery disease (CAD) in both male and female populations [19].

Limited research has been conducted on the impact of Lp-PLA2 inhibitors on the risk of cardiovascular disease. Nevertheless, there is variability in the outcomes. The darapladib research demonstrated that the administration of a Lp-PLA2 inhibitor did not result in a significant reduction in major cardiovascular events [20]. The VISTA-16 clinical trial investigated the efficacy of varespladib, an additional inhibitor of Lp-PLA2, and demonstrated a noteworthy decrease in the recurrence of cardiac illness. Lipoprotein-associated phospholipase A2 (Lp-PLA2) has been proposed as a possible biomarker for type 2 diabetes mellitus (T2DM) [21]. A further investigation revealed that individuals with type 2 diabetes mellitus (T2DM) exhibited elevated levels of lipoprotein-associated phospholipase A2 (Lp-PLA2) in comparison to those without diabetes. There was a favorable correlation observed between levels of Lp-PLA2 and the measure of long-term glycemic management, HbA1c [22].

Multiple epidemiological studies have provided evidence that Lp-PLA2 holds promise as a potential biomarker for cardiovascular disease (CVD) prognosis. These studies have also revealed that Lp-PLA2 exhibits superior efficacy as a risk marker compared to CRP in individuals diagnosed with acute coronary syndrome [6]. According to the research conducted by Hargens and colleagues, it has been determined that Lp-PLA2 serves as a noteworthy and autonomous indicator for low-risk individuals with coronary conditions, as categorized by the Framingham risk score. Conversely, conventional risk markers such as lipids and glucose do not possess the same predictive capability [23]. Therefore, the current study was undertaken to determine the significance of Lp-PLA2 in the evaluation of coronary artery disease among individuals diagnosed with type 2 diabetes.

The precise mechanism that underlies the association between Lp-PLA2 and Lp(a) remains incompletely elucidated; nonetheless, it is hypothesized that both biomarkers may exert their influence on atherosclerosis development via shared pathways. Lipoprotein-associated phospholipase A2 (Lp-PLA2) has the potential to facilitate the development and advancement of atherosclerotic plaques by its enzymatic activity in breaking down oxidized phospholipids. This process can result in the generation of molecules that possess pro-inflammatory and proatherogenic properties [24]. Lipoprotein(a) (Lp(a)) has been implicated in the pathogenesis of atherosclerosis due to its ability to facilitate the accumulation of low-density lipoprotein (LDL) cholesterol within the artery wall and its capacity to impede fibrinolysis, hence boosting thrombin production [21].

In a population-based sample of adults, Abbasi et al. (2008) found a positive connection between HbA1c levels and LP(a), as indicated in their study. Lipoprotein-associated phospholipase A2 (LpPLA2) has also been linked to the association between glycated hemoglobin (HbA1c) levels and the risk of coronary artery disease (CAD) [25]. In a study conducted by Jia et al., it was discovered that patients diagnosed with type 2 diabetes mellitus exhibited heightened LpPLA2 activity in correlation with elevated HbA1c levels [26]. Cohen et al. conducted an additional investigation, which revealed a significant positive association between

HbA1c levels and LpPLA2 in individuals diagnosed with metabolic syndrome [27].

Limitation of the study

The study did not include coronary angiography in the study group who had type 2 diabetes mellitus without coronary artery disease, in order to confirm the presence of the condition. Conducting a further investigation using a substantial sample size might prove advantageous in order to forecast the role of Lp-PLA2 in the development of atherosclerosis.

Conclusion

The routine use of Lp-PLA2 testing in patients with type 2 diabetes mellitus (T2DM) has the potential to facilitate the early identification and management of coronary artery disease (CAD), consequently mitigating the likelihood of unfavorable cardiovascular incidents including myocardial infarction and stroke. Nevertheless, additional investigation is required to ascertain the most advantageous threshold values for Lp-PLA2 and to confirm its clinical efficacy in customary healthcare procedures.

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Author contribution Conceptualization: SKM, SN, BA, KP, SS, and VB
Methodology: SKM, SN, and KP
Formal analysis and investigation: SKM, SN, and KP
Writing—original draft preparation: SKM, SN, and KP
Writing—review and editing: SKM, SN, BA, KP, SS, and VB
Supervision: SKM, SN, BA, SS, and VB

Data Availability Data supporting the findings of this study are available within the article text and tables.

Declarations

Ethical clearance and consent of patient All study procedures complied with the ethical guidelines of the Declaration of Helsinki and the study was approved by hospital/institutional ethics committee (Ref.no:PBAC No :2023/2021). After the subjects were agreed to participate, written informed consent was obtained. All participants underwent a personal interview in conformance with institutional guidelines for studies including human subjects. Data was collected on socio-demographic characteristics, lifestyle behavior, medical history, family history, and physical examination.

Conflict of interest The authors declare no competing interests.

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