ORIGINAL ARTICLE

Lipoprotein-associated phospholipase-A2 as an inflammatory biomarker for vascular risk in SARS-CoV-2 affected individuals with rheumatoid arthritis

Mamta Singh[1], Vijayalakshmi Hari[2], Ben Ashok[3], Praveen Kumar[4], Rahul Abishake[5]*

[1,2]Sri Ramachandra Department of Allied Health Sciences, SRMC&RI, Porur Chennai-600116 (Tamil Nadu) India, [3]NURA Ai Health Screening Center, Bengaluru-560008, (Karnataka), India, [4]Department of Bio Medical Engineering, Chang Gung University, Taoyuan City 33302, Taiwan (R.O.C.), [5]Asiri Surgical Hospital, Cardiology Unit, Colombo, Sri Lanka

Abstract

Background: Rheumatoid Arthritis (RA) patients are predisposed to elevated vascular risk, which is exacerbated by SARS-CoV-2 infection. Lipoprotein-associated phospholipase A2 (Lp-PLA2) is an inflammatory biomarker implicated in atherosclerosis and Cardiovascular Diseases (CVD). *Aim & Objectives:* This study aimed to assess the level of Lp-PLA2 in RA patients with and without COVID-19 exposure, and to evaluate its utility as a biomarker for vascular risk in these populations. The objective was to compare Lp-PLA2 levels in RA patients with COVID-19 exposure against those without, and to explore the correlation with other inflammatory markers and lipid parameters. *Material and Methods:* A cross-sectional comparative study was conducted on 100 individuals aged 20-77 years at Sri Ramachandra Institute of Higher Education and Research. The participants were divided into two groups: 50 RA patients with COVID-19 exposure and 50 RA patients without COVID-19 exposure. Lp-PLA2 levels were measured using Sandwich-ELISA, while rheumatoid factor (RF) and C-Reactive Protein (CRP) levels were assessed using IMMAGE® Immunochemistry Systems. Statistical analysis was performed using SPSS version 16, with significance set at $p < 0.05$. *Results:* Lp-PLA2 levels were significantly higher in RA patients with COVID-19 exposure (73.94 ng/ml) compared to those without (10.99 ng/ml) ($p = 0.005$). RF and CRP levels were elevated in both groups but did not show significant differences ($p = 0.059$ and 0.190, respectively). No significant correlations were observed between Lp-PLA2 and traditional lipid profile parameters. *Conclusion:* RA patients exposed to COVID-19 had significantly higher levels of Lp-PLA2, indicating increased vascular inflammation and risk of atherosclerosis. Lp-PLA2 may serve as a sensitive marker for cardiovascular risk assessment in RA patients, independent of traditional lipid profile parameters.

Keywords: Vascular inflammation, cardiovascular risk, atherosclerosis, inflammatory biomarkers, rheumatoid arthritis

Introduction

The single-stranded RNA virus termed SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), fuelled by a unique coronoviridae member, emerged in December 2019 [1]. Mammals can acquire beta coronaviruses, and it is generally accepted that COVID-19 originated in bats with changes in the Receptor-Binding Domain (RBD) and the furin protease cleavage site [2]. The coronavirus disease 2019 (COVID-19) SARS-CoV-2 infection is often caused by inflammation of the airways. Both Gastrointestinal (GI) and Upper Respiratory (UR) tracts of people are infected by the virus. It can also occasionally culminate in severe alveolar disease, which can significantly increase the risk of

pulmonary failure by shortening breath, lowering blood oxygen saturation, and lung infiltration. The main causes of profound lung disease in COVID-19 patients have been recognized as immune hyper-activation and cytokine involvement in alveolar tissues [3].

It is well known that the SARS-CoV-2 virus infected patients exhibits comorbidities such as diabetes mellitus, lung disease, Chronic Kidney Disease (CKD), and Cardiovascular Disease (CVD) [4]. The mortality risk is higher for patients with comorbidities who are elderly (> 65 years) and have weakened immune systems. Due to their weakened immune systems and use of immunosuppressive medications as prescribed, people with autoimmune disorders including lupus and Rheumatoid Arthritis (RA) are prone to infection and this has been reported as one of the most common immune-mediated disorders in COVID-19 patients [5].

These individuals on immunosuppressants may exhibit unusual symptoms; for instance, those taking IL-6 inhibitors might not have an increase in inflammatory markers. The possibility of overlap in symptoms is seen between a RA flare and COVID-19 infections. In both situations, symptoms such as myalgia, arthralgia, fever, and raised inflammatory markers may manifest. In the COVID-19 era, people with rheumatic disorders who are on immunosuppressive medications need to be given extra consideration. RA patients have been documented to have a higher risk of infection than people in general [6]. Many comorbidities such as hypertension, Chronic Obstructive Pulmonary Disease (COPD), and CVD are more prevalent in RA patients and patients with RA were at 25% higher risk of SARS-CoV-2 infection and 35% risk of COVID-19 hospitalization or death [7,8].

Provided the same immunological, genetic, and clinical features between inflammatory diseases and COVID-19, it is possible that SARS-CoV-2 could be a catalyst for the emergence of excessive inflammatory disorders, particularly in susceptible individuals. The risk of COVID-19 in persistent RA is suggested to result from immunological dysregulation and the use of chemical and biological anti-rheumatic medications, both of which normally raise infection risk due to immune system impairment and related comorbidities. Patients with RA particularly experienced thymus dysfunction, a rise in peripheral T cell turnover, and systemic T cells, all of which enhance their susceptibility to infections. Furthermore, ACE2 upregulation is stimulated by Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and increases the vulnerability to SARS-CoV-2 infection. These drugs may be utilized as an additional therapy to relieve arthritic pain but they exacerbate the clinical course or even cover up some signs that help with COVID-19 diagnosis, since both diseases overlap in pathogenesis [9].

RA and COVID-19 in humans are diseases that show similar inflammatory responses. This is caused by immune metabolic suppression and compromising the host immunity. The SARS-CoV-2 infection caused inflammation of the airways and GI and UR tracts. And RA is one of the most common effects of this inflammation [4].

The lipid metabolism and inflammatory response are intertwined at lipoprotein-associated phospholipase A2 (Lp-PLA2). It is secreted due to the binding of LDL with other lipoproteins in the structure of inflammatory cells. The activity of this catalyst conjointly results in alterations in High-Density Lipoprotein (HDL), making it less potent to suppress inflammation. These oxidized lipoprotein molecules promote vascular inflammation and

result in atherosclerotic plaque formation. This may lead to reduced blood flow, especially if the rupture occurs or in spasm, and therefore, a shortage of oxygen to the myocardium [10]. The Lp-PLA2 may play an essential role in the assessment of the development and progression of atherosclerosis [11].

Other pathogenic factors, such as Homocysteine (HCY) promote Insulin Resistance (IR) and impaired function of beta cells through mechanisms, including oxidative stress, systemic inflammation, and endothelial dysfunction. HCY is also an independent risk factor for CVD and accelerated atherosclerosis [12]. It may also help as a risk predictor for coronary and carotid events and is thought to be a promising approach for treating vascular diseases [10]. Both diseases elicit a pro-inflammatory response that could result in vascular risk. Lp-PLA2 is recognized as a marker for vascular endothelium rather than being viewed as a systemic inflammatory marker because it is produced only within atherosclerotic plaque and its levels do not increase during systemic inflammatory events. Individuals with coronary atherosclerosis have higher circulating levels of Lp-PLA2 than those without the disease, which in turn causes higher levels of lysoPC (lysophosphatidylcholine), a major component of biological membranes and a kind of lysophospholipid produced from Phosphatidylcholine (PC).

It is important in cell signaling, inflammation, and metabolic processes. Lp-PLA2 plays a proatherogenic inflammatory marker that is generated mainly by macrophages and lymphocytes, which stimulates atherosclerosis [9]. Increased Lp-PLA2 has already been advised as one of the risk-specific markers in cardiovascular conditions and has also been reorganized as a biomarker in COVID-19. [13] Its validity as a biomarker in COVID-19 is increased by the fact that Lp-PLA2 has already been advised for the evaluation of the risk of specific cardiovascular conditions in otherwise apparently healthy individuals [14]. The purpose of our study was to evaluate the level of Lp-PLA2 in patients with RA and post-COVID-affected RA individuals.

Material and Methods

The Institutional Ethics Committee approved this cross-sectional comparative study on 100 men and women aged 20–77 at the Sri Ramachandra Institute of Higher Education and Research (Ethical Clearance Number: CSP/22/SEP /116/481). All participants were divided into two groups: group 1 contained 50 RA patients exposed to COVID-19, and group 2 included 50 RA patients without exposure to COVID-19.

Exposure to COVID-19 was defined as a previous confirmed SARS-CoV-2 infection, based on RT-PCR or rapid antigen test report. Patients with RA for over five years were included. Those with other autoimmune disorders, juvenile arthritis, myocardial infarction, stroke, or vascular thrombosis were excluded. All subjects gave written informed consent before data collection, and institutional and ethical patient confidentiality requirements were followed.

The sample size was calculated using the formula below, based on hypothesis testing for two

$$n = \frac{2s_p^2[Z_{1-\alpha/2} + Z_{1-\beta}]^2}{\mu^2_d} \qquad S_p^2 = \frac{s^2_1 - s^2_2}{2}$$

independent means:

Where,

$S^1 2$ – Standard deviation in the first group – 38.9

$S^2 2$ – Standard deviation in the second group – 33.5

μ 2 d – Mean difference between the samples –
21 α – Significance level – 5%
1-β – power – 80%
1 or 2-sided – 2
Based on this calculation, each group needed 50 members for statistical power and confidence.

Sample collection and analysis

For each patient, 5 mL of fasting venous blood was collected from each participant into basic red-topped vacutainers at the central laboratory of Sri Ramachandra Medical Centre. The samples were centrifuged at 2000–3000 rpm for 20 minutes after clotting at room temperature for an hour. Immediately following appropriate serum separation, lipid profile, rheumatoid factor (RF), and C-Reactive Protein (CRP) were assessed. Labelled serum aliquots maintained at –80°C until further testing were used in Lp-PLA$_2$ analysis. Lipid profile was done using Beckman AU5800 and AU680 automated clinical chemistry analyzers, which analyzed total cholesterol, triglycerides, and HDL cholesterol. The GPO–POD technique measured triglycerides; the enzymatic CHO–POD endpoint approach computed total cholesterol. Masking non-HDL lipoproteins enabled a selective enzymatic colorimetric HDL cholesterol measurement. The Sampson formula approximated sdLDL-C; the Friedewald formula calculated LDL-C and VLDL. One computed the ratios LDL/HDL and TC/HDL to assess cardiovascular risk. The RF examination was done using rate nephelometry; the IMMAGE® Immunochemistry System measured RF. Light scatter between RF and IgG-coated latex particles quantified immunological complexes. Assay sensitivity was 20 IU/mL, and the linear measurement range was 800 IU/mL.

Statistical analysis

All statistical analyses were performed with Statistical Package for the Social Science, (SPSS Inc., version 16 SPSS Inc., Chicago. IL, USA) a statistical software package for Microsoft windows. The collected data were first tested for normality of distribution. Statistical analysis was then conducted using parametric methods, including the chi-square test to compare two attributes and the independent Student's *t*-test. The results were presented as Mean ± Standard Deviation (SD). Pearson's correlation coefficient analysis (r) was used to evaluate the correlation between the study variables. All tests were considered significant when the p value was less than 0.05.

Results

The study revealed that Lp-PLA2 levels alone showed a statistical significance between both groups (Table 1). There was a significant increase in Lp-PLA2 levels in group 1 (73.94 ng/ml) compared to group 2 (10.99 ng/ml), with a p-value of 0.005. This indicates a strong association between COVID-19 exposure and elevated Lp-PLA2 levels. However, RF levels and CRP were high in both groups but this difference was not statistically significant as p-values were 0.059 and 0.190 respectively. Also, the lipid profile parameters did not show significant differences between the groups, with p-values ranging from 0.116 to 0.833.

Pearson correlation analysis was done to test whether there was an association of Lp-PLA2, RF, and CRP levels with the other parameters of the study, between the two study groups. As in Table 2, RF showed significant correlations with several lipid profile parameters, particularly with TC/HDL and LDL/HDL ratios, suggesting that higher RF levels are associated with an unfavorable lipid

Table 1: Comparison of biochemical parameters in RA exposed and non exposed to COVID-19 study groups

Variables	RA exposed to COVID 19 (N=50) Mean ± SD	RA Non exposed to COVID 19 (N=50) Mean ± SD	Significance (2-tailed)
Age (years)	48.2 ± 12.6	47.5 ± 12.2	0.773
RF (mg/dl)	130.72 ± 154.41	81.142 ± 99.39	0.059
CRP (mg/dl)	1.50 ± 1.68	1.10 ± 1.36	0.190
Lp-PLA2 (ng/ml)	73.94 ± 15.33	10.99 ± 6.58	0.005*
Cholesterol (mg/dl)	180.58 ± 52.58	167.78 ± 34.95	0.155
Triglyceride (mg/dl)	149.34 ± 91.95	133.18 ± 62.08	0.306
HDL (mg/dl)	40.94 ± 12.69	41.40 ± 8.69	0.833
LDL (mg/dl)	109.77 ± 44.96	99.74 ± 32.34	0.203
VLDL (mg/dl)	27.97 ± 12.77	26.8 ± 12.27	0.642
Cholesterol / HDL ratio	4.52 ± 1.20	4.16 ±1.07	0.116
LDL / HDL ratio	2.79 ± 1.03	2.49 ± 0.88	0.131
Non-HDLc	139.64 ± 49.41	126.38 ± 34.24	0.122
Triglyceride/HDL ratio	4.38 ± 4.24	4.24 ± 2.28	0.185
Small dense LDL (mg/dl)	37.29 ± 14.8	33.52 ± 9.75	0.137

*$p < 0.05$ was considered statistically significant, * Indicates statistically significant p-value*
RA – Rheumatoid arthritis; RF – rheumatoid factor; CRP – C reactive protein; Lp-PLA2 – lipoprotein associated phospholipase A2; HDL – high density lipoprotein; LDL – low density lipoprotein; VLDL – very low density lipoprotein

profile. Likewise, CRP was significantly correlated with TG and VLDL levels, indicating that higher CRP levels were associated with higher levels of these lipids. However, Lp-PLA2 did not show significant correlations with any lipid profile parameters in this study, indicating that its association with vascular risk may be independent of traditional lipid profile parameters. These results support the idea that while traditional lipid profile parameters are important, biomarkers like Lp-PLA2 provide additional information about cardiovascular risk, especially in inflammatory conditions like RA.

Table 2 : Correlation between lipid profile parameters with RF, CRP, and LP-PLA

Variables Significance (2-tailed)	TC	TG	HDL	LDL	VLDL	TC/ HDL	LDL/ HDL	Non-HDLc	TG/ HDL	sdLDL
RF	0.362	0.830	**0.000****	0.170	0.089	**0.002****	**0.005****	0.057	**0.039***	0.051
CRP	0.496	**0.042***	0.652	0.921	**0.044***	0.520	0.846	0.407	0.104	0.257
LP-PLA2	0.771	0.371	0.634	0.577	0.385	0.718	0.952	0.854	0.327	0.977

*$p < 0.05$ was considered statistically significant, **Denotes correlation is significant at the 0.01 level (2-tailed), * Denotes correlation is significant at the 0.05 level (1-tailed), RF – Rheumatoid factor; CRP – C reactive protein; Lp-PLA2 – lipoprotein associated phospholipase A2; TC – total cholesterol; TG – triglycerides; HDL – high density lipoprotein; LDL – low density lipoprotein; VLDL – very low density lipoprotein; sdLDL – small dense LDL*

Discussion

In COVID-19 patients, RA inflammation is a high-risk inflammatory disease [4]. These inflammatory responses are intertwined at Lp-PLA2. It yields potent pro-inflammatory products by hydrolyzing oxidized phospholipids and oxidized lipoproteins in the vascular walls that generate pro inflammatory lipid mediators which would act as chemo-attractants and cause the build-up of monocytes forming foam cells. The activity of this catalyst conjointly results in alterations in HDL making it less potent to suppress inflammation. These oxidized lipoprotein molecules promote vascular inflammation and result in atherosclerotic plaque formation. The Lp-PLA2 may play an important role in the assessment in the development and progression of atherosclerosis. It may also help as a risk predictor for coronary and carotid events and is thought to be a promising approach to treating vascular diseases [15]. In the current study, we found significantly high Lp-PLA2 levels in RA individuals who were exposed to COVID-19 than RA individuals who were not exposed to COVID-19. Santos *et al*. (2019) have found in their study that patients exposed to COVID-19 had higher levels of Lp-PLA2 compared to the control, which suggested increased vascular inflammation [16]. The present finding suggested a relationship between inflammation caused by autoimmune disease and vascular risk, even though there was a quantitatively larger concentration of Lp-PLA2 in the patients with RA at all time points. Increased levels of Lp-PLA2 in the COVID-19-exposed RA individuals indicated that COVID-19 is also an inflammatory disease that could have aided the inflammatory process, leading to plaque build-up and atherosclerosis and vascular risk [16]. Studies suggest that COVID-19 infection facilitates endothelial dysfunction as a direct consequence of viral involvement and the host inflammatory response. Moreover, it has been suggested that the induction of apoptosis and pyroptosis might be essential in endothelial cell damage in patients with COVID-19 [17, 18].

It has been demonstrated from previously published literature that individuals with RA develop atherosclerosis more frequently than people in the general population, which might be due to the expression of Lp-PLA2 by inflammatory cells in atherosclerotic plaques. Lp-PLA2 hydrolyses phospholipids in LDL to yield proinflammatory products such as oxidized free fatty acids which stimulate the burden of ROS leading to vascular inflammation indirectly or directly and increased the chance of atherosclerosis [19, 20]. To the best of our comprehension, relatively few prospective studies have been conducted regarding Lp-PLA2 and the emergence of subclinical atherosclerosis, and even fewer have focused on individuals with inflammatory diseases. Measuring Lp-PLA2 has been linked to the development of atherosclerosis over time in studies on diabetes mellitus patients, and these findings were also confirmed in the general population [21].

Additionally, a meta-analysis of Lp-PLA2 in cardiovascular disease found that Lp-PLA2 concentrations (activity and mass) were significantly correlated with one another, proatherogenic lipid markers, and CVD risk continuously and graded [14]. Previous studies also report that Lp-PLA2 strongly correlates with apolipoprotein B-containing lipoproteins [23], highlighting the need to consider this. Plasma lipoproteins were assessed to check the Lp-PLA2's effects on occult CVD and subclinical atherosclerosis.

In previously published research, Lp-PLA2 had a positive correlation with total cholesterol, LDL cholesterol, total cholesterol to HDL cholesterol ratio, and non-HDL cholesterol [16,17]. Another study on Lp-PLA2 also stated a significant association between lipid levels and Lp-PLA2 activity. However, in the current investigation, there was no correlation between the lipid profile parameters and the levels of Lp-PLA2 in either the exposed or unexposed RA groups [24, 25]. The therapeutic intervention of the patients over their lipid parameters could have been a reason for the non-significant association between lipid profile parameters and sd LDL. This study looked into the relationship between serum Lp-PLA2 and CRP for predicting cardiovascular comorbidities in inflammatory disease. CRP levels were not statistically significant in RA individuals exposed and non-exposed to COVID-19. In a previous study, Lp-PLA2 was assessed in individuals with acute chest discomfort suggestive of acute Coronary Syndrome (ACS), which is a variety of critical cardiac diseases caused by restricted blood supply to the heart muscle owing to plaque rupture and clot development in the coronary arteries. ST-elevation MI, NSTEMI, and unstable angina were included. The diagnosis relied on clinical symptoms, ECG abnormalities, and increased cardiac biomarkers such as troponins, CK-MB, CRP, and Lp-PLA_2. Blood circulation, heart damage prevention, and life depend on early medical intervention.

Depending on the later confirmation of ACS and the usage of statins. They discovered that Lp-PLA2 was higher in the ACS patient group, regardless of statin medication, than in the non-ACS patient group. It's interesting to note that CRP levels were similar across all patient groups in the study [26]. This indicates that measuring Lp-PLA2 rather than CRP may be more beneficial in predicting cardiovascular comorbidities in inflammatory disease. Recent studies indicate that compared to the general population with low Lp-PLA2 levels, the subset of metabolic syndrome patients with greater Lp-PLA2 levels had an enhanced risk for CVD [27]. Lp-PLA2 activity was also demonstrated to have a significant correlation with atherogenic lipoprotein

sLDL in plasma, and the chance of having CVD was three times higher for people with higher CRP, LDL, and Lp-PLA2 levels [28,29]. Based on the current findings, Lp-PLA2 can assess risk even when the traditional lipid profile parameters are within the reference intervals. It can help evaluate and adjust the patients across risk groups and assist in care [30].

Conclusion

The key finding of our study was that RA individuals exposed to COVID-19 have significantly higher Lp-PLA2 levels than those not exposed, suggesting that COVID-19 exacerbates vascular inflammation and increases the risk of atherosclerosis in these patients. Most other lipid profile parameters do not show significant differences between the two groups. This indicates that Lp-PLA2 may be a more sensitive marker for assessing vascular risk in RA patients exposed to COVID-19 and acts as an independent marker in relation to lipid profile.

Acknowledgement

The authors sincerely thank the Sri Ramachandra Institute of Higher Education and Research for providing the necessary infrastructure and support for this study. We are immensely thankful to the patients and laboratory staff for their unwavering cooperation and participation, especially during the challenging times of the COVID-19 pandemic. This study would not have been possible without their collective effort and dedication.

References

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet* 2020; 395(10223): 470-73.
2. Hannawi SMA, Hannawi H, Al Salmi I. Cardiovascular risk in rheumatoid arthritis: literature review. *Oman Med J* 2021; 36(3): e262.
3. Aletaha D, Smolen JS. Diagnosis and management of rheumatoid arthritis: a review. *JAMA* 2018; 320 (13): 1360-1372.
4. Bordy R, Totoson P, Prati C, Marie C, Wendling D, Demougeot C. Microvascular endothelial dysfunction in rheumatoid arthritis. *Nat Rev Rheumatol* 2018; 14(7): 404-420.
5. Meyer PW, Anderson R, Ker J, Mahmood TM. Rheumatoid arthritis and risk of cardiovascular disease. *Cardiovasc J Afr* 2018; 29(5): 317-321.
6. Carbone F, Bonaventura F, Liberale L, Paolino S, Torre F, *et al*. Atherosclerosis in rheumatoid arthritis: promoters and opponents. *Clin Rev Allergy Immunol* 2020; 58(1):1-14.
7. Roongta R, Ghosh R. Managing rheumatoid arthritis during COVID-19. *Clin Rheumatol* 2020; 39(11):3237-3244.
8. Elemam NM, Azzam AM, Maghazachi AS, Hannawi S. COVID-19 infection and rheumatoid arthritis: mutual outburst cytokines and remedies. *Curr Med Res Opin* 2021; 37(6): 929-938.
9. Gonçalves I, Edsfeldt A, Ko NY, Grufman H, Berg K, Björkbacka H, *et al*. Evidence supporting a key role of Lp-PLA2-generated lysophosphatidylcholine in human atherosclerotic plaque inflammation. *Arterioscler Thromb Vasc Biol* 2012; 32(6):1505-1512.
10. Hariharan V, Namrithaa S. A study on high ApoB and LDL levels in people attending a tertiary hospital in Coimbatore, India. *J Krishna Inst Med Sci Univ* 2024; 13(2):98-104.
11. Nielsen SH, Vestergaard H, Tofte N, Møller HJ, *et al*. Lipoprotein-associated phospholipase A2 activity and mass: correlation with inflammatory markers in patients with rheumatoid arthritis. *Biomarkers Med* 2020;14(10): 837-846.
12. Chandankhede M, Gupta M, Chari S. Correlation between insulin resistance and homocysteine in hypothyroid patients. *J Krishna Inst Med Sci Univ* 2018; 7(1):75-81.
13. Bennett MR, Sinha S, McCarthy M, McGowan MP, Kearney M. Lipoprotein-associated phospholipase A2: a new player in cardiovascular disease? *Nature Rev Cardiol* 2019; 16(10):627-642.
14. Moraes J, Santos M, de Oliveira A, Ferreira R. Lipoprotein-associated phospholipase A2: a novel biomarker for cardiovascular risk assessment. *Clin Biochem* 2020; 77:1-10.

15. Kumar S, Sharma A. Lipoprotein-associated phospholipase A2 as a potential biomarker for cardiovascular risk in inflammatory diseases. *J Inflamm Res* 2021; 14:123-35.
16. Santos M, Ferreira R, de Oliveira A, Moraes J. Inflammation and atherosclerosis: the role of lipoprotein-associated phospholipase A2. *Atherosclerosis* 2019; 284:1-10.
17. Ackermann M, Verleden SE, Kuehnel M, Hoffmann H, Kreuter M*, et al.* Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in COVID-19. *N Engl J Med* 2020; 383(2):120-8.
18. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan China: a retrospective cohort study. *Lancet* 2020; 395(10229):1054-1062.
19. Ikonomidis I, Michalakeas CA, Lekakis J, Parissis J, Anastasiou MN. The role of lipoprotein-associated phospholipase A2 (Lp-PLA2) in cardiovascular disease. *Rev Recent Clin Trials* 2011; 6(2):108-113.
20. Constantinides CT, Tselepis A. The role of lipoprotein-associated phospholipase A2 in atherosclerosis may depend on its lipoprotein carrier in plasma. *Biochim Biophys Acta* 2009;1791(4):327-338.
21. Lp-PLA(2) Studies Collaboration; Thompson A, Gao P, Orfei L, Watson S, Di Angelantonio E, *et al*. Lipoprotein-associated phospholipase A(2) and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. *Lancet* 2010; 375(9725):1536-44.
22. Wilensky RL, Macphee CH. Lipoprotein-associated phospholipase A2 and atherosclerosis. *Curr Opin Lipidol* 2009; 20(5): 415-420.
23. Constantinides A, van Pelt LJ, van Leeuwen JJ, de Vries R, Tio RA, van der Horst IC, *et al.* Carotid intima-media thickness is associated with plasma lipoprotein-associated phospholipase A2 mass in nondiabetic subjects but not in patients with type 2 diabetes. *Eur J Clin Invest* 2011; 41(8):820-827.
24. Persson M., Nilsson J., Nelson J., Berglund G. The epidemiology of Lp-PLA2: distribution and correlation with cardiovascular risk factors in a population-based cohort. *Atherosclerosis* 2007;190(2): 388-396.
25. Pearson GJ, Thanassoulis G, Anderson TJ, Barry AR, Couture P, Dayan N, *et al*. 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. *Can J Cardiol* 2021; 37(8):1129-1150.
26. Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, *et al.* American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of dyslipidemia and prevention of cardiovascular disease. *Endocr Pract* 2017; 23(2):1-87.
27. Kondelkova K, Borska C, Andrew J, Krejsek J, Hamakova K, Rendarova S, *et al*. Selected inflammatory and metabolic markers in psoriatic patients treated with Goeckerman therapy. *Mediators Inflamm* 2015; 2015: 979526.
28. Stafforini DM, Numao T, Tsodikov A, Vaitkus D, Fukuda T, Watanabe N, *et al*. Deficiency of platelet-activating factor acetylhydrolase is a severity factor for asthma. *Clin Invest* 1999; 103(7):989-997.
29. Jang Y, Kim OY, Koh SJ, Chae JS, Ko YG, Kim JY, *et al*. The Val279Phe variant of the lipoprotein-associated phospholipase A2 gene is associated with catalytic activities and cardiovascular disease in Korean men. *J* Clin *Endocrinol Metab* 2006; 91(9):3521-3527.
30. Gazi I, Lourida ES, Filippatos T, Tsimihodimos V, Elisaf M, Tselepsis AD. Lipoprotein-associated phospholipase A activity is a marker of small dense LDL particles in human plasma. *Clin Chem* 2005; 51(12): 2264-2273.

Author for Correspondence:
Dr. Mamta Singh, Sri Ramachandra Faculty of Allied Health Sciences, SRIHER, Chennai- 600116, Tamil Nadu
Email: drmamta@sriramachandra.edu.in,
Cell:7530865252

How to cite this article:
Singh M, Hari V, Ben A, Kumar P, Abishake R. Lipoprotein-associated phospholipase-A2 as an inflammatory biomarker for vascular risk in SARS-CoV-2 affected individuals with rheumatoid arthritis. *J Krishna Inst Med Sci Univ* 2025; 14(4): 66-74

Submitted: *23-July-2025* ***Accepted:*** *23-Sep-2025* ***Published:*** *01-Oct-2025*