

Lipoprotein(a) and D-dimer in Adults with Stage 1 Hypertension: A Hospital-based Cross-sectional Pilot Study

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Abstract:

Background: Lipoprotein(a) [Lp(a)] is an inherited atherogenic lipoprotein and an established cardiovascular risk factor. D-dimer reflects activation of coagulation and fibrinolysis, but the relationship of these biomarkers in early, uncomplicated hypertension remains incompletely defined. We evaluated serum Lp(a) and plasma D-dimer in adults with stage 1 hypertension and normotensive comparison participants and examined their correlation.

Methods: This hospital-based cross-sectional pilot study was conducted at R.N.T. Medical College and associated M.B. Hospital, Udaipur between April 2024 and March 2025. The study enrolled adults aged 30–60 years with stage 1 hypertension and normotensive comparison participants. There were 35 hypertensive and 30 normotensive participants. Lp(a) was measured by immunoturbidimetry on a Cobas c311 analyser and D-dimer by turbidimetric immunoassay on a STA Compact Max analyser. Between-group comparisons used Welch's t test and Mann–Whitney U test; categorical variables were assessed using Fisher's exact test; Pearson and Spearman correlations were calculated.

Results: Mean Lp(a) was 34.74 ± 29.49 mg/dL in the hypertensive group versus 14.96 ± 11.62 mg/dL in controls (Welch $p = 0.00067$; Mann–Whitney $p = 0.0126$). Mean D-dimer was 0.403 ± 0.164 mg/L versus 0.287 ± 0.124 mg/L, respectively (Welch $p = 0.00192$; Mann–Whitney $p = 0.00143$). Lp(a) > 30 mg/dL occurred in 16/35 (45.7%) hypertensive and 5/30 (16.7%) normotensive participants (Fisher $p = 0.0169$; OR 4.21, 95% CI 1.29–13.77). D-dimer > 0.5 mg/L occurred in 9/35 (25.7%) and 2/30 (6.7%), respectively (Fisher $p = 0.0517$; OR 4.85, 95% CI 0.99–23.73). Within-group correlations between Lp(a) and D-dimer were weak and not statistically significant (hypertension $r = 0.219$, $p = 0.207$; controls $r = 0.255$, $p = 0.174$).

Conclusions: In this small hospital-based pilot cohort, stage 1 hypertension was associated with higher Lp(a) and D-dimer concentrations, but Lp(a) and D-dimer were not significantly correlated within either group. The findings support further adequately powered prospective studies to determine whether these biomarkers provide complementary rather than directly linked information in early hypertension.

Keywords: Hypertension; Lipoprotein(a); D-dimer; Coagulation; Fibrinolysis; Cardiovascular Risk; Biomarkers; Cross-Sectional Study.

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Introduction

Hypertension is a major modifiable determinant of cardiovascular disease, and cardiovascular risk increases continuously with blood pressure rather than beginning abruptly at a diagnostic threshold [1]. Stage 1 hypertension, defined in the contemporary ACC/AHA framework as systolic blood pressure 130–139 mmHg or diastolic blood pressure 80–89 mmHg, therefore represents a clinically relevant early phenotype in which additional biological risk markers may be informative [1,2].

Lipoprotein(a) [Lp(a)] is an LDL-like particle containing apolipoprotein B-100 covalently linked to apolipoprotein(a). Its circulating concentration is predominantly genetically determined and is relatively stable over the life course [2,4]. Large epidemiological and genetic studies support a causal and continuous association between Lp(a) concentration and atherosclerotic cardiovascular disease [2,4]. Contemporary guidance classifies Lp(a) < 30 mg/dL as low risk, 30–50 mg/dL as intermediate risk and ≥ 50 mg/dL as high risk, while recommending measurement at least once in

adulthood [3,4]. Importantly, current evidence does not support treating Lp(a) as a general venous-thrombotic marker; its strongest established role is in atherosclerotic and aortic-valve disease [2,3,5].

D-dimer is generated when plasmin degrades cross-linked fibrin and therefore reflects activation of both coagulation and fibrinolysis [4-6]. Raised D-dimer concentrations have been associated with vascular disease and with biological states characterised by increased thrombin generation, although D-dimer is non-specific and is influenced by age, inflammation, malignancy, pregnancy, renal dysfunction and acute thrombosis [4-7]. Studies in hypertension have reported evidence of altered haemostatic activity, but the clinical meaning of modest D-dimer elevations in uncomplicated stage 1 hypertension remains uncertain [7,8].

Because Lp(a) has atherogenic and potentially pro-inflammatory properties while D-dimer reflects fibrin turnover, a relationship between the two could provide insight into overlapping vascular and haemostatic processes [9,10]. However, prior work has produced mixed evidence, and the biological relationship may be confounded by age, renal function and other cardiovascular risk factors [11,12]. The present pilot study therefore evaluated Lp(a) and D-dimer concentrations in adults with stage 1 hypertension compared with normotensive participants and tested the hypothesis that the two biomarkers would be positively correlated within each group.

Methods

This was a hospital-based cross-sectional pilot study conducted in the Department of Biochemistry, R.N.T. Medical College, Udaipur, Rajasthan between April 2024 and March 2025, with participants recruited through the Medicine outpatient department of M.B. Hospital, an associated teaching hospital. The study was approved by the Institutional Ethics Committee of R.N.T. Medical College (RNT/ACAD./IEC/2023/722). Written informed consent was obtained from all participants. Reporting was structured in accordance with the STROBE recommendations for cross-sectional studies [6]. The study was conducted in accordance with the ethical principles applicable to human research.

The study included adults aged 30–60 years, of either sex. The hypertensive group comprised participants with stage 1 hypertension (systolic 130–139 mmHg or diastolic 80–89 mmHg). Normotensive comparison participants were recruited from the same Medicine OPD. The study excluded participants with elevated blood pressure or stage 2 hypertension, stroke or transient ischaemic attack, myocardial ischaemia/infarction

or other cardiovascular disease, diabetes mellitus, deep-vein thrombosis, renal disorders, pregnancy, and use of antihypertensive drugs, statins, anticoagulants, heparin or low-molecular-weight heparin.

The primary analytic sample comprised 35 participants with stage 1 hypertension and 30 eligible normotensive participants (N = 65). A sensitivity analysis was also performed to determine whether this eligibility correction altered the principal findings.

Demographic and clinical information was recorded using the study proforma, including age, sex, smoking, alcohol use, dietary pattern, anthropometry and blood pressure. Blood samples were collected after an overnight fast. Routine biochemical investigations included fasting blood glucose, urea and creatinine. Serum was separated by centrifugation at 3000 rpm for 10 minutes within approximately one hour of collection.

Lp(a) was measured in serum by immunoturbidimetry using a Cobas c311 analyser (Roche Diagnostics). D-dimer was measured in plasma by turbidimetric immunoassay using a STA Compact Max analyser (Diagnostica Stago). The laboratory proforma recorded an Lp(a) reference value of <30 mg/dL and a D-dimer reference range of 0.0–0.5 µg/mL; for consistency with the manuscript's numerical reporting, D-dimer values are presented as mg/L, which is numerically equivalent to µg/mL. The study did not document whether the D-dimer assay was calibrated/reported as fibrinogen-equivalent units (FEU) or D-dimer units (DDU); therefore, no FEU/DDU conversion has been applied.

Continuous variables are summarised as mean±standard deviation. Between-group comparisons were assessed using Welch's t test and, as a distribution-robust sensitivity analysis, the Mann–Whitney U test. Categorical variables were compared using Fisher's exact test because of the small cell counts. Odds ratios (ORs) with exact or profile-likelihood 95% confidence intervals were calculated for binary biomarker thresholds. Pearson correlation was used for the primary assessment of linear association between Lp(a) and D-dimer, with Spearman correlation reported as a non-parametric sensitivity analysis. Two-sided P<0.05 was considered statistically significant. No multiplicity adjustment was applied because this was an exploratory pilot study. Microsoft Excel, SPSS version 29 and Python version 3.12 were used to analyse the data.

Results

The primary analysis included 65 participants: 35 with stage 1 hypertension and 30 normotensive comparison participants. Mean age was 45.97±8.94

years in the hypertensive group and 43.57 ± 7.81 years in controls (Welch $p = 0.251$). Sex distribution was similar (19 women/16 men vs 16 women/14

men; $p = 0.811$). Mean BMI was also similar (22.22 ± 1.67 vs 22.08 ± 1.84 kg/m²; Welch $p = 0.740$).

Table 1: Baseline characteristics

Variable	Stage 1 hypertension (n=35)	Normotensive (n=30)	P-value
Age, years; mean $\pm$ SD	45.97 $\pm$ 8.94	43.57 $\pm$ 7.81	0.251
Female, n (%)	19 (54.3)	16 (53.3)	0.811
Male, n (%)	16 (45.7)	14 (46.7)	0.811
BMI, kg/m ² ; mean $\pm$ SD	22.22 $\pm$ 1.67	22.08 $\pm$ 1.84	0.740

Lp(a) Concentrations: Mean Lp(a) was substantially higher among participants with stage 1 hypertension than among normotensive controls (34.74 ± 29.49 vs 14.96 ± 11.62 mg/dL). The between-group difference was significant by both Welch's t test ($P=0.00067$) and Mann–Whitney U test ($p = 0.0126$). Using the 30 mg/dL threshold, Lp(a)>30 mg/dL was present in 16/35 (45.7%) hypertensive participants and 5/30 (16.7%) controls (Fisher $p = 0.0169$; OR 4.21, 95% CI 1.29–13.77).

D-dimer Concentrations: Mean D-dimer was 0.403 ± 0.164 mg/L in the hypertensive group and 0.287 ± 0.124 mg/L in controls. The between-group difference was significant by Welch's t test ($p = 0.00192$) and Mann–Whitney U test ($p = 0.00143$). D-dimer>0.5 mg/L occurred in 9/35 (25.7%) hypertensive participants and 2/30 (6.7%) controls. The corresponding Fisher exact test was borderline ($p = 0.0517$; OR 4.85, 95% CI 0.99–23.73), whereas the uncorrected chi-square test was $p = 0.041$. Because of the small cells, Fisher's exact result is treated as the primary categorical inference.

Table 2: Lp(a) and D-dimer comparisons

Biomarker	Stage 1 hypertension	Normotensive	p-value	Threshold	OR (95% CI)
Lp(a), mg/dL; mean $\pm$ SD	34.74 $\pm$ 29.49	14.96 $\pm$ 11.62	0.00067	>30 mg/dL	4.21 (1.29–13.77)
Lp(a)>30 mg/dL, n (%)	16 (45.7)	5 (16.7)	0.0169	—	—
D-dimer, mg/L; mean $\pm$ SD	0.403 $\pm$ 0.164	0.287 $\pm$ 0.124	0.00192	>0.5 mg/L	4.85 (0.99–23.73)
D-dimer>0.5 mg/L, n (%)	9 (25.7)	2 (6.7)	0.0517	—	—

Correlation between Lp(a) and D-dimer: In participants with stage 1 hypertension, Pearson correlation between Lp(a) and D-dimer was weak and positive ($r = 0.219$, $p = 0.207$). In normotensive controls, the correlation was similarly weak ($r =$

0.255 , $p = 0.174$). Spearman correlations were 0.059 ($p = 0.738$) and 0.258 ($p = 0.168$), respectively. Thus, the study did not demonstrate a statistically significant within-group linear or monotonic relationship between the two biomarkers.

Table 3: Correlation between Lp(a) and D-dimer

Group	n	Pearson r (p)	Spearman ρ (p)
Stage 1 hypertension	35	0.219 (0.207)	0.059 (0.738)
Normotensive	30	0.255 (0.174)	0.258 (0.168)

Sensitivity analysis using all 70 master-chart records: Mean Lp(a) remained higher in stage 1 hypertension (34.74 ± 29.49 vs 14.54 ± 10.93 mg/dL; Welch $p = 0.00045$), and mean D-dimer remained higher (0.403 ± 0.164 vs 0.293 ± 0.117 mg/L; Welch $p = 0.00188$). Pearson correlations were $r = 0.219$ in the hypertensive group and $r = 0.223$ in the full control group. This sensitivity analysis supports the robustness of the observed group-level differences.

Discussion

The principal finding of this pilot study was that adults with stage 1 hypertension had higher Lp(a) and D-dimer concentrations than normotensive comparison participants. The magnitude and direction of the Lp(a) difference were consistent with the established role of Lp(a) as an atherogenic cardiovascular risk factor. Contemporary consensus

statements emphasise that Lp(a) is largely genetically determined and that its association with atherosclerotic cardiovascular disease is continuous rather than dependent on a single biological threshold [2,3,13,14]. The present study does not establish that stage 1 hypertension causes Lp(a) elevation, nor can it determine whether the observed difference reflects a causal relationship, residual confounding or characteristics of the selected hospital population.

The D-dimer finding is also biologically plausible but requires cautious interpretation. D-dimer represents degradation of cross-linked fibrin and therefore integrates coagulation activation with fibrinolysis. Previous work in hypertensive populations has reported associations between blood pressure, haemostatic markers and D-dimer, but D-dimer is non-specific and is not an established

screening test for thrombotic risk in otherwise asymptomatic patients [4,5,15,16]. In this study, the continuous D-dimer difference was statistically significant, whereas the categorical comparison using the laboratory threshold of 0.5 mg/L was borderline by Fisher's exact test. This discrepancy illustrates why dichotomising a continuous biomarker can reduce statistical information and should not be used as the sole basis for inference.

The central negative finding was the absence of a statistically significant correlation between Lp(a) and D-dimer within either group. The correlation of $r = 0.219$ in the hypertensive group and $r = 0.223$ in control group. These corrected values remain weak and non-significant. The discrepancy therefore changes the numerical estimate but not the substantive interpretation.

An important distinction is that higher biomarker concentrations between groups do not imply that the biomarkers are directly correlated with each other [17,18]. Lp(a) and D-dimer represent different biological domains: Lp(a) is predominantly genetically determined and linked principally to atherogenesis, whereas D-dimer reflects dynamic fibrin turnover. Any shared association with hypertension could therefore arise through partly overlapping but non-identical pathways, including endothelial dysfunction, inflammation, vascular remodelling or other unmeasured determinants [19,20].

The study has several strengths. It used a predefined clinical phenotype of stage 1 hypertension, excluded major cardiovascular and thrombotic disorders and relevant medications, used automated laboratory assays, and retained the participant-level master-chart values for an independent statistical audit. The eligibility audit and sensitivity analysis are also strengths because they make the final analytic population transparent.

The limitations are substantial. First, the sample was small and recruited from a single hospital, limiting precision and generalisability. Second, the cross-sectional design prevents determination of temporality or prediction of cardiovascular events. Third, the study did not include a lipid profile, apolipoprotein B, inflammatory biomarkers, renal estimated glomerular filtration rate, medication-independent ambulatory blood pressure measurements, or detailed cardiovascular risk scores that could have improved adjustment for confounding. Finally, the study did not document whether the D-dimer result was expressed as FEU or DDU, limiting comparison of the numerical threshold with other assays.

Conclusions

In this hospital-based cross-sectional pilot study, adults with stage 1 hypertension had higher

circulating Lp(a) and D-dimer concentrations than normotensive comparison participants. However, the two biomarkers were not significantly correlated within either group. The findings support further prospective, adequately powered studies incorporating comprehensive cardiovascular risk factors, renal function, standardised Lp(a) measurement and clearly specified D-dimer calibration to determine whether these biomarkers provide complementary information in early hypertension.

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