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Lipoprotein (a) is not associated with thrombus burden derived from CT pulmonary angiography in patients with acute pulmonary embolism

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Lipoprotein (a) [Lp(a)] is suspected to have antifibrinolytic effects, however, its relevance for the severity of venous thromboembolic events remains unclear. We studied the association of Lp(a) levels with thrombus load in pulmonary embolism (PE). 90 patients (40% female, median age 70 [56–79] years) at our tertiary care hospital with a diagnosis of acute PE, available Lp(a) levels and CT pulmonary angiography (CT-PA) performed between April 2017 and December 2019 were included. All CT-PA scans were reanalyzed and thrombus load was determined via Qanadli CT obstruction index (CTOI) and most proximal thrombus location. Median Lp(a) levels were 11.4 [9.3–29.1] mg/dL, median D-dimer levels were 4.6 [2.1–9.8] mg/L, median CTOI was 23 [8–50], central PE was present in 27 (30%) patients. Lp(a) did not correlate with CTOI ($r = 0.02$, $p = 0.922$) and was not associated with thrombus location ($p = 0.369$). CTOI significantly correlated with D-dimer ($r = 0.43$, $p < 0.001$) and right to left ventricular diameter ratio ($r = -0.49$, $p = < 0.001$). Our findings showed that Lp(a) is not associated with thrombus burden in PE, which suggests that a relevant effect of Lp(a) on the extent of venous thromboembolism is unlikely.

Lipoprotein(a) (Lp(a)) is a lipoprotein similar to low-density lipoprotein which is characterized by the glycoprotein apolipoprotein(a). Lp(a) plasma levels are genetically determined and stable over time[1]. Elevated Lp(a) levels are considered an additional risk factor for the development of atherosclerotic cardiovascular diseases such as cerebrovascular disease, peripheral artery disease, or coronary heart disease[2–6]. Suggested pathogenic mechanisms of Lp(a) include proinflammatory and prothrombotic activity[7,8]. The latter can be explained by structural similarities of apolipoprotein(a) with plasminogen resulting in a competitive inhibitory effect on fibrinolysis[9]. However, it remains unclear whether this antifibrinolytic effect is sufficient to play a relevant role in the development of venous thromboembolism (VTE)[10]. Though results from case-control and prospective cohort studies are inconsistent[11,12], large meta-analyses suggest an effect of Lp(a) on VTE risk[13].

Pulmonary embolism (PE) can be a life-threatening condition, especially if massive PE is present[14,15]. The imaging modality most frequently used to diagnose PE is CT pulmonary angiography (CT-PA) as it is fast, widely available and accurate. CT-PA directly visualizes thrombus material as a contrast filling defect in the pulmonary arterial tree which allows precise analysis of the location, morphology and extent of embolized thrombi. A

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previous study correlating Lp(a) levels with clinical PE severity according to the current ESC guidelines for the management of PE[16] did not find an association between elevated Lp(a) levels and clinical PE severity[17].

CT-PA offers a more direct quantification of thrombus burden when compared to clinical severity, which is not solely determined by clot burden but is also strongly influenced by individual resilience and comorbidities. Because of the potential effect of Lp(a) on fibrinolytic activity, Lp(a) levels may still be associated with morphological thrombus burden in PE, which, to the best of our knowledge, has not been evaluated yet.

This study aims to investigate the association between Lp(a) levels and morphological thrombus burden in patients with acute PE using quantitative measures from CT-PA. Understanding this relationship could provide valuable insights into the role of Lp(a) in the pathophysiology of PE and potentially identify Lp(a) as a target for therapeutic intervention.

Methods

In this retrospective study we correlated Lp(a) levels with thrombus extent in patients with PE. For that purpose, the hospital information system of the University Hospital Graz (Graz, Austria) was searched for patients with available Lp(a) and a PE diagnosis confirmed with CT-PA. Female and male patients aged above 18 years were included who underwent their CT-PA scan between April 2017 and December 2019. Patients with a CT scan after this period were not included in the study to avoid possible confounding effects of COVID-19[18]. The latency between PE diagnosis and Lp(a) measurement was limited to a maximum of 1 year.

We reanalyzed CT-PA images of these patients and determined thrombus extent as described below. Patients were excluded if PE was not confirmed on reanalysis.

The study was approved by the ethics committee of the Medical University of Graz (internal reference number 32-333ex19/20), that waived the requirement for patients' informed consent.

All methods were performed in accordance with the relevant guidelines and regulations.

Imaging and image analysis

Details on the scan protocol and image analysis have been previously described[19].

PE was defined as a sharply delineated contrast-filling defect in a pulmonary artery. Findings were carefully correlated to imaging artifacts and apparent filling defects likely caused by artifacts were not diagnosed as PE.

PE location was classified according to the most proximal thrombus as central, proximal lobar, distal lobar, segmental or subsegmental as illustrated in Fig. 1.

Thrombus load was determined using the CT obstruction index (CTOI) suggested by Qanadli et al.[20]. The CTOI is determined by adding the number of occluded segmental arteries after assigning a weighting factor and is reported as a percentage of the maximum possible score. Expressed in a formula, CTOI is calculated as $\Sigma(n \times d) / 40 \times 100$, where n is the number of segmental branches (1 to a maximum of 20 pulmonary segments) arising distally to the proximal thrombus, and d is the degree of obstruction (no thrombus = 0, partially occlusive thrombus = 1, total occlusion = 2). Subsegmental emboli were regarded as partially occlusive emboli.

To assess hemodynamic relevance of PE, the ratio of the right ventricular to left ventricular diameter (RV/LV ratio) was used. Diameters were measured as the maximum ventricular diameter perpendicular to the interventricular septum in an axial plane. Planes could differ between the right and left ventricle.

Each scan was independently analyzed by one of the study readers (consultant radiologists and radiology residents with a minimum experience in thoracic radiology of 3 years), supervised by a radiology consultant

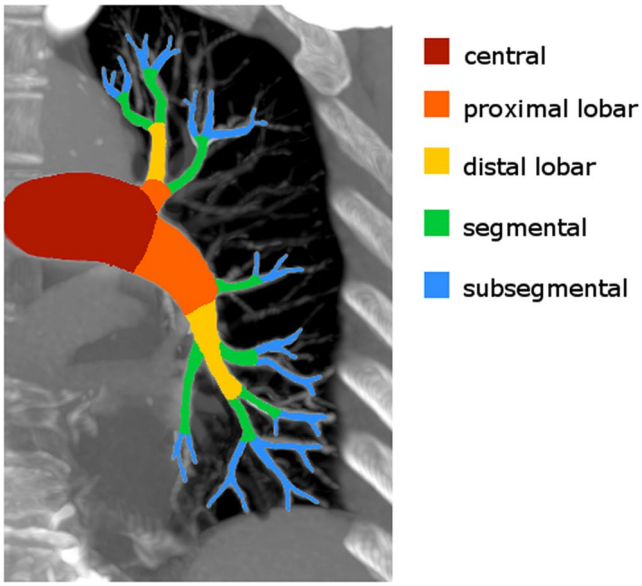

Figure 1. Classification of proximal thrombus location. Schematic overlay of the left pulmonary artery tree on a CT-PA reformation (coronal maximum intensity projection). Not all segmental arteries are visible.

with 6 years' experience (J.Sc.), who second-read at least all findings that were equivocal or that differed from the original clinical reports.

Statistics

All statistical analyses were performed with Stata 17.0 (Windows version, Stata Corp., Houston, TX, USA). Continuous variables were reported as medians [25th-75th percentile], and count data as absolute frequencies (%). Correlations and associations between variables were studied with Spearman's rank-based correlation coefficients, rank-sum tests, χ^2-tests, Fisher's exact tests, simple and multiple linear regression, as appropriate. Baseline characteristics of the study population (distribution overall and by Lp(a) level) are reported in Table 1, and a complete case analysis was performed.

There is limited prior data to accurately estimate the expected effect of Lp(a) on CTOI and calculate sample size. Assuming a Cohens f^2 of 0.1, that is considered a small to medium effect size[21], a power of 0.8 and a significance level of 0.05, the required sample size is 81 patients.

Results

Ninety patients were included in the analysis (Table 1), of whom 36 (40%) were female and 27 (30%) had central PE. Median Lp(a) levels were 11.4 mg/dL (25th -75th percentile: 9.3–29.1; range: 0.6–218) and included two outliers with very high Lp(a). A histogram and boxplot of Lp(a) levels in the cohort are provided in Supplementary Fig. S1.

Lp(a) levels were dichotomized into binary variables according to the established cut-off at 30 mg/dL[22]. The distribution of baseline characteristics, radiographic and clinical PE variables, and D-Dimer was similar between patients with and without an Lp(a) ≥ 30 mg/dL (Table 1). Lp(a) neither correlated with CTOI, nor with RV/LV-Ratio or D-Dimer, whereas higher RV/LV-ratios and higher D-Dimer correlated with a higher CTOI (Table 2).

In simple linear regression, Lp(a) did not emerge as a determinant of CTOI (change in CTOI per 10 mg/dL increase in Lp(a)=-0.4, 95%CI: -1.8-1.09, $p=0.626$) and explained only 0.3% of the variation in CTOI (R^2=0.0027, Fig. 2). These results remained similar upon exclusion of three patients with an Lp(a) > 100 mg/dL (change in CTOI per 10 mg/dL increase in Lp(a) = 1.2, -1.2-3.6, $p=0.312$, R^2=0.012, Fig. 2). Moreover, Lp(a) levels did not significantly differ between anatomical PE extent categories (Kruskal-Wallis $p=0.369$, Fig. 3). In multiple linear regression adjusting for ESC clinical PE risk and history of cancer, the lack of association between Lp(a) and CTOI prevailed (Table 3).

In sensitivity analysis, median time between Lp(a) determination and PE diagnosis was +1 day (25th -75th percentile: -2916 days - +137 days), and further adjusting for this time difference did not alter the main finding

Variable	*n* (%miss.)	Overall (*n* = 90)	Lp(a) < 30 mg/dL (*n* = 68)	Lp(a) ≥ 30 mg/dL (*n* = 22)	*p*
Demographic variables					
Age (years)	90 (0%)	70 [56–79]	68 [55–78]	76 [59–80]	0.116
Female sex	90 (0%)	36 (40%)	26 (38%)	10 (45%)	0.548
BMI (kg/m²)	56 (38%)	27 [25–29]	27 [25–29]	26 [24–32]	0.978
History of cancer	90 (0%)	20 (22%)	13 (19%)	7 (32%)	0.213
Radiographic PE variables					
CTOI (%)	90 (0%)	23 [8–50]	20 [8–45]	35 [13–55]	0.301
PE location	90 (0%)	/	/	/	0.256
- Subsegmental	/	11 (12%)	7 (10%)	4 (18%)	/
- Segmental	/	23 (26%)	20 (29%)	3 (14%)	/
- Distal lobar	/	12 (13%)	10 (15%)	2 (9%)	/
- Proximal lobar	/	17 (19%)	14 (21%)	3 (14%)	/
- Central	/	27 (30%)	17 (25%)	10 (45%)	/
RV/LV ratio	89 (1%)	1.00 [0.87–1.26]	1.00 [0.83–1.17]	1.10 [0.95–1.38]	**0.025**
Clinical PE variables					
ESC risk stratification:	90 (0%)	/	/	/	**0.044**
- High-risk	/	8 (9%)	5 (7%)	3 (14%)	/
- Intermediate-high-risk	/	7 (8%)	3 (4%)	4 (18%)	/
- Intermediate-low-risk	/	42 (47%)	31 (46%)	11 (50%)	/
- Low-risk	/	33 (37%)	29 (43%)	4 (18%)	/
D-Dimer (mg/L)	70 (22%)	4.6 [2.1–9.8]	4.3 [2.5–8.4]	6.2 [1.3–14.1]	0.747

Table 1. Baseline characteristics of the study population – distribution overall and by lp(a) level ($n=90$). Reported data are medians [25th-75th percentile] for continuous data, and absolute frequencies (column %) for count data, respectively. Lp(a) was dichotomized into a binary variable according to the established cut-off at 30mg/dL. P-values refer to comparisons of Lp(a) groups by rank-sum tests, χ^2-tests, and Fisher's exact tests, as appropriate. Abbreviations: CTOI – CT obstruction index, Lp(a) – Lipoprotein(a), p – p-value, BMI – Body mass index, PE – Pulmonary embolism, LV – Left ventricle, RV – Right ventricle.

Variable	Lp(a)	CTOI (%)	RV/LV ratio	D-Dimer
Lp(a)				
CTOI (%)	0.02 ($p=0.922$)			
RV/LV ratio	0.05 ($p=0.616$)	0.49 ($p<0.001$)		
D-Dimer	-0.13 ($p=0.294$)	0.43 ($p<0.001$)	0.51 ($p<0.001$)	

Table 2. Correlation matrix of Lp(a) with radiographic PE parameters and D-Dimer. Reported data are Spearman's correlation coefficients (p-value of a test of the null hypothesis that the correlation coefficient is zero). Abbreviations: CTOI – CT obstruction index, Lp(a) – Lipoprotein(a), RV/LV – right ventricle to left ventricle diameter ratio.

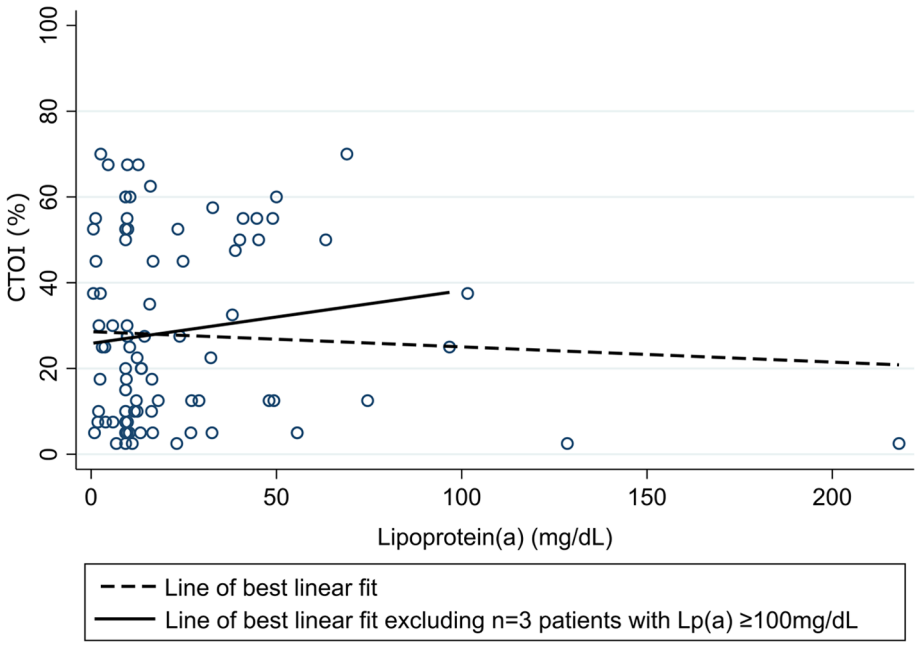

Figure 2. Scatter plot of CTOI versus Lipoprotein(a) levels. The dashed line represents the ordinary least squares line of linear best fit for all data, and the solid line the corresponding line of best for for all data excluding the three patients with Lp(a) levels ≥ 100 mg/dL (i.e. datapoints with very high leverage). Abbreviations: CTOI – CT obstruction index, Lp(a) – Lipoprotein(a).

of a lack of association between Lp(a) and CTOI. Supplementary Table S1 provides the results of a multivariate regression model that additionally includes time to Lp(a) determination.

Discussion

In a cohort of patients with acute PE, we correlated Lp(a) with thrombus burden, accurately quantified with CT-PA. We did not find an association between plasma Lp(a) levels and morphological thrombus load.

Although previous in vitro findings[7] and mechanistic considerations indicate that Lp(a) may influence pathways of thrombogenesis[9], our findings suggest that Lp(a) does not play a clinically relevant role in the severity and extent of thrombus formation in VTE. This is in line with the results of previous studies that did not find an association of Lp(a) with risk of first VTE[12], risk of recurrent VTE[23], or clinical PE severity[17].

Studies assessing the correlation of biomarkers with PE severity often rely on a severity grading based on clinical parameters, that are easy to obtain[17,24–26]. Such clinical grading may be a relevant parameter for the prediction of outcomes, however, it does not reflect true thrombus load as precisely as direct quantification from morphologic imaging. In our study, PE extent was quantified via CT-PA using CTOI, a well-established scoring system for quantification of thrombus load in PE[27]. Additionally, we classified PE location according to the most central thrombus found.

Although thrombus load was significantly different between the extreme high- and low-risk categories of the four-tier clinical ESC grading, no significant differences in CTOI were found between the clinical low- to intermediate-high-risk groups, illustrating that clinical scoring alone does not adequately reflect true thrombus burden, as suggested by previous studies[28]. Confirming earlier reports[29,30], our study found a strong correlation between thrombus load and D-dimer, one central laboratory parameter in the diagnostic workup of PE. Similar to thrombus load and PE extent, D-dimer was not associated with Lp(a). CTOI correlated well with RV/LV

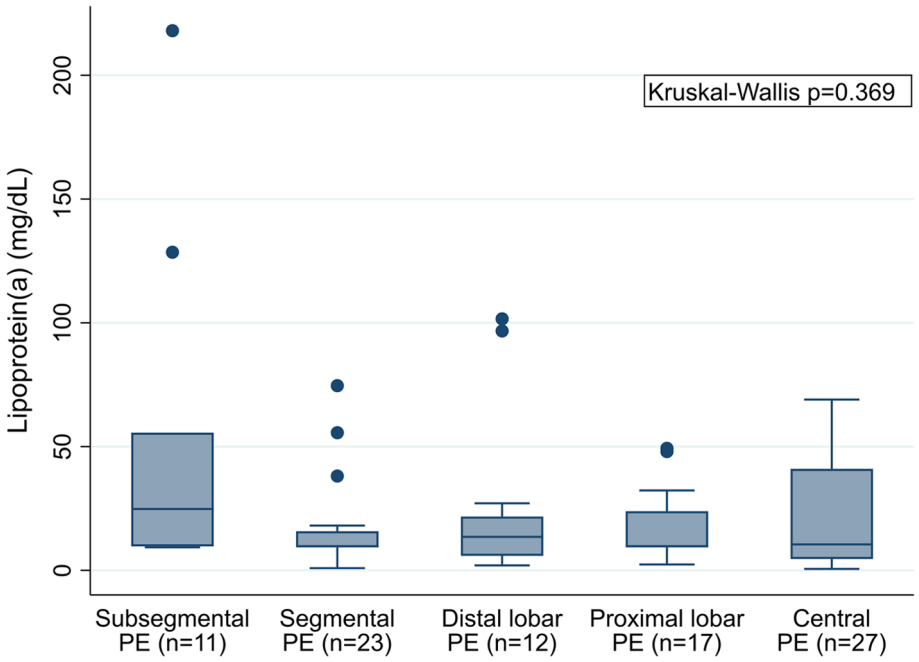

Figure 3. Box-and-whiskers-plots of Lipoprotein(a) levels by PE anatomical extent. The upper and lower boundaries of the boxes represent the 25th and 75th percentile, and the solid line within the box represents the median. The upper and lower adjacent line on the whiskers represent the most extreme value within 1.5x the interquartile range. Values outside the whiskers are outliers.

Dependent variable	Predictor variables	β	95%CI	*p*
CTOI (%)	Lp(a) (per 10 mg/dL increase)	-0.8	-2.2-0.7	0.300
	ESC PE clinical risk:			
	- Low-risk	Ref.	Ref.	Ref.
	- Intermediate-low-risk	4.7	-5.4-14.8	0.356
	- Intermediate-high-risk	13.9	-3.8-31.5	0.121
	- High-risk	23.4	6.7–40.0	0.006
	History of cancer	4.27	-6.8-15.3	0.444

Table 3. Multivariable linear regression model of predictors of the CTOI. β represents the β-coefficient, i.e. the change in CTOI (in%) per one unit increase (or specified unit increase) in the predictor variable (i.e. β of 23.4 means that after adjusting for Lp(a) and cancer, patients with ESC high-risk PE have on average 23% more PE thrombus mass than patients with ESC low-risk PE). Ref. denotes the reference category. Abbreviations: 95%CI: 95% confidence interval, CTOI – CT obstruction index, Lp(a) – Lipoprotein(a), p – Wald test p-value, PE – Pulmonary embolism, ESC – European Society of Cardiology.

diameter ratio, a marker of right heart strain, as previously shown[31]. Although patients with extremely elevated Lp(a) carry a disproportionally high cardiovascular risk[22], the exclusion of three outliers with Lp(a) above 100 mg/dL did not materially change our results, further supporting the apparently missing impact of Lp(a) on PE extent.

Even though our study did not find a significant association between Lp(a) levels and thrombus burden in patients with acute pulmonary embolism, this finding holds clinical significance. While elevated Lp(a) is an established cardiovascular risk factor, our results suggest that it may not have a substantial impact on thrombus formation in the setting of acute PE. These findings imply that therapeutic interventions aimed at reducing Lp(a) levels may not be necessary or beneficial in the management of PE.

Strengths and limitations

We systematically reanalyzed CT-PA images according to a pre-specified protocol, and are thus able to reliably quantitate thrombus load, a relevant parameter when assessing the thrombogenic potential of Lp(a). Though we included all PE patients at our institution with available Lp(a) levels and CT-PA within the specified timeframe, due to the retrospective nature of our study a selection bias is possible.

While we have a reasonable sample size, large enough to detect a relevant association between Lp(a) and thrombus load, the possibility of a type 2 error cannot be ruled out and a small undetected association may exist. Our sample size does not allow definite conclusions on the effect of extremely elevated Lp(a) or extensive adjustment for all potential confounders. Possible additional confounding factors are anticoagulant therapy that interferes with thrombus formation, concurrent prothrombotic conditions such as immobilization or inherited thrombophilia and genetic factors that influence Lp(a) levels.

The time between Lp(a) determination and CT-PA was extended in some cases. However, as the stability of Lp(a) levels over time has been confirmed in large cohorts[32], the effect of time should not have a relevant effect on our results, which was also confirmed in sensitivity analysis. Nonetheless, the potential impact of acute-phase reactions or other transient clinical conditions on Lp(a) levels at the time of PE diagnosis cannot be entirely excluded.

Conclusion

In conclusion, we did not find an association between Lp(a) and thrombus burden in acute PE. These results suggest that the antifibrinolytic activity of Lp(a) does not entail a relevant effect on the extent of venous thromboembolism. Further larger and prospective studies are needed to confirm our results.

Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions

P.G. and J.Sc. conceptualized the study and wrote the manuscript. P.G. collected clinical and laboratory data. J.Sc. supervised CT-PA analysis. J.Sc., G.A., E.N., A.K., J.St., M.J., C.R., M.E., E.J. and N.S. analyzed CT-PA scans. F.P. performed statistical analysis and wrote sections of the manuscript. All authors critically revised the manuscript, read and approved the final manuscript.

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Declarations

Competing interests

The authors declare no competing interests.

Additional information

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