Natural Resources for Human Health
eISSN: 2583-1194

Original Research

Received 08 Aug 2026
Revised 12 Sep 2026
Accepted 30 Sep 2026

Natural Resources for Human Health 2026, Vol. 6 (23s): 392–399

KEYWORDS:
plasminogen activator inhibitor-1; cancer-associated thrombosis; deep vein thrombosis; solid malignancies; fibrinolysis; biomarker

Plasma Plasminogen Activator Inhibitor-1 Antigen and Deep Vein Thrombosis in Patients with Solid Malignancies in a Developing Country

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ABSTRACT: Cancer-associated thrombosis involves not only increased coagulation but also impaired fibrinolysis. Plasminogen activator inhibitor-1 (PAI-1) may contribute to this process, although evidence concerning circulating PAI-1 antigen and objectively confirmed deep vein thrombosis (DVT) in patients with solid malignancies remains limited. In this single-center cross-sectional study, 56 adults with histologically confirmed solid malignancies and intermediate- or high-risk Khorana scores were consecutively enrolled between January and September 2026. Plasma PAI-1 antigen was measured by enzyme-linked immunosorbent assay, and DVT was assessed using compression ultrasonography. Between-group differences, associations with DVT, and receiver operating characteristic (ROC) performance were examined. Logistic regression was adjusted for current chemotherapy. DVT was detected in 27 of 56 participants (48.2%). Median PAI-1 antigen concentrations were higher in participants with DVT than in those without DVT (0.986 vs 0.789 ng/mL; p<0.001). PAI-1 antigen discriminated DVT with an area under the ROC curve (AUC) of 0.812 (95% confidence interval [CI], 0.698–0.925). A study-derived threshold of 0.96 ng/mL yielded 66.7% sensitivity and 89.7% specificity. At this threshold, the prevalence ratio for DVT was 3.33 (95% CI, 1.85–6.01), while the odds ratio adjusted for current chemotherapy was 17.10 (95% CI, 3.94–74.32). PAI-1 antigen outperformed D-dimer in this selected cohort (AUC 0.812 vs 0.571; p=0.022). Higher plasma PAI-1 antigen concentrations were associated with prevalent, ultrasound-confirmed DVT among patients with solid malignancies selected for elevated thrombotic risk. These findings warrant prospective evaluation and independent validation of the assay-specific threshold before clinical use.omnis iste natus error sit voluptatem accusantium doloremque laudantium

1. INTRODUCTION

Venous thromboembolism (VTE) remains a clinically important complication of malignancy. Its consequences extend beyond the acute thrombotic event to recurrent thrombosis, interruptions in anticancer treatment, bleeding during anticoagulation, and reduced survival. The thrombotic burden is heterogeneous across solid malignancies and is influenced by tumor biology, disease stage, treatment exposure, and patient-related factors (Wan et al., 2025; Hisada and Mackman, 2023; Tsantes et al., 2024).

The mechanisms underlying cancer-associated thrombosis extend beyond activation of the coagulation cascade. Tumor-derived tissue factor, extracellular vesicles, platelet activation, neutrophil extracellular traps, vascular injury, and impaired fibrinolysis may contribute in varying proportions. Plasminogen activator inhibitor-1 (PAI-1), encoded by SERPINE1, inhibits tissue-type and urokinase-type plasminogen activators, thereby limiting plasmin generation and fibrin degradation (Hisada and Mackman, 2023; Sillen and Declerck, 2021; Declerck and Gils, 2013). PAI-1 also participates in tumor–stromal interactions, angiogenesis, and matrix remodeling, making its circulating concentration potentially relevant to both malignant progression and thrombotic complications (Declerck and Gils, 2013; Li et al., 2018).

In pancreatic cancer, higher active PAI-1 has been associated with subsequent VTE; however, active PAI-1 and PAI-1 antigen are not interchangeable measures. Antigen assays detect immunoreactive PAI-1 in active, latent, and complexed forms, whereas activity assays quantify functional inhibition of plasminogen activators (Declerck and Gils, 2013; Hisada et al., 2021; Bollen et al., 2014). Evidence from a single cancer type or from incident VTE therefore cannot automatically be extrapolated to a heterogeneous population with solid malignancies or to concurrent DVT detection.

We examined the association between plasma PAI-1 antigen and compression-ultrasound-confirmed DVT in Indonesian patients with solid malignancies and intermediate-to-high Khorana scores. We also explored an assay-specific discriminatory threshold and compared PAI-1 antigen with D-dimer. Given the cross-sectional design, our aim was to investigate concurrent association and discrimination rather than predict future thrombotic events.

2. MATERIALS AND METHODS

2.1 Study design and participants

This single-center observational cross-sectional study was conducted at Dr. Wahidin Sudirohusodo General Hospital, Makassar, Indonesia, from January to September 2026. Adult inpatients and outpatients with histologically confirmed solid malignancies were recruited consecutively. Eligibility required age ≥18 years, data sufficient to calculate the Khorana score, an intermediate- or high-risk Khorana category (score ≥1), and written informed consent for blood sampling and Doppler ultrasonography. Exclusion criteria were anticoagulant or antiplatelet therapy during the previous three months, known previous VTE, known inherited coagulation disorders, active autoimmune disease, severe hepatic or renal failure, and acute infection or severe inflammatory conditions. The minimum required sample size, calculated using the Slovin formula, was 45; 56 participants were ultimately included. Patients were screened consecutively in the inpatient wards and outpatient clinics. Enrolment was restricted to intermediate- or high-risk Khorana scores to enrich the sample for clinically relevant thrombotic risk, in whom DVT evaluation and thromboprophylaxis decisions matter most, rather than to estimate DVT prevalence in an unselected oncology population. This restriction selects patients with higher baseline thrombotic risk, so the findings cannot be extrapolated to patients with low-risk Khorana scores.

2.2 Clinical and laboratory assessments

Age, sex, body mass index, diabetes, hypertension, primary cancer category, cancer stage, treatment type (current chemotherapy vs no chemotherapy), and routine hematologic indices were collected from clinical assessment and medical records. Khorana and Wells scores were recorded. Venous blood for plasma PAI-1 antigen was collected between 07:00 and 10:00 local time to reduce variability related to its circadian rhythm (Scheer and Shea, 2014). Samples were collected into EDTA tubes, and plasma was stored at −30°C until analysis. Plasma samples were assayed undiluted, as specified by the kit protocol. PAI-1 antigen was quantified using a double-antibody sandwich ELISA (MyBioSource, MBS263153; reported detection range 0.312–20 ng/mL) at the Hasanuddin University Medical Research Center. Absorbance was measured at 450 nm on a Multiskan FC microplate reader and concentrations derived from a second-order polynomial (quadratic) standard curve fitted in Microsoft Excel to the six non-zero calibrators (0.3125–10 ng/mL). D-dimer was measured by the institutional laboratory according to standard procedures. The ELISA quantified antigen rather than PAI-1 functional activity. Plasma was separated by centrifugation according to the kit instructions and stored at −30°C until batch analysis; exact processing times and storage durations were not recorded. In accordance with the kit protocol, the 20-ng/mL standard was serially diluted to 10, 5, 2.5, 1.25, 0.625, and 0.312 ng/mL, and each plate included these calibrators and blank wells; patient samples were assayed in single wells. The manufacturer reports a sensitivity of 0.06 ng/mL and intra- and inter-assay precision of ≤8% and ≤12%, respectively; run-specific quality-control samples were not available, so study-specific coefficients of variation were not determined. Laboratory personnel performing the ELISA were blinded to DVT status.

2.3 Reference standard and outcome

The primary outcome was prevalent DVT detected by compression ultrasonography performed by a radiology specialist using a GE LOGIQ E10 system with a linear transducer. Loss of full venous compressibility, with supportive intraluminal thrombus or Doppler flow findings, indicated DVT. Participants without thrombus in examined deep venous segments were classified as non-DVT. All 56 analysed participants underwent ultrasonographic assessment, irrespective of the plasma biomarker result.

2.4 Statistical analysis

Analyses were performed using R version 4.4.2, including the pROC package (version 1.19). Categorical variables were summarized as counts and percentages; continuous variables were summarized as mean ± standard deviation or median (range), as appropriate. Shapiro–Wilk testing informed the choice of the Mann–Whitney U test for between-group PAI-1 comparisons. Categorical associations were assessed using chi-square or Fisher exact tests. ROC curves were evaluated against ultrasonography, with AUC 95% CIs calculated using the DeLong method. A threshold was selected by maximizing Youden's index; sensitivity, specificity, positive and negative predictive values, and accuracy were then calculated in the same dataset. The prevalence ratio compared DVT prevalence above and below this threshold. Logistic regression examined associations before and after adjustment for treatment type, which met the prespecified screening criterion for potential confounding ($p<0.25$ for its relationship with DVT). Paired AUCs were compared using DeLong tests; incremental performance of the D-dimer plus PAI-1 model was also evaluated using a likelihood-ratio test. All tests were two-sided, with $p<0.05$ considered statistically significant. The threshold and performance estimates are exploratory and were not externally validated. Nonparametric tests were used because PAI-1 antigen and D-dimer were not normally distributed. Eight potential confounders (age, sex, body mass index, diabetes, hypertension, cancer type, cancer stage, and treatment type) were prespecified on clinical grounds and from the literature. Factors with $p<0.25$ for DVT were candidates for the main model and were regarded as confounders if they changed the odds ratio for PAI-1 antigen by more than 10%. Because only 27 DVT events were available, we applied a conservative criterion of approximately 20 events per variable, which permitted a single covariate; even the less conservative minimum of ten events per variable would allow no more than two (Peduzzi et al., 1996). In a sensitivity analysis, each of the eight prespecified factors was added separately to the model. Previous VTE and recent anticoagulant or antiplatelet therapy were exclusion criteria and therefore could not confound the association. Model fit was assessed with the Hosmer–Lemeshow test. Paired ROC curves of PAI-1 antigen and D-dimer were compared with the two-sided DeLong test for correlated AUCs because both markers were measured in the same participants.

2.5 Ethical considerations

The study was approved by the Hasanuddin University Research Ethics Committee (approval no. 1006/UN4.6.4.5.31/PP36/2025; protocol UH25111019; 24 November 2025). Written informed consent was obtained from participants.

3. RESULTS AND DISCUSSION

3.1 Participants and clinical characteristics

Of 56 included participants, 27 (48.2%) had ultrasound-confirmed DVT and 29 (51.8%) did not. Most participants were female (69.6%), younger than 60 years (76.8%), and had stage IV disease (67.9%). Gynecologic (32.1%) and gastrointestinal/pancreatobiliary (30.4%) cancers were the most frequent malignancies, followed by breast and bone/soft-tissue cancers (8.9% each) and other solid malignancies (19.6%). Stage II and stage III disease were each present in nine participants (16.1%), and no participant had stage I disease. Thirty-two participants (57.1%) had high Khorana scores, and 55 (98.2%) met the Wells category indicating that DVT was likely. Among the 27 DVT cases, 25 involved the lower limbs and two the upper limbs (Table 1).

Table 1. Baseline characteristics of patients with solid malignancies according to DVT status

Characteristic	Overall (n = 56)	DVT (n = 27)	Non-DVT (n = 29)
Age ≥60 years, n (%)	13 (23.2)	7 (25.9)	6 (20.7)
Female sex, n (%)	39 (69.6)	19 (70.4)	20 (69.0)

Gynecologic cancer, n (%)	18 (32.1)	12 (44.4)	6 (20.7)
Gastrointestinal/pancreatobiliary cancer, n (%)	17 (30.4)	7 (25.9)	10 (34.5)
Stage IV disease, n (%)	38 (67.9)	17 (63.0)	21 (72.4)
Current chemotherapy, n (%)	21 (37.5)	7 (25.9)	14 (48.3)
High Khorana score (≥3), n (%)	32 (57.1)	18 (66.7)	14 (48.3)
D-dimer, mg/L, median (range)	5.29 (0.67–63.70)	6.41 (1.32–63.70)	5.02 (0.67–29.50)
PAI-1 antigen, ng/mL, median (range)	0.875 (0.430–1.663)	0.986 (0.711–1.663)	0.789 (0.430–1.116)

Values are n (%) or median (range). Percentages are calculated within each DVT-status group, except the overall column. DVT, deep vein thrombosis; PAI-1, plasminogen activator inhibitor-1.

3.2 Plasma PAI-1 antigen and DVT

Plasma PAI-1 antigen was higher in the DVT group than in the non-DVT group (median 0.986 [range 0.711–1.663] vs 0.789 [0.430–1.116] ng/mL; Mann–Whitney U=147.5, p<0.001). Concentrations overlapped between groups despite the overall distributional difference. None of the evaluated baseline clinical factors had a statistically significant univariable association with DVT, including cancer type (p=0.436) and stage (p=0.780); DVT was present in 5 of 9 participants with stage II, 5 of 9 with stage III, and 17 of 38 with stage IV disease. Current chemotherapy showed a nonsignificant association (p=0.084) and was carried forward into the adjusted analysis.

3.3 Threshold-based association and multivariable analysis

The AUC for PAI-1 antigen was 0.812 (95% CI, 0.698–0.925). A Youden-derived threshold of 0.9582 ng/mL, rounded to 0.96 ng/mL, gave 66.7% sensitivity and 89.7% specificity. DVT was detected in 18 of 21 participants (85.7%) with PAI-1 antigen ≥0.96 ng/mL, compared with 9 of 35 (25.7%) below this threshold, yielding a prevalence ratio of 3.33 (95% CI, 1.85–6.01; p<0.001). In logistic regression, the unadjusted odds ratio was 17.33 (95% CI, 4.11–73.03). After adjustment for current chemotherapy, the odds ratio remained 17.10 (95% CI, 3.94–74.32; p<0.001). The wide interval reflects limited precision. The adjusted model showed adequate fit (Hosmer–Lemeshow p=0.604), and current chemotherapy itself was not significantly associated with DVT (odds ratio 0.39; 95% CI, 0.10–1.55; p=0.181). In sensitivity analyses adjusting separately for each of the eight prespecified factors, the odds ratio for PAI-1 antigen ≥0.96 ng/mL ranged from 15.85 to 22.96 (all p<0.001); adjustment for age or stage changed the estimate by more than 10%, but away from the null.

Table 2. Distribution of DVT according to the study-derived PAI-1 antigen threshold

PAI-1 antigen category	DVT, n (%)	Non-DVT, n (%)	Total, n
PAI-1 antigen ≥0.96 ng/mL	18 (85.7)	3 (14.3)	21
PAI-1 antigen <0.96 ng/mL	9 (25.7)	26 (74.3)	35

DVT prevalence was 85.7% versus 25.7% (prevalence ratio 3.33, 95% CI 1.85–6.01). Crude OR 17.33 (95% CI 4.11–73.03); OR adjusted for current chemotherapy 17.10 (95% CI 3.94–74.32). The threshold was selected within this dataset. OR, odds ratio; CI, confidence interval.

3.4 Discrimination compared with D-dimer

The AUC for PAI-1 antigen exceeded that of D-dimer (0.812 vs 0.571; DeLong p=0.022). At its data-derived threshold of 7.31 mg/L, D-dimer showed 48.2% sensitivity and 72.4% specificity. Incorporating both markers in a logistic model increased the AUC relative to D-dimer alone to 0.820 (DeLong p=0.004; likelihood-ratio test p<0.001), but did not significantly improve discrimination relative to PAI-1 antigen alone (p=0.786; Table 3; Figure 1). These are apparent, within-sample estimates and may be optimistic.

Table 3. Apparent diagnostic discrimination of PAI-1 antigen and D-dimer for ultrasound-confirmed DVT

Biomarker	AUC (95% CI)	Sensitivity (%)	Specificity (%)	Accuracy (%)
PAI-1 antigen	0.812 (0.698–0.925)	66.7	89.7	78.6
D-dimer	0.571 (0.418–0.724)	48.2	72.4	60.7
PAI-1 antigen + D-dimer	0.820 (0.709–0.931)	74.1	86.2	80.4

Thresholds: PAI-1 antigen ≥0.96 ng/mL; D-dimer ≥7.31 mg/L; combined-model predicted probability ≥0.484. All cutoffs and performance estimates were derived from the same dataset and have not been externally validated. AUC, area under the receiver operating characteristic curve; CI, confidence interval.

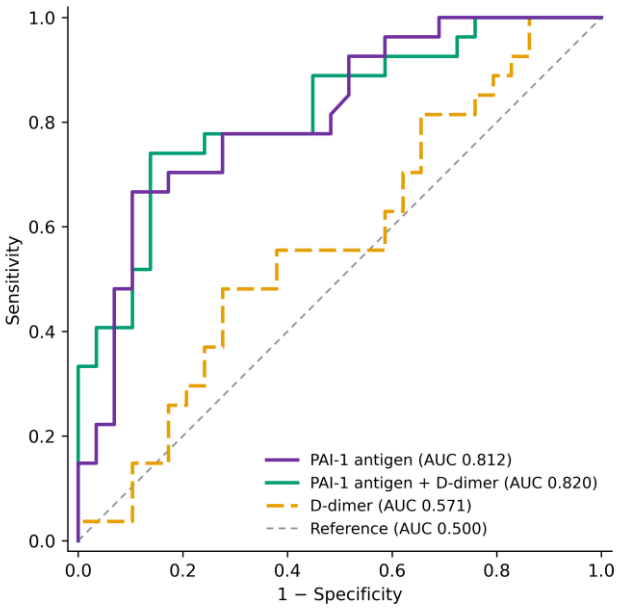


Figure 1. Receiver operating characteristic curves of PAI-1 antigen, D-dimer, and their combination for ultrasound-confirmed DVT

The combination is the predicted probability from a logistic model including ln-transformed D-dimer and PAI-1 antigen. The dashed gray diagonal is the reference line (AUC 0.500). All estimates are apparent, within-sample values and have not been externally validated. AUC, area under the receiver operating characteristic curve; DVT, deep vein thrombosis; PAI-1, plasminogen activator inhibitor-1.

3.5 Discussion

In this cross-sectional cohort of patients with solid malignancies who had intermediate or high Khorana scores, plasma PAI-1 antigen was higher in those with ultrasound-confirmed DVT. The association remained pronounced after adjusting for current chemotherapy, and PAI-1 antigen provided better apparent discrimination than D-dimer. These findings support a relationship between the fibrinolytic pathway and concurrent thrombosis, but they do not establish that PAI-1 elevation preceded thrombus formation.

PAI-1 provides a biologically plausible link between malignant disease and persistent fibrin deposition. By inhibiting tissue-type and urokinase-type plasminogen activators, increased PAI-1 may impair fibrin clearance. Tumor-derived factors, systemic inflammation, and endothelial and platelet responses can all alter this pathway (Hisada and Mackman, 2023; Sillen and Declerck, 2021; Declerck and Gils, 2013; Li et al., 2018). Nevertheless, circulating PAI-1 antigen is a heterogeneous measure that includes inactive and complexed protein. Elevated antigen concentrations do not necessarily indicate a proportionate increase in

antifibrinolytic activity. Distinguishing antigen from functional activity is therefore important when interpreting both mechanisms and the modest absolute separation in measured concentrations (Declerck and Gils, 2013; Bollen et al., 2014).

Our findings are broadly consistent with the prospective investigation by Hisada and colleagues in pancreatic cancer, in which higher active PAI-1 was associated with VTE (Hisada et al., 2021). They differ in several material respects: the previous study assessed active protein and future VTE, whereas our study measured antigen in a mixed population with solid malignancies at the time DVT status was established. The results should be considered complementary rather than direct replication. Other work has shown that assays of active and total PAI-1 can provide different discriminatory performance, further cautioning against transporting thresholds between methods (Bollen et al., 2014).

The 48.2% proportion of DVT in our cohort appears high but is a feature of patient selection, not a population prevalence estimate. Participants were required to have intermediate-to-high Khorana scores, almost all had Wells scores indicating probable DVT, and more than two-thirds had stage IV malignancy. This case mix substantially differs from an unselected ambulatory oncology population. The same selection may affect the observed positive and negative predictive values and could partly explain why D-dimer discrimination was limited. D-dimer is frequently elevated in malignancy even without acute thrombosis and must be interpreted in relation to clinical pretest probability (Di et al., 2023; Di et al., 2016).

The AUC of 0.812 suggests meaningful apparent separation between ultrasound-positive and ultrasound-negative participants. At the study-specific 0.96 ng/mL threshold, specificity was relatively high, whereas sensitivity was insufficient to support ruling out DVT when the test was negative. Adding PAI-1 to D-dimer increased apparent AUC, but the resulting model was scarcely different from PAI-1 alone. Importantly, these ROC comparisons were conducted in the dataset used both to select the thresholds and to estimate performance. Neither cross-validation nor testing in an independent cohort was performed. Accordingly, the threshold should not be proposed as a diagnostic standard or used to replace compression ultrasonography.

Absolute PAI-1 antigen concentrations in this study (median 0.875 ng/mL; range 0.430–1.663 ng/mL) were substantially lower than most published values. Among patients with cancer, Kondo et al. reported medians of 20.0 and 18.0 ng/mL in those with and without VTE (Kondo et al., 2018), and Kumara et al. reported a preoperative median of 17.30 ng/mL in colorectal cancer (Kumara et al., 2022). An early ELISA study reported means of 18 ng/mL in healthy subjects and 44 ng/mL in patients with recurrent DVT (Declerck et al., 1988), and a study from Malaysia reported 30.2 ng/mL in normal subjects (Al-Hamodi et al., 2011). Lower values have also been described, including a mean of 2.4 ng/mL in control subjects in another ELISA-based study (Joseph et al., 2016). These comparisons are descriptive because assays, anticoagulants, and study populations differed.

The cause of this difference cannot be determined from our data, although the assay is the most likely contributor. In a multicenter evaluation, commercial kits gave values from 7.4 to 28 ng/mL for the same pooled normal plasma (Declerck et al., 1993). Antigen assays can also respond differently to PAI-1 forms: one ELISA was 12 times less sensitive to the PAI-1/t-PA complex than to free PAI-1 (Declerck et al., 1988). Even so, this nearly fourfold range does not fully explain a median about 20 times lower than that reported by Kondo et al. (Kondo et al., 2018; Declerck et al., 1993). The kit manual did not state that the calibrator was traceable to an international standard and did not specify which PAI-1 forms the antibodies recognize. All calculated concentrations (0.430–1.663 ng/mL) fell within the calibrator range (0.312–10 ng/mL), but in its lower portion, so absolute values depend on the calibration of this kit. Pre-analytical factors may also contribute. We used EDTA plasma, which the kit permits but one study considered unsuitable for PAI-1 determination (Eriksson et al., 1989). Delayed processing and inadequate centrifugation would be expected to raise rather than lower values (Declerck et al., 1988; Eriksson et al., 1989; Macy et al., 1993), and morning sampling coincides with the circadian peak (Scheer and Shea, 2014), so neither explains the low concentrations. The effect of storage at −30°C was not assessed. Population differences are also unlikely to be the main explanation, because Chinese participants in a multi-ethnic cohort had among the highest PAI-1 levels (Lutsey et al., 2006) and Malaysian data do not suggest low concentrations (Al-Hamodi et al., 2011). The absolute concentrations and the 0.96 ng/mL threshold should therefore be regarded as specific to this kit and procedure. All samples were measured with the same kit and procedure, so between-kit differences do not affect the comparison between DVT and non-DVT groups, but the findings require confirmation because concentrations lay near the lower end of the standard curve.

Several aspects strengthen the study. DVT status was established objectively by ultrasound in all included participants, reducing differential verification bias. Blood sampling was restricted to morning hours in consideration of PAI-1 circadian variation (Scheer and Shea, 2014), and the analysis distinguished a prevalence ratio from logistic-regression odds ratios. However, the

sample size was small, with only 27 DVT cases; the adjusted effect estimate had a wide confidence interval, indicating uncertainty around its magnitude. Because DVT was common in this cohort, the odds ratio was much larger than the prevalence ratio and should not be interpreted as a risk ratio or prevalence ratio. Residual confounding remains possible because treatment was represented by a broad chemotherapy indicator and other thrombotic determinants, such as immobility, recent surgery, and detailed chemotherapy exposure, were not fully modeled. The cross-sectional design cannot resolve reverse causation; a thrombotic event itself could influence circulating PAI-1. The single-center and enriched cohort restrict generalizability, while assay differences and pre-analytical handling constrain the transportability of the observed threshold. The kit calibrator was not stated to be traceable to an international standard, and no comparison with another kit or reference material was performed. These considerations mean that larger prospective cohorts, together with paired antigen/activity measurements and prespecified external validation, are needed before the assay can be considered for clinical decision-making. Hospitalization status was not among the prespecified factors. PAI-1 antigen was measured in single wells without independent quality-control samples, so analytical imprecision could not be quantified, and concentrations lay in the lower portion of the standard curve. Finally, the sample size was calculated with the Slovin formula and was not designed to provide precision for AUC estimation or multivariable modelling.

4. CONCLUSION

Among adults with solid malignancies selected for intermediate or high thrombotic risk, elevated plasma PAI-1 antigen was associated with concurrent ultrasound-confirmed DVT and showed better within-sample discrimination than D-dimer. The findings are hypothesis-generating and require prospective and external validation before PAI-1 antigen can be recommended as a clinical DVT biomarker.

ACKNOWLEDGEMENTS

None.

FUNDING

None.

AUTHOR CONTRIBUTIONS

EYW contributed to the conceptualization and methodology of the study, participant recruitment and data collection, investigation, project administration, and preparation of the original manuscript draft. SS contributed to study conceptualization, methodology, formal analysis, interpretation of the findings, and critical revision of the manuscript. TH contributed to participant recruitment, clinical investigation, validation of clinical data, interpretation of the findings, and critical revision of the manuscript. SB contributed to methodological evaluation, formal analysis, validation, interpretation of the results, and critical revision of the manuscript. HR contributed to study supervision, data curation, clinical interpretation, and critical revision of the manuscript. AFB contributed to supervision, validation, interpretation of the findings, and critical revision of the manuscript. IJP contributed to statistical methodology and data curation. RM contributed to supervision, validation, clinical interpretation, and critical revision of the manuscript. DB contributed to supervision, data curation, interpretation of the findings, and critical revision of the manuscript. All authors contributed to the final interpretation of the findings, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ETHICS STATEMENT

Approved by the Hasanuddin University Research Ethics Committee (1006/UN4.6.4.5.31/PP36/2025; UH25111019). Participants provided written informed consent. Consent for publication: Not applicable to the de-identified aggregate findings reported here.

DATA AVAILABILITY STATEMENT

Data are available on reasonable request.

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