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Association of platelet indices with thrombotic events in patients with malignancy: A retrospective study

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Abstract

Background: Cancer-associated thrombosis is a major complication of malignancy, and accurate identification of patients at increased thrombotic risk is clinically important. Although platelet count is incorporated into the Khorana score, the additional value of routinely reported platelet indices remains uncertain. **Objective:** This study evaluated the associations of platelet indices with thrombotic events in patients with malignancy and compared their discriminatory performance with the Khorana score. **Methods:** In this retrospective study of 280 patients with malignancy, baseline platelet count, mean platelet volume, platelet distribution width, plateletcrit, platelet-large-cell ratio, and Khorana score were evaluated in relation to subsequent objectively confirmed thrombotic events. Group comparisons, receiver operating characteristic analysis, and multivariable logistic regression were performed. **Results:** Thrombotic events occurred in 42 patients (15.0%). Platelet count and plateletcrit were significantly higher among patients who developed thrombosis, while platelet distribution width showed a smaller difference. Mean platelet volume and platelet-large-cell ratio did not differ significantly. Platelet count showed the highest discrimination (AUC 0.760), followed by plateletcrit (0.745), Khorana score (0.708), and platelet distribution width (0.650). In multivariable analysis, platelet count was independently associated with thrombosis (OR 2.66, 95% CI 1.74-4.07). **Conclusion:** Platelet count showed the strongest association and discriminatory performance among the evaluated platelet parameters, whereas mean platelet volume was not independently associated with thrombotic events.

Keywords: *Cancer-associated thrombosis, Platelet indices, Mean platelet volume, Platelet distribution width, Plateletcrit, Khorana score, Thrombocytosis, Malignancy*

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1. Introduction

Thrombosis is among the most frequent and most serious complications of malignancy, and it is second only to the cancer itself as a cause of death in patients receiving chemotherapy (Khorana *et al.*, 2007; Timp *et al.*, 2013). The association between cancer and thrombosis is longstanding and reciprocal: the tumour and its

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treatment activate coagulation through the release of procoagulant factors, the expression of tissue factor and the provocation of inflammation, while the resulting hypercoagulable state produces venous and arterial thromboembolism at a rate several times that of the general population (Mulder *et al.*, 2021; Falanga *et al.*, 2013; Ay *et al.*, 2017). Because this thrombosis is both common and preventable, the identification of the patients at greatest risk, in whom thromboprophylaxis is justified, is an important clinical task.

The instrument developed for this task is the Khorana score, which stratifies the ambulatory cancer patient beginning chemotherapy by the site of the primary tumour and by four laboratory and clinical variables (Khorana *et al.*, 2008). Among these variables, one is haematological and directly relevant to the present study: a platelet counts of three hundred and fifty times ten to the ninth per litre or more, the thrombocytosis that is itself a recognised feature of the prothrombotic state of cancer and a marker of its activity (Moik *et al.*, 2020; van Es *et al.*, 2017). The platelet count thus already occupies a place in the assessment of cancer-associated thrombotic risk, and its inclusion reflects the central part that the platelet plays in the pathogenesis of thrombosis in malignancy.

The complete blood count, however, reports not only the number of platelets but also a set of platelet indices that describe their size and its variation, namely the mean platelet volume, the platelet distribution width, the plateletcrit and the platelet-large-cell ratio, all obtained at no additional cost (Budak *et al.*, 2016; Vinholt *et al.*, 2017). Of these the mean platelet volume has attracted the most attention, on the reasoning that larger platelets are younger, denser in granules and more reactive, so that a raised mean platelet volume should mark a more thrombogenic platelet population; the index has indeed been linked to arterial thrombosis and proposed as a marker of platelet activation (Gasparyan *et al.*, 2011; Korniluk *et al.*, 2019; Handtke and Thiele, 2020; Vinholt, 2019).

When applied to cancer-associated thrombosis, however, the evidence on the mean platelet volume has proved strikingly inconsistent. Some studies report that a high volume accompanies thrombosis, in keeping with the activation hypothesis, while several larger and carefully conducted cohorts have found the opposite, a low rather than a high volume marking the patients who go on to thrombose, and others have found no association at all, raising the possibility that any elevation is a consequence of the thrombus rather than its cause (Bilir *et al.*, 2013; Riedl *et al.*, 2014; Ferroni *et al.*, 2015). The platelet distribution width and the plateletcrit have been studied less, and their relation to thrombosis in cancer is correspondingly uncertain. This inconsistency leaves it unclear which, if any, of the platelet indices beyond the count itself add usefully to the assessment of thrombotic risk in malignancy.

The present study was therefore undertaken to evaluate the platelet indices for their association with thrombotic events in a cohort of patients with malignancy. Its objectives were to compare the platelet count, the mean platelet volume, the platelet distribution width, the plateletcrit and the platelet-large-cell ratio between the patients who did and did not develop thrombosis; to determine and rank their ability to discriminate a thrombotic event and to compare them with the Khorana score; and to identify by multivariable analysis which of the indices were independently associated with thrombosis.

2. Materials and methods

2.1. Study design and participants

This retrospective study examined 280 adult patients with a histologically confirmed malignancy whose baseline complete blood count and clinical records were available. Reporting follows the recommendations for observational studies (Vandenbroucke *et al.*, 2007). Patients receiving therapeutic anticoagulation at baseline, those with a thrombotic event already present at presentation, and those with a primary haematological disorder or a recent transfusion that would independently influence the platelet indices were excluded, so that the indices were assessed at baseline and as antecedents of any thrombotic event.

2.2. Platelet indices and risk stratification

The baseline complete blood count, obtained before the start of chemotherapy, provided the platelet count and the platelet indices, namely the mean platelet volume, the platelet distribution width, the plateletcrit and the platelet-large-cell ratio, all measured on an automated haematology analyser from the same

ethylenediaminetetraacetic-acid sample and reported in their standard units. The Khorana score was calculated according to the original model using tumour site, platelet count, haemoglobin concentration or use of erythropoiesis-stimulating agents, leukocyte count, and body mass index. The site of the primary tumour was categorised, as in that score, as very high risk for stomach and pancreatic cancer, high risk for lung and renal cancer, and standard risk for the remaining solid tumours.

2.3. Outcome

The outcome was an objectively confirmed thrombotic event, comprising deep vein thrombosis or pulmonary embolism confirmed by imaging, occurring after the baseline assessment during the period of observation. The ascertainment of the outcome was made from the clinical and imaging records by an assessor who was unaware of the baseline platelet indices, so that the outcome was determined independently of the predictors under study.

2.4. Statistical analysis

The platelet indices, some of which were skewed, are summarised as median with interquartile range or mean with standard deviation, and were compared between the patients with and without a thrombotic event by the Mann-Whitney or t test. The ability of each index and of the Khorana score to discriminate a thrombotic event was quantified by the area under the receiver operating characteristic curve. The indices independently associated with thrombosis were identified by multiple logistic regression, into which the platelet count, the mean platelet volume, the platelet distribution width, the cancer site and the stage were entered, the results being expressed as adjusted odds ratios with ninety-five percent confidence intervals. A probability below 0.05 was accepted as significant.

2.5. Ethical considerations

The study was approved by the Institutional EthicsCommittee before commencement and was conducted in accordance with the principles of the Declaration of Helsinki. Because it was a retrospective analysis of anonymised records, the requirement for individual informed consent was waived by the committee, and all records were identified only by a study code.

3. Results

3.1. Cohort and thrombotic events

Among the 280 patients, 186 (66.4%) had tumour sites classified as standard risk in the Khorana model, 67 (23.9%) had high-risk sites involving the lung or kidney, and 27 (9.6%) had very-high-risk sites involving the stomach or pancreas. A thrombotic event occurred in 42 patients (15.0%). Thrombocytosis was present in 73 patients (26.1%), while 41 (14.6%) had a Khorana score e"3. The event rate increased across Khorana risk categories. The cohort characteristics are presented in Table 1, with tumour-site distribution and event rates by Khorana category shown in Figure 1.

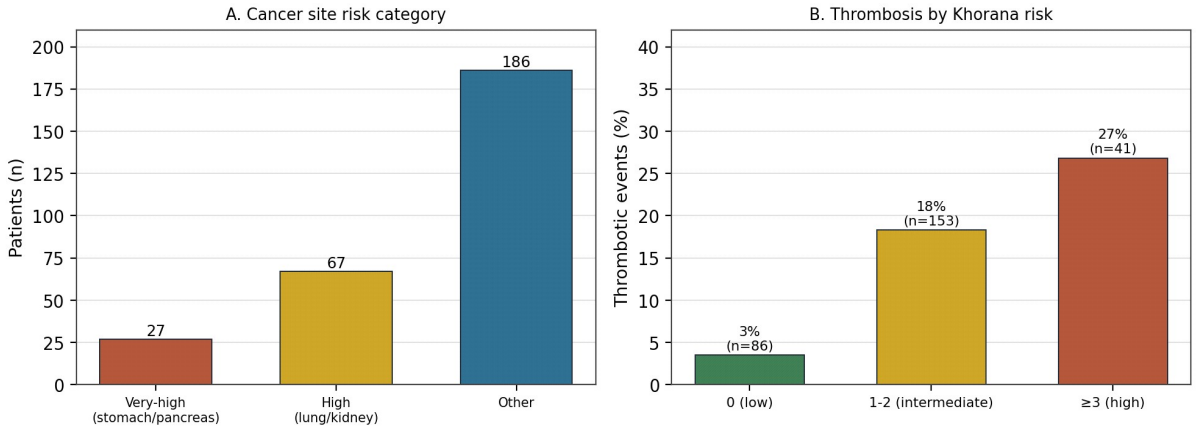


Figure 1: Distribution of cancer sites (A) and thrombotic event rate by Khorana risk category (B)

Table 1: Clinical and disease characteristics of the 280 patients with malignancy	
Characteristic	**N (%)**
Tumour site	
Very-high-risk site (stomach/pancreas)	27 (9.6)
High-risk site (lung/kidney)	67 (23.9)
Other cancer site	186 (66.4)
Disease characteristics	
Stage III–IV	162 (57.9)
Haematological characteristics	
Thrombocytosis (platelet ≥350 ×10⁹/L)	73 (26.1)
Anaemia (Hb <10 g/dL)	86 (30.7)
Leucocytosis (WBC >11 ×10⁹/L)	63 (22.5)
Risk and outcome	
Khorana score ≥3 (high risk)	41 (14.6)
Female	144 (51.4)
Thrombotic event	42 (15.0)

3.2. Platelet indices and thrombosis

The platelet indices differed sharply in their relation to thrombosis. The platelet count was markedly higher in the patients who developed a thrombotic event, at a median of 373 against 257 times ten to the ninth per litre, and the plateletcrit, which is the product of the count and the volume, was correspondingly higher, both differences being highly significant. The platelet distribution width was modestly but significantly higher in the thrombosis group. Mean platelet volume and platelet-large-cell ratio did not differ significantly between the groups, indicating no clear association between these platelet-size-related indices and subsequent thrombosis in this cohort (Table 2 and Figure 2).

Table 2: Platelet indices and Khorana score in patients with and without a thrombotic event			
Parameter	**Thrombosis**	**No thrombosis**	**p**
Platelet count (x10^9/L)	373 [289-426]	257 [186-338]	<0.001
Mean platelet volume (fL)	10.3 ± 0.9	10.4 ± 1.0	0.350
Platelet distribution width (%)	16.9 ± 2.5	15.6 ± 2.5	0.003
Plateletcrit (%)	0.38 [0.29-0.45]	0.27 [0.20-0.35]	<0.001
Platelet-large-cell ratio (%)	27.7 ± 7.7	27.7 ± 7.2	0.999
Khorana score	2.0	1.0	<0.001

3.3. Discrimination of thrombotic events

Platelet count showed the highest observed discriminatory performance, with an AUC of 0.760 (95% CI 0.671–0.848), followed by plateletcrit (AUC 0.745, 95% CI 0.655–0.835) and the Khorana score (AUC 0.708, 95% CI 0.616–0.801). Platelet distribution width showed modest discrimination (AUC 0.650, 95% CI 0.555–0.746),

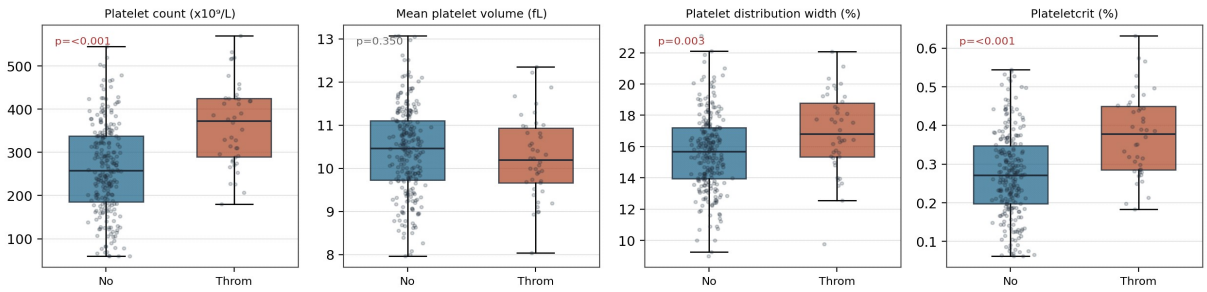


Figure 2: Platelet count, mean platelet volume, distribution width and plateletcrit by thrombotic status

whereas platelet-large-cell ratio and mean platelet volume showed poor discrimination, with AUCs of 0.474 and 0.451, respectively.

Table 3: Discrimination of thrombotic events by each platelet index and the Khorana score

Parameter	AUC	95% CI
Platelet count	0.760	0.671-0.848
Plateletcrit	0.745	0.655-0.835
Khorana score	0.708	0.616-0.801
Platelet distribution width	0.650	0.555-0.746
Platelet-large-cell ratio	0.474	0.381-0.568
Mean platelet volume	0.451	0.359-0.543

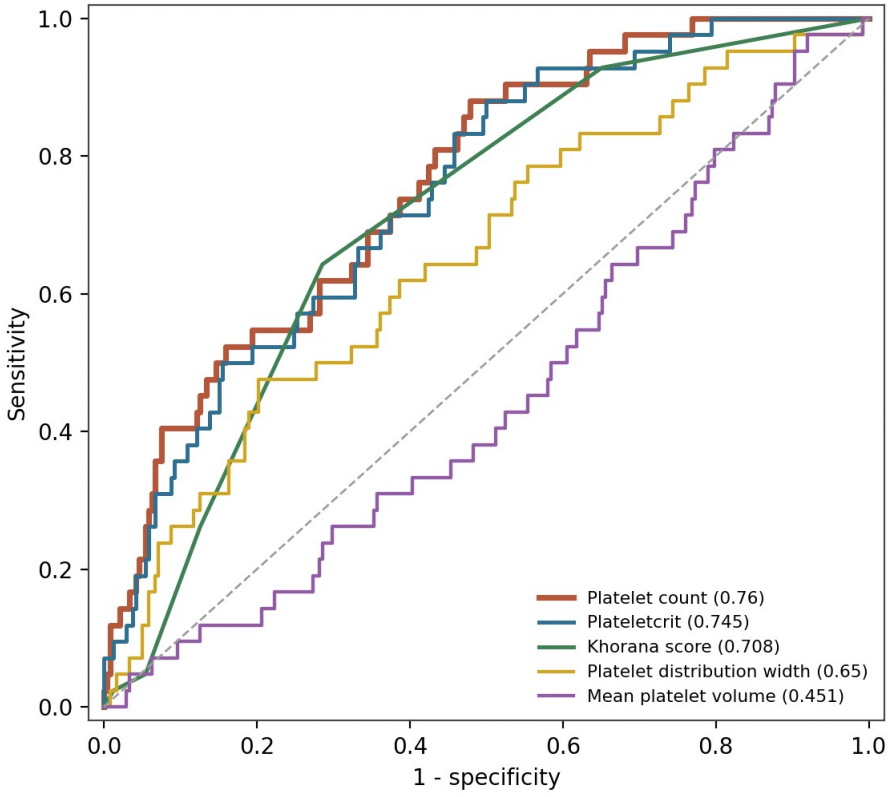


Figure 3: Receiver operating characteristic curves for the prediction of thrombotic events

3.4. Independent predictors

In the multivariable logistic regression model, platelet count was independently associated with subsequent thrombotic events (OR 2.66 per standard-deviation increase, 95% CI 1.74–4.07, p<0.001). Neither mean platelet volume (OR 0.87, 95% CI 0.60–1.25, p=0.439) nor platelet distribution width (OR 1.30, 95% CI 0.89–1.90, p = 0.180) showed an independent association. Very-high-risk tumour site and stage III–IV disease were also not independently associated with thrombosis. Thus, among the variables included in the multivariable model, platelet count showed the strongest independent association with thrombotic events (Table 4 and Figure 4).

Table 4: Multiple logistic regression for thrombotic events

Predictor	Odds ratio	95% CI	p
Platelet count (per SD)	2.66	1.74 to 4.07	<0.001
MPV (per SD)	0.87	0.60 to 1.25	0.439
PDW (per SD)	1.30	0.89 to 1.90	0.180
Very-high-risk site	0.95	0.32 to 2.81	0.928
Stage III-IV	1.35	0.64 to 2.85	0.424

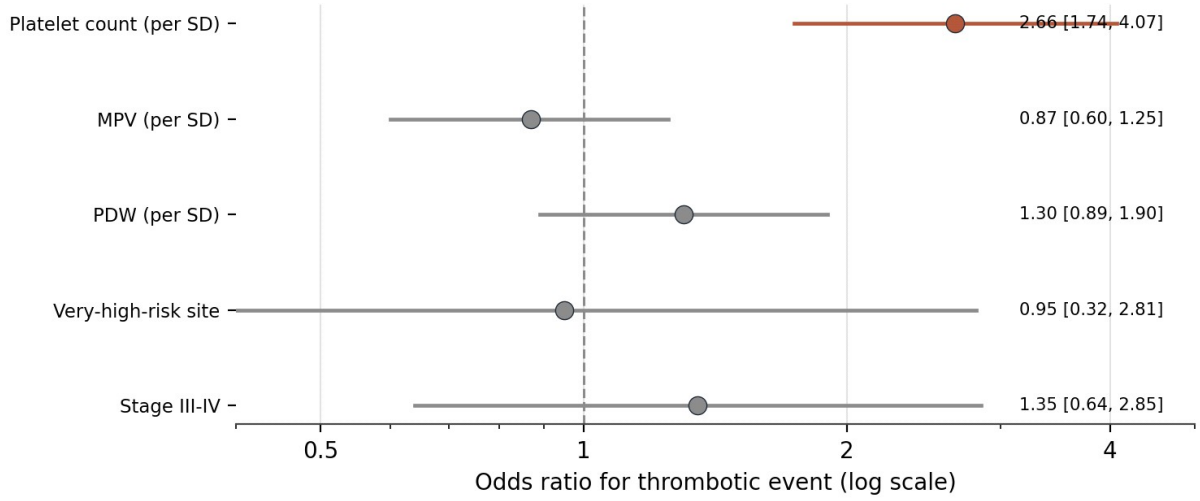


Figure 4: Independent predictors of thrombotic events

4. Discussion

This retrospective study found that platelet count and plateletcrit were significantly associated with subsequent thrombotic events in patients with malignancy, while platelet distribution width showed a weaker association. Mean platelet volume and platelet-large-cell ratio were not significantly associated with thrombosis. Platelet count also showed the highest observed discriminatory performance among the evaluated platelet indices and remained independently associated with thrombosis after adjustment for selected clinical variables.

The strong association of platelet count with thrombosis is consistent with its established role in cancer-associated thrombosis and its inclusion in the Khorana score (Kaushansky, 2005). In the present cohort, platelet count had a higher observed AUC than the Khorana score (0.760 versus 0.708); however, because formal statistical comparison of the AUCs was not performed, this difference should be interpreted descriptively rather than as evidence of superior predictive performance.

The finding of chief interest, however, is the negative one. The mean platelet volume, which the activation hypothesis predicts should be raised in the more thrombogenic patient, did not differ between those who did and did not thrombose, and it did not discriminate the event. This accords not with the smaller studies that first proposed the volume as a marker of cancer-associated thrombosis but with the larger and more rigorous

cohorts that have since failed to confirm it, several of which found, paradoxically, that a low rather than a high volume accompanied thrombosis, and with the population data suggesting that any elevation of the volume is a consequence of the thrombus rather than its cause. In malignancy, however, MPV may be influenced by disease-related and treatment-related factors, potentially contributing to variability in its association with thrombotic risk.

The platelet distribution width occupied an intermediate position, being modestly raised in the thrombosis group and a weak discriminator, but losing independent significance in the multivariable model. A widened platelet distribution reflects greater heterogeneity in platelet size and has been proposed as an indirect marker of platelet activation and thrombo-inflammatory activity. The modest association observed here is compatible with this hypothesis, but its lack of independent association and only moderate discriminatory performance do not support its use as a standalone marker of thrombotic risk.

These findings support the continued relevance of platelet count within established clinical risk assessment for cancer-associated thrombosis. However, the present study does not demonstrate that platelet count alone should replace validated risk models such as the Khorana score. The other platelet indices, particularly mean platelet volume, did not show sufficient independent association or discriminatory performance to support their use as standalone markers of thrombotic risk. Future studies should determine whether platelet indices provide incremental predictive value when combined with established clinical risk models and other validated biomarkers.

5. Limitations

Several limitations should be considered when interpreting these findings. First, platelet indices were assessed at a single baseline time point and therefore do not capture changes occurring during cancer progression or treatment that may influence thrombotic risk. Second, MPV is susceptible to preanalytical factors, including the anticoagulant used and the interval between blood collection and analysis, which may contribute to measurement variability. Third, the cohort included multiple cancer types and disease stages with potentially different thrombotic risks and platelet characteristics, and the sample size did not permit reliable subgroup analyses by individual tumour type. Finally, the study was conducted at a single centre, which may limit generalisability and warrants confirmation in larger multicentre cohorts.

6. Conclusion

In this retrospective cohort of patients with malignancy, platelet count and plateletcrit were associated with subsequent thrombotic events, while platelet distribution width showed a weaker association. Mean platelet volume and platelet-large-cell ratio were not significantly associated with thrombosis. Platelet count showed the highest observed discriminatory performance among the evaluated platelet indices and remained independently associated with thrombotic events after adjustment for selected clinical characteristics. These findings support the relevance of platelet count in cancer-associated thrombotic risk assessment, consistent with its incorporation into the Khorana score, but do not establish that platelet count alone can replace validated clinical risk models. The additional platelet indices should therefore be considered investigational rather than standalone predictors of cancer-associated thrombosis.

Ethical approval

The study was approved by the Institutional Ethics Committee and was conducted in accordance with the Declaration of Helsinki. As a retrospective analysis of anonymised records, the requirement for individual consent was waived.

Conflict of interest

The authors declare that no conflict of interest exists in relation to this work.

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Data availability

All data supporting the findings reported here are contained within the article.

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