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Is platelet-lymphocyte ratio (PLR) a predictor of thrombosis and together with circulating tumor cells capable to determine recurrence-free survival in patients with gastric cancer?

A razão plaqueta-linfócito (PLR) é um preditor de trombose e, juntamente com as células tumorais circulantes, é capaz de determinar a sobrevida livre de recorrência em pacientes com câncer gástrico?

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ABSTRACT

Introduction: Cancer-associated thrombosis (CAT) is a major cause of morbidity and mortality in oncology patients. There are no accurate risk assessment tools to predict venous thromboembolism (VTE). Circulating tumor cells (CTCs), circulating tumor microemboli (CTM), and high platelet-lymphocyte ratio (PLR) may predispose to VTE. **Objective:** To evaluate correlations of CTCs, CTM, and PLR with VTE and recurrence-free survival (RFS) in gastric cancer patients. **Material and Methods:** Patients with gastric cancer (localized and metastatic disease) were recruited (March 2016 to April 2017). CTCs were analysed by ISET at two timepoints: before neoadjuvant treatment (CTC1) and after surgery/before adjuvant therapy (CTC2) for patients with localized disease, and before first-line chemotherapy (CTC1) and after 6 months (CTC2) for patients with metastases. VTE incidence was determined retrospectively. RFS was estimated by Kaplan-Meier analysis. **Results:** We evaluated 93 patients. According to Khorana scores, 63 (67.7%) patients were at intermediate and 30 (32.3%) were at high risk for VTE. VTE incidence was 20.4% and CTM were found in 39.8%. VTE developed in 7/37 (18.9%) CTM-positive and in 11/50 (22%) CTM-negative patients (p=0.93). When PLR >288, VTE occurred in 7/14 patients (p=0.005). PLR also associated with poor RFS (p<0.0001). CTC2 was associated with poor RFS (p<0.0001). CTC2, PLR and VTE were independent prognostic factors for RFS (p=0.005, 0.043, and <0.0001, respectively). **Conclusion:** PLR is a prognostic indicator for VTE and RFS in gastric cancer patients. Neither CTC, nor CTM improved risk stratification for VTE in our studied population. PLR, CTC2, and VTE were independent prognostic factors for RFS.

Keywords: Platelet-lymphocyte ratio; Circulating tumor cells; Circulating tumor microemboli; Thrombosis; Gastric cancer.

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RESUMO

Introdução: A trombose associada ao câncer (TAC) é uma das principais causas de morbidade e mortalidade em pacientes oncológicos. Não existem ferramentas de avaliação de risco precisas para prever tromboembolismo venoso (TEV). Células tumorais circulantes (CTCs), microêmbolos tumorais circulantes (MTC) e alta relação plaquetas-linfócitos (RPL) podem predispor ao TEV. **Objetivo:** Avaliar as correlações de CTCs, MTC e RPL com TEV e sobrevida livre de recorrência (SLR) em pacientes com câncer gástrico. **Material e Métodos:** Foram recrutados pacientes com câncer gástrico (doença localizada e metastática) (março de 2016 a abril de 2017). As CTCs foram analisadas pelo ISET em dois momentos: antes do tratamento neoadjuvante (CTC1) e após a cirurgia/antes da terapia adjuvante (CTC2) para pacientes com doença localizada, e antes da quimioterapia de primeira linha (CTC1) e após 6 meses (CTC2) para pacientes com metástases. A incidência de TEV foi determinada retrospectivamente. A SLR foi estimada pela análise de Kaplan-Meier. **Resultados:** Avaliamos 93 pacientes. De acordo com os escores de Khorana, 63 (67,7%) pacientes estavam no nível intermediário e 30 (32,3%) estavam em alto risco para TEV. A incidência de TEV foi de 20,4% e MTC foram encontrados em 39,8%. TEV desenvolveu-se em 7/37 (18,9%) pacientes MTC-positivos e em 11/50 (22%) pacientes MTC-negativos (p=0,93). Quando RPL >288, ocorreu TEV em 7/14 pacientes (p=0,005). A RPL também associou-se à baixa SLR (p<0,0001). CTC2 foi associado com SLR ruim (p<0,0001). CTC2, RPL e TEV foram fatores prognósticos independentes para SLR (p=0,005, 0,043 e <0,0001, respectivamente). **Conclusão:** RPL é um indicador prognóstico para TEV e SLR em pacientes com câncer gástrico. Nem CTC, nem MTC melhoraram a estratificação de risco para TEV em nossa população estudada. RPL, CTC2 e TEV foram fatores prognósticos independentes para SLR.

Descritores: Relação plaqueta-linfócito; Células tumorais circulantes; Microêmbolos tumorais circulantes; Trombose; Câncer de intestino.

INTRODUCTION

Cancer associated thrombosis (CAT) is a major cause of morbidity and mortality in cancer patients.[1] The risk of venous thromboembolism is 4.1 higher in oncology patients compared to those without cancer;[2] idiopathic venous thromboembolism (VTE), which is composed of deep vein thrombosis (DVT) and pulmonary embolism (PE), is associated with 20% of further diagnose of malignant disease.[3] Tumor type, stage and extent of the cancer and antineoplastic regimen influence the incidence of CAT,[4] but there are no accurate clinical algorithms to identify cancer patients at high risk for VTE.

While the majority of cancer patients remain at low risk for VTE, the identification of patient candidates for surveillance or thromboprophylaxis remains a daunting clinical challenge.[5] The development of accurate risk assessment tools to stratify VTE risk in cancer patients had been attempted previously. The Khorana score is calculated by five validated variables: site of cancer; platelet count; hemoglobin level; leukocyte count; and body mass index.[6] Two studies sought to improve the predictive value of the Khorana score by incorporating additional variables. The Protech score included treatment with cisplatin, carboplatin and/or gemcitabine,[7] whereas the Vienna prediction score added biomarkers of platelet and coagulation activation (P-selectin and D-dimer, respectively).[8] Recently, another score (Indicate) was published, which evaluates albumin and LDH levels to predict risk of thrombosis.[9]

Maybe, variables not included in these tools may influence the risk of VTE. The discovery of additional factors associated with CAT is a pivotal step for the refinement of risk assessment strategies. The level of circulating tumor cells (CTCs) is a prognostic biomarker of progression-free survival and overall survival for many solid tumors.[10] We recently correlated CTC counts with prognosis in patients with non-advanced gastric cancer.[11] In addition, a preclinical study suggested that CTCs may promote VTE,[12] and two clinical studies associated CTCs with an increased risk of VTE in metastatic breast cancer patients.[13,14]

CTCs aggregate with platelets and coagulation factors to form circulating tumor microemboli (CTM) that are more likely than CTCs to overcome the stressors of physical shear forces and immune surveillance in the bloodstream.[15] In addition to facilitating hematogenous metastasis, CTM may activate the coagulation cascade through the interactions of platelets, tissue factor, fibrin, and selectin.[16] Consequently, CTM could link CTCs to the pathophysiology of CAT. However, a possible association of CTM with VTE has not been evaluated in patients with advanced neoplasms.

Clinicians currently include platelet counts in Khorana score calculations, but do not incorporate the platelet-lymphocyte ratio (PLR). PLR is a marker for poor prognosis in coronary artery disease.[17,18] In a cohort PLR was associated with higher VTE incidence in an ambulatory cancer population.[19] The aim of the present study was to evaluate the correlations of CTCs, CTM, and PLR with VTE and assessing these variables relationships to recurrence-free survival (RFS).

MATERIAL AND METHODS

We conducted a prospective single-center study at the A.C. Camargo Cancer Center, São Paulo, Brazil. Patients with gastric cancer were recruited at the Department of Abdominal Surgery, from March 2016 to April 2017, and were followed until January 2018. This study was approved by the institutional research ethic committee (Protocol No. 2134/15).

Inclusion criteria were diagnosis of gastric adenocarcinoma; age >18 years; measurable or evaluable disease; and no surgery for <4 weeks prior to sample collection. Patients receiving therapeutic anticoagulation were excluded. Methods of CTC analysis of patients with non-metastatic gastric cancer were published recently.[10] After obtaining written consent, blood samples for CTC assays were collected before the start of the first cycle of neoadjuvant chemotherapy (usually FOLFOX or XELOX) for patients with locally advanced tumors, and prior to the first cycle of first-line chemotherapy for patients with metastases. The second CTC evaluation was completed after surgery or before adjuvant treatment for patients with localized disease, and after 6 months of treatment for patients with metastases. The incidence of VTE was the only variable determined by retrospective review of electronic medical files. The VTE examinations were performed by clinicians when patients were symptomatic and the asymptomatic cases where incidentally found. Data regarding age, tumor histology, and metastasis were recorded and analyzed for their associations with VTE. We also evaluated complete blood counts, liver function, and serum tumor markers collected at the clinical analysis laboratory of AC Camargo Cancer Center. PLR was evaluated only at baseline, due to difficulties in obtaining data from medical records. We estimated PLR cut-off point for VTE using receiver operating characteristic curve (ROC curve). We established 288 because it was the point of high specificity, improving positive predictive value (Figure 1). PLR cut-off point (297) for RFS was estimated by using the maximum of the standardized log-rank statistic proposed by Lausen and Schumacher (1992).[20]

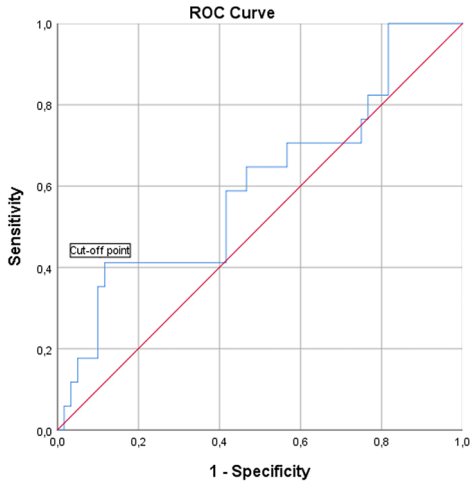

Figure 1. Receiver operating characteristic curve (ROC curve) showing the point where the cut-off value (PLR = 288) was determined.

Patients were stratified for VTE risk by using a predictive model for chemotherapy-associated thrombosis (Khorana score), which includes the following variables: site of cancer; platelet count; hemoglobin level; leukocyte count; and body mass index.[6] We chose the Khorana score because it is a simple and validated method, indicated for outpatients under chemotherapy. This score was recently included in the ASCO Clinical Practice Guideline Update for VTE prophylaxis in patients with cancer.[21]

CTC/CTM measurement

CTCs and CTM in peripheral blood were quantified by ISET® (Isolation by SizE of Tumor Cells, Rarecells, France) as described previously by Abdallah et al. (2019).[11] Briefly, after collection of 8ml of blood in ethylenediamine tetraacetic acid (EDTA) tubes, samples were kept under homogenization for up to 4 hours until filtration on ISET, following the manufacturer's instructions. CTCs were identified by hematoxylin staining and analyzed by light microscopy. CTCs were characterized according to high nuclear-cytoplasmic ratio (0.8), hyperchromatic and irregular nuclei, and cell diameter larger than 16µm[22] (Figure 2).

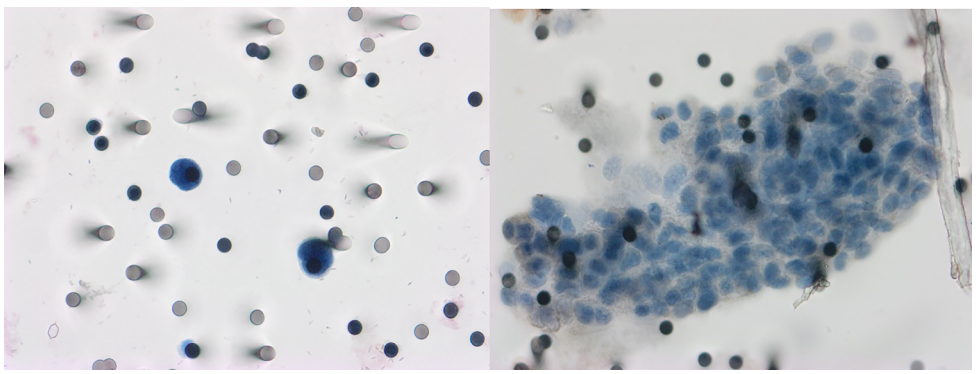

Figure 2. Circulating tumor cell (CTC) and circulating tumor microemboli (CTM) isolated from blood of a patient with metastatic gastric cancer after filtration on ISET. CTC and CTM were visualized by hematoxylin. CTM were characterized by the conglomeration of monomorphic overlapping cells with oval nuclei featuring condensed chromatin and poorly visible nucleoli. Small and black circles represent pores of ISET membrane. Images were taken at 400x magnification using a light microscWope (Research System Microscope BX61 – Olympus, Tokyo, Japan) coupled to a digital camera (SC100 – Olympus, Tokyo, Japan).

CTM were defined as clusters composed of at least three CTCs (Figure 2). Baseline CTCs and CTM were dichotomized as present or absent.

Definition of events

VTE comprised upper and lower limb deep vein thrombosis (DVT), pulmonary embolism, catheter-related thrombosis, and visceral vein thrombosis. Objective tests (ultrasonography or helical computed tomography) confirmed all VTE episodes.

Statistical analysis

We performed a descriptive analysis in which patient baseline characteristics were expressed as absolute and relative frequencies for qualitative variables and as the mean, median, minimum, maximum, and standard deviation for quantitative variables. Associations between qualitative variables were evaluated by the chi-squared test. RFS was assessed to the date of the event of interest. Patients who died or lost the follow-up were censored on the date of death or on the last study visit, respectively. Kaplan-Meier analysis was used to estimate survival curves, and differences between curves were evaluated by the log-rank test. For variables such as PLR and CTCs, the determination of two groups of observations with respect to a simple cut-off point was estimated by using the maximum of the standardized log-rank statistic proposed by Lausen and Schumacher (1992).[20] PLR cut-off point for VTE was estimated by ROC curve as described. The significance level of tests was fixed at 0.05. All statistical analyses were performed using R software version 3.5 (R Development Core Team).

RESULTS

Patient characteristics

Ninety-three patients were included; 4 patients were lost to follow-up and two did not have blood available for evaluation due technical reasons. So, a total of 6 cases were not included in the statistical analysis. The median age was 59 years (range 34-86); 59 (63.4%) were male. Metastatic disease was present in 21 (22.6%) cases. CTM was positive in 41 (44%) patients. The median follow-up duration was 531 days. Thirty-seven (39.8%) patients died during the study. VTE developed in 19 (20.4%) patients. There were 7 (36.8%) patients with pulmonary embolism, 4 (21%) with upper limb DVT, 3 (15.8%) lower limb DVT, 2 (10.5%) catheter-related DVT, two (10.5%) with splanchnic DVT, and one (5.25%) patient with superficial thrombophlebitis. According to Khorana scores, 63 (67.7%) patients were at intermediate and 30 (32.3%) were at high- risk for VTE. Demographic characteristics are described in Table 1.

Table 1. Demographic characteristics.

Variable	Category	n (%)
Gender	Male	59 (63)
	Female	34 (37)
Age (years)	Mean (SD)	59.67 (13.93)
	Median (Min-Max)	59 (34 - 86)
Stage	Localized disease	67 (75)
	Metastatic disease	22 (25)
Histologic subtypes	Intestinal	33 (35)
	Diffuse	46 (49)
	Mixed	13 (14)
	Indeterminate	1 (2)
Surgical treatment	Yes	49 (53)
	No	44 (47)
Khorana score	Intermediate	63 (68)
	High	30 (32)
VTE episode	PE	7 (37)
	Proximal DVT lower limbs	3 (16)
	Distal DVT lower limbs	0 (0)
	Proximal DVT upper limbs	4 (21)
	Distal DVT upper limbs	0 (0)
	Splanchnic DVT	2 (10.5)
	DVT associated with central venous catheter	2 (10.5)
	Thrombophlebitis	1 (5)

Abbreviations: DVT: Deep venous thrombosis; PE: Pulmonary embolism; VTE: Venous thromboembolism.

VTE incidence

The incidence of VTE during the study period was 20.4% (n=19 cases). The 1-year cumulative incidence of VTE was 14.2% (95% confidence interval 7.2-21.2). VTE developed in 7 (18.9%) of 37 CTM-positive patients, and in 11 (22%) of 50 CTM-negative patients (p=0.93 for the association of CTM with VTE, total of 6 missing cases). This lack of association persisted when adjusted for stage of the disease. A high-risk Khorana score was not associated with an increased risk of VTE compared to intermediate-risk scores (Table 2). VTE developed in 11 (16.1%) of 68 patients with localized disease and in 8 (38%) of 21 with metastases (p=0.055 for the association of stage with VTE, 3 missing cases).

We found that PLR >288 was associated with a higher incidence of VTE; 7 of 14 developed VTE (probability of 50%, p=0.005). This association persists when adjusted for metastases (Table 3). In the metastatic group, when PLR >288, 5 out of 8 patients developed VTE (probability 62%, p=0.048).

CTC counts at baseline (CTC1) higher than zero were associated with better RFS, whereas <2 CTCs/mL at the second collection (CTC2) was associated with better RFS (p=0.0054 and p<0.0001, respectively) (Figures 3 and 4). PLR >297 was associated with poor RFS (p<0.0001) (Figure 5). VTE was associated with poor RFS according to Kaplan-Meier estimates (p<0.0001). Because there were correlations between high PLR and CTC2 with worse RFS, we queried whether these variables correlated with each other, but found no relationship (p>0.05). By multiple Cox regression analysis, CTC2, PLR, and VTE were independent prognostic factors for RFS (p=0.005; 0.0043, and <0.0001, respectively) (Table 4).

Table 2. VTE distribution according to CTM and Khorana scores.

Variable	Category	VTE		p-value
		No	Yes	
Microemboli	No	39 (56.5%)	11 (61.1%)	0.934*
	Yes	30 (43.5%)	7 (38.9%)	
Khorana	Intermediate	49 (70%)	10 (52.6%)	0.251**
	High	21 (30%)	9 (47.4%)	

Abbreviations: CTM: Circulating tumor microemboli; VTE: Venous thromboembolism; *6 missing cases, **4 missing cases.

Table 3. Both metastasis and PLR associated with VTE by simple logistic model. PLR remains associated with VTE after adjusting for metastasis by logistic regression.

Variable	Category	Simple logistic model				Multiple logistic model			
		OR	95% CI for OR		p-value	OR	95% CI for OR		p-value
			Lower	Upper			Lower	Upper	
PLR	<=288								
	>288	5,300	1,524	18,437	0,009	4,298	1,135	16,270	0,032
Metastases	No								
	Yes	2,872	,976	8,449	0,055	1,765	,488	6,375	0,386

Abbreviation: PLR: Platelet-lymphocyte ratio.

Table 4. CTC2, PLR, and VTE were independent prognostic factors for PFS by multiple Cox regression analysis.

Variable	Category	Simple Cox regression model				Multiple Cox regression model*				
		n	HR	CI (95%) for HR		p-value	n	HR	CI (95%) for HR		p-value
				Lower	Upper				Lower	Upper	
CTC1	0	12									
	>0	74	0.388	0.194	0.775	0.007					
CTC2	≤2	31					30				
	>2	14	4.92	1.81	13.41	0.002	9	9.61	1.97	46.82	0.005
PLR	≤297	64					33				
	>297	12	4.03	1.90	8.53	<0.0001	6	5.28	1.05	26.58	0.043
VTE	No	68					30				
	Yes	18	8.44	4.16	17.31	<0.0001	9	60.12	8.90	406.0	<0.0001

Abbreviations: CTC2: CTCs counts at second collection; PFS: Progression free survival); PLR: Platelet-lymphocyte ratio); VTE: Venous thromboembolism.

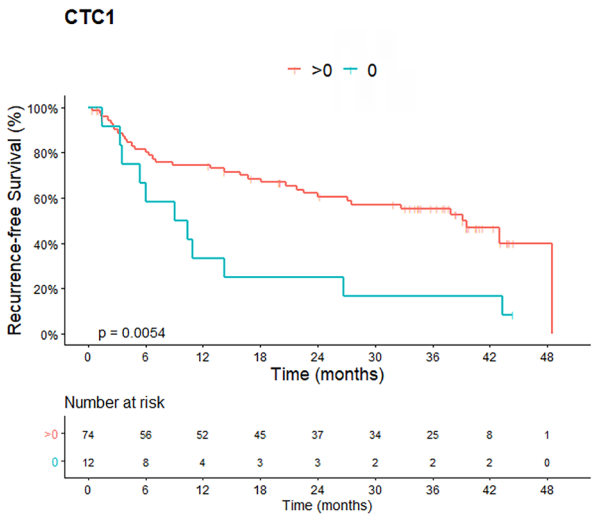

Figure 3. Kaplan-Meier estimate of recurrence-free survival according to CTCs counts at baseline (CTC1). CTC1 higher than 0 were associated with better recurrence-free survival (p=0.0054).

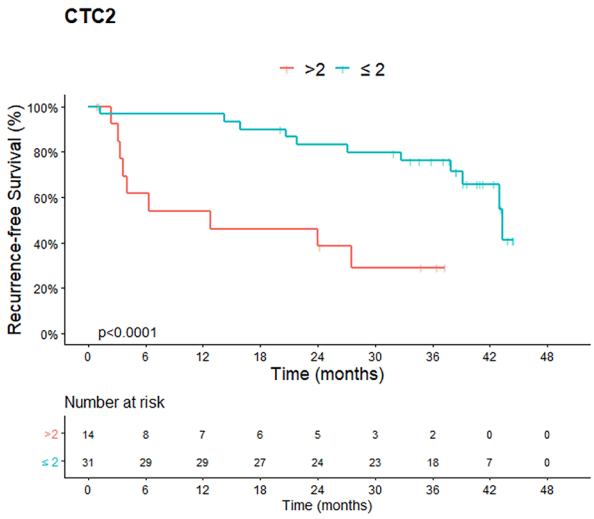

Figure 4. Kaplan-Meier estimate of recurrence-free survival according to CTC counts at second collection (CTC2). CTC2 < 2 CTCs/mL were associated with better recurrence-free survival (p<0.0001).

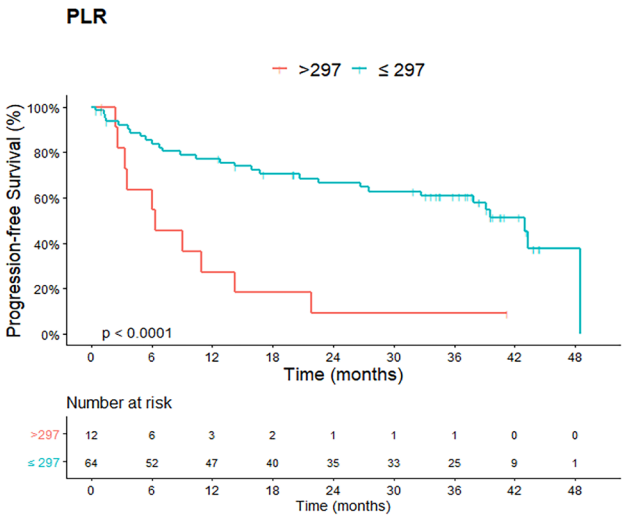

Figure 5. Kaplan-Meier estimate of progression-free survival according to platelet-lymphocyte ratio (PRL). PLR higher than 297 associated with poor PFS (p<0.0001).

DISCUSSION

Because a previous study suggested an association of CTCs with an increased risk of VTE in breast cancer patients (12), and due the procoagulant potential of CTM, our rationale was to determine if CTCs/CTM levels together with PLR could more accurately predict VTE incidence in patients considered at intermediate or high risk according to the Khorana score.

We found a cumulative VTE incidence of 20.4%, which is consistent with the literature. An epidemiologic study of a gastric cancer population found a 2-year cumulative VTE incidence that ranged from 0.5% to 24%, varying according to tumor stages, from I (M0) to IV (M1).[23] We found no difference in VTE incidence between CTM-positive or negative groups. As Khorana scores, metastatic disease, and cancer stage could be associated with VTE incidence, we conducted a multivariate analysis, which also showed that VTE incidence persisted unrelated to CTM-positive group. These results suggest that the prediction of VTE will require a complex model that incorporates multiple variables.[24]

Although there is rationale to suggest a hypothetical relationship of CTM with the incidence of VTE, this potential association was not empirically validated in our clinical setting. Interestingly, patients with high- and intermediate-risk Khorana scores also showed no statistical difference of VTE incidence. Probably, the fact that we analyzed these factors in patients with localized and metastatic disease had interfered with the results.

Our finding of a 50% probability of VTE when PLR is >288 supports the role of platelets in activating the coagulation cascade. This is a strong finding as it correlated with VTE even in a mixture patient population. In addition, higher baseline PLR was also associated with poor PFS, corroborating previous findings that platelets enable CTCs to evade immune responses and facilitate epithelial-mesenchymal transition.[16] Thus, our findings suggest that CTCs at the second assessment (CTC2), PLR, and VTE have roles in metastasis, leading to treatment failure and poor RFS.

An interesting finding was that patients with CTCs at baseline had better PFS. We suggest that the early presence of these cells in the bloodstream stimulated effective anti-tumor immune responses. More interesting is the finding that patients with higher CTC levels at CTC2 had poor RFS. We suggest that CTC bloodstream invasion at varying timepoints may have differential effects on RFS.

These results underscore the complexity of CTC, CTM, and platelet interactions and the difficulty to predict which cancer patient will develop VTE.[23] Meanwhile, in our population, disease progression was strongly correlated with VTE, which reflects the need for effective thromboprophylaxis. This study highlights that a solution to this conundrum could be the development of safer anticoagulants. Recently, two trials not specific for gastric cancer compared apixaban and rivaroxaban with placebo for CAT thromboprophylaxis.[25,26]

Lower doses of both rivaroxaban and apixaban seemed safe. Moreover, in the rivaroxaban trial, patients who received pharmacological prophylaxis had a lower, although not statistically different, mortality rate. Unfortunately, direct oral anticoagulants, especially rivaroxaban and edoxaban, may increase the bleeding risk in upper gastrointestinal cancers.[27]

The burden of CAT imposes not only mortality, but also morbidity, anti-coagulation costs, and anti-neoplastic treatment interruption.[28] A better predictive tool is mandatory. Most factors included in prediction models are static, whereas the risk of thrombosis is dynamic during the patient's life span and may be determined simply by chance. We found that the PLR associated not only with poor prognosis, but also with a higher incidence of VTE. PLR could potentially further improve the prediction of VTE. Therefore, PLR could be a new biomarker for VTE risk stratification in the oncology setting.

The drawbacks of our study are first a limited number of patients with localized and metastatic gastric cancer. In our cohort, 86 patients had blood collection for CTC1 analysis and 45 for CTC2. Probably, there was a survivor bias and consequently, selection of patients with better prognosis in the metastatic group. It is possible that most of patients did not make the second blood collection (CTC2) for poor prognosis or death. CTC1 and CTC2 had different timepoints depending on whether the disease was localized or metastatic and this could influence RFS as also the presence of CTM and VTE. Although PLR association with VTE was not our primary outcome, this finding is congruent with previous studies. Besides, our cut-off (288) value was quite similar to Ferroni cut-off (260).[19] In the metastatic group when PLR >288, 5 of 8 patients developed VTE, although statistically significant (p=0.048), this group contains limited number of patients. Further studies are necessary to confirm this result.

To the best of our knowledge, our study is one of the very first to find that PLR, CTC2, and VTE are independent prognostic factors for RFS in gastric cancer. Our findings reinforce the difficulty to foresee which cancer patients will develop VTE. Neither CTC, nor CTM improved this prediction, but PLR could constitute new prognostic biomarker with the advantage of being easy, feasible and of low cost. A study of a larger cohort could better evaluate these factors. Until there, the use of safer anticoagulants in patients at low risk of hemorrhage could be continued to address this dilemma.

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AUTHORS' CONTRIBUTIONS

B.S.P: data analysis and interpretation, manuscript writing; E.A.A: data analysis and interpretation, collection and/or assembly of data; C.A.L.M: conception/design, data analysis and interpretation; V.F.C: statistical analysis; K.N.: data analysis and interpretation; A.P.C.R.: collection and/or assembly of data; M.F.F.: interpretation and manuscript writing; G.Y: data analysis and interpretation, final approval of manuscript; L.T.D.C: conception/design, data analysis and interpretation, manuscript writing, final approval of manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

Approved by the ethics committee: (CEP 2134/15).

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