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Platelet Count and Major Bleeding in Patients Receiving Vitamin K Antagonists for Acute Venous Thromboembolism, Findings From Real World Clinical Practice

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Abstract: The outcome of patients with acute venous thromboembolism (VTE) and abnormal platelet count (PIC) at baseline has not been consistently studied. In real-world clinical practice, a number of patients with abnormal PIC receive vitamin K antagonists (VKAs) to treat acute VTE despite their higher risk of bleeding.

We used the Registro Informatizado de Enfermedad TromboEmbólica registry database to compare the rate of major bleeding in patients receiving VKA for long-term therapy of acute VTE according to PIC levels at baseline. Patients were categorized as having very low (<100,000/ μ L), low (100,000–150,000/ μ L), normal (150,000–300,000/ μ L), high (300,000–450,000/ μ L), or very high (>450,000/ μ L) PIC at baseline.

Of 55,369 patients recruited as of January 2015, 37,000 (67%) received long-term therapy with VKA. Of these, 611 patients (1.6%) had very low PIC, 4006 (10.8%) had low PIC, 25,598 (69%) had normal PIC, 5801 (15.6%) had high PIC, and 984 (2.6%) had very high PIC at baseline. During the course of VKA therapy (mean, 192 days), there were no differences in the duration or intensity (as measured by international normalized ratio levels) of treatment between subgroups. The rate of major bleeding was 3.6%, 2.1%, 1.9%, 2.1%, and 3.7%, respectively, and the rate of fatal bleeding was 0.98%, 0.17%, 0.29%, 0.34%, and 0.50%, respectively. Patients with very low or very high PIC levels were more likely to have severe comorbidities.

We found a nonlinear “U-shaped” relationship between PIC at baseline and major bleeding during therapy with VKA for VTE.

Consistent alteration of PIC values at baseline suggested a greater frailty.

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Abbreviations: DVT = deep vein thrombosis, INR = international normalized ratio, LMWH = low molecular weight heparin, MB = major bleeding, PE = pulmonary embolism, PIC = platelet count, RIETE = Registro Informatizado de Enfermedad TromboEmbólica, VKA = vitamin K antagonist, VTE = venous thromboembolism.

INTRODUCTION

Venous thromboembolism (VTE) is a major health problem, with substantial morbidity and mortality. Reliable information on the factors influencing the risk for major bleeding appearing during the course of anticoagulant therapy may facilitate better use of therapy by improving the selection of patients in whom its benefit will likely outweigh the risk, and by identifying those who may benefit from careful management.

A number of prognostic scores identified patients with abnormal platelet count (PIC) to be at increased risk for major bleeding during the course of anticoagulant therapy. Accordingly, current guidelines on antithrombotic therapy suggest caution when using long-term anticoagulant therapy in patients with abnormal PIC at baseline.^{1–6} Certainly, many patients with abnormal PIC may also have active cancer, and low molecular weight heparin (LMWH) is the first choice of treatment in cancer patients with VTE.^{7,8} In the real-world clinical practice, a substantial proportion of these patients, however, receive in fact long-term therapy with vitamin K antagonists (VKAs).

Vitamin K antagonists interfere with the coagulation cascade through inhibition of different factors, have a low onset of anticoagulant action, a long half-life, multiple food and drug interactions, and a very narrow therapeutic window outside of which the risk of recurrence or bleeding increases exponentially. For all these reasons, the use of VKA is not recommended in patients with a high risk of bleeding in which it is desirable as an alternative treatment. A previous study of Registro Informatizado de Enfermedad TromboEmbólica (RIETE) investigators found a relationship between abnormal PIC and major bleeding in patients with VTE receiving anticoagulant therapy with either LMWH, VKA, or direct oral anticoagulants. This study did not consider the different risk of bleeding associated with any specific treatment. Moreover, the patients were followed up for only 3 months.⁹

In this study, we aimed to analyze the influence of PIC at baseline in patients receiving long-term VKA treatment for

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A full list of the RIETE investigators is given in the appendix.

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acute VTE. The primary end point was to evaluate the correlation between PIC at baseline and major bleeding appearing in patients treated with VKA for long-term therapy of VTE in real-life clinical practice. The secondary end point was to correlate PIC at baseline with the severity, the time course, and the site of major bleeding.

PATIENTS AND METHODS

Population

The RIETE registry is an ongoing, multicenter, international (Spain, Italy, France, Israel, Portugal, Germany, Switzerland, Czech Republic, Macedonia, United States, Brazil, and Ecuador), observational registry of consecutive patients with symptomatic, objectively confirmed, acute VTE. It started in Spain in 2001, and 6 years later the database was translated into English with the aim to expand the registry to other countries, ultimately allowing physicians worldwide to use the database to select the most appropriate therapy for their patients. Data from this registry have been used to evaluate outcomes after acute VTE, such as the frequency of recurrent VTE, bleeding and mortality, and risk factors for these outcomes. As previously described,¹⁰ at each participating center, a registry coordinator controlled the quality, the internal validity, and the coherence of the data collection. Coordinators or their staff members recorded the data from each patient on a computer-based case report form. The database of each analysis was controlled, and the information was transferred online via a secure Web site to the study coordinating center responsible for data management. Data quality was also monitored by members of contract research organizations who compared the data on medical records with the data transferred online during period visits to participating hospitals.

Inclusion Criteria

Consecutive patients with symptomatic, acute deep vein thrombosis (DVT), or pulmonary embolism (PE), confirmed by objective tests (compression ultrasonography or contrast venography for DVT; helical computed tomography scan or ventilation-perfusion lung scintigraphy for PE), were enrolled in RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients (or their relatives) provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements. This analysis was approved by the ethics committee of the Hospital Universitari Germans Trias i Pujol (Badalona, Spain) and by the institutional review board of NorthShore University Health System (Evanston, IL).

Physicians participating in the RIETE registry ensured that eligible patients were consecutively enrolled. Data were recorded on to a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure Web site. The study coordinating center assigned patients with a unique identification number to maintain patient confidentiality and was responsible for all data management. Data quality was regularly monitored electronically, including checks to detect inconsistencies or errors, which were resolved by contacting the local coordinators. Data quality was also monitored by periodic visits to participating hospitals by contract research organizations that compared medical records with the submitted data.

Study Design

For this study, only patients receiving VKA for long-term therapy of VTE were considered. Platelet count at baseline was

obtained using a Coulter counter method. Patients were categorized as having very low ($<100,000/\mu\text{L}$), low ($100,000\text{--}150,000/\mu\text{L}$), normal ($150,000\text{--}300,000/\mu\text{L}$), high ($300,000\text{--}450,000/\mu\text{L}$), or very high ($>450,000/\mu\text{L}$) PIC. We choose a cutoff value of $100,000/\mu\text{L}$ to identify patients with very low PIC because Nieto et al showed in 2010 this value to be an independent risk factor for fatal bleeding,⁵ and the upper value of $450,000/\mu\text{L}$ from the definition of thrombocytosis.¹¹ Intermediate groups, with low and high PIC, were individuated between the limits of normal range ($150,000\text{--}300,000/\mu\text{L}$) and values of very low and very high PIC values ($100,000\text{--}150,000$ and $300,000\text{--}450,000/\mu\text{L}$, respectively). Patients with normal PIC were used as reference, and their outcome was compared with that in the other 4 subgroups. The outcomes for this study were the rate of major bleeding and fatal bleeding during follow-up. The time course of bleeding was reported considering 3 periods of treatment: 1–30 days, 31–90 days, and over 90 days. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode, in the absence of an alternative cause of death. Major bleeding was defined as an overt bleed that required a transfusion of 2 or more units of blood, was retroperitoneal, spinal or intracranial, or was fatal.

Baseline Variables

The following parameters were recorded when the qualifying episode of VTE was diagnosed: patient's sex, age, and body weight and height; presence of coexisting conditions such as chronic heart or lung disease; concomitant therapies; recent (<30 days earlier) major bleeding; presence of risk factors for VTE, including recent immobility, surgery, active cancer [defined as newly diagnosed cancer or cancer that is being treated (ie, surgery, chemotherapy, radiotherapy, support therapy, or combined treatments)], hormonal therapy, pregnancy, puerperium, prior VTE and recent travel; and laboratory data at baseline, including whole blood counts and serum creatinine levels.

Treatment and Follow-Up

Patients were managed according to the clinical practice of each participating hospital (ie, there was no standardization of treatment). The type, dose, and duration of anticoagulant therapy were recorded. Patients were followed up for at least 3 months in the outpatient clinic. During each visit, any signs or symptoms suggesting VTE recurrences or bleeding complications were noted. Most outcomes were classified as reported by the clinical centers. If the staff at the coordinating center, however, were uncertain how to classify a reported outcome, a central adjudicating committee reviewed that event.

Statistical Analysis

The significance of a number of clinical variables on the rate of major bleeding and fatal bleeding in the course of follow-up was tested by a χ^2 test for categorical variables, and a P value <0.05 was considered statistically significant. Incidence rates were calculated as cumulative incidence (events/100 patient-years) and compared using the rate ratio.

RESULTS

As of January 2015, 55,369 patients had been enrolled in RIETE: 27,085 presenting with PE (with or without concomitant DVT) and 28,284 with DVT alone. In all, 37,000 patients (67%) received long-term therapy with VKA. Of these, 611

patients (1.6%) had very low PIC, 4006 (10.8%) had low PIC, 25,598 (69%) had normal PIC, 5801 (15.6%) had high PIC, and 984 (2.6%) had very high PIC. Patients with very low or low PIC were more likely to be men, significantly older, and to have cancer or renal insufficiency than those with normal PIC (Table 1). Patients with high or very high PIC were more likely to be women and significantly younger, to have recent major bleeding, recent immobility or surgery, and cancer than those with normal count.

Most patients in all subgroups were initially treated with LMWH, with no differences in mean daily doses between subgroups, except in patients with very low count, who received slightly lower LMWH doses and more likely underwent vena cava filter insertion than those in the other subgroups (Table 2). During the course of VKA therapy (mean, 192 days), there were no differences in the duration or intensity of treatment between subgroups. There were no differences either in the rate of VTE recurrences during the course of therapy, but patients with abnormal PIC at baseline had a higher mortality rate (Table 2). During the course of anticoagulant therapy with VKA, the rate of major bleeding was 3.6% ($P < 0.01$), 2.1%, 1.9%, 2.1%, and 3.7% ($P < 0.001$), respectively (Table 2). The rate of fatal bleeding was 0.98% ($P < 0.01$), 0.17%, 0.29%, 0.34%, and 0.50%, respectively (Fig. 1; Table 2).

Major bleeding occurred during the first month of therapy in 54%, 47%, 38%, 44%, and 43%, respectively. Among patients with normal PIC, 45% of major bleeds occurred after the third month of treatment (Fig. 2; Table 3).

There were no differences according to site of bleeding in each subgroup (Table 3). Fatal bleeds were more common in patients with very low PIC (0.98%), most likely because of the

higher rate of active cancer and advanced cancer among patients with very low PIC (Fig. 3). The rate of fatal bleeding among patients with very high PIC, however, was similar to that in the remaining subgroups. Finally, there were no differences among subgroups in the duration of VKA treatment. An overtherapeutic value of international normalized ratio (INR) (higher than 3) was found at the time of bleeding in patients with very low and in very high PIC (41% and 40%, respectively) (Fig. 4).

DISCUSSION

Our study analyzed the influence of an abnormal PIC at baseline on outcome in VTE patients undergoing long-term VKA therapy. A number of previous studies found that patients with low PIC are at an increased risk for major and fatal bleeding during the course of anticoagulant therapy. Hence, VTE patients with low PIC present a particularly challenging therapeutic dilemma because they are at increased risk for bleeding if anticoagulation is prescribed, and for recurrent VTE in the absence of treatment. In our study, patients categorized as having very low and very high PIC receiving VKA therapy were a not negligible proportion and they had a significant increased risk for major bleeding, describing a U-shaped curve. Mild PIC disorders, even if nonstatistically significant, confirmed the increased rate of bleeding and the U-shaped trend. We, however, found additional differences among subgroups in their severity, but not in time course or site of bleeding. At variance with previously reported findings,⁹ the rate of fatal bleeding was significantly higher in patients with very low PIC, but not in the very high PIC subgroup. Moreover, we found no differences in the site of bleeding, even

TABLE 1. Clinical Characteristics of the Patients, According to Platelet Count at Baseline

	<100,000	100,000–150,000	150,000–300,000	300,000–450,000	>450,000
Patients, N	611	4006	25,598	5801	984
Clinical Characteristics					
Age (years)	67 ± 16 [‡]	69 ± 15 [‡]	65 ± 18	62 ± 19 [‡]	62 ± 19 [‡]
Sex (male)	361 (59%) [‡]	2523 (63%) [‡]	12,861 (50%)	2284 (39%) [‡]	413 (42%) [‡]
Body weight (kg)	75 ± 16 [†]	77 ± 15 [*]	77 ± 16	74 ± 16 [‡]	72 ± 15 [‡]
Initial VTE presentation					
Pulmonary embolism	307 (50%)	2154 (54%)	13,507 (53%)	3063 (53%)	550 (56%)
Risk Factors for VTE					
Cancer	136 (22%) [‡]	552 (14%) [‡]	2850 (11%)	766 (13%) [‡]	160 (16%) [‡]
Active chemotherapy	61 (10%) [‡]	195 (4.9%) [‡]	763 (3.0%)	206 (3.6%)	46 (4.7%)
Metastatic cancer	48 (7.9%) [‡]	137 (3.4%)	640 (2.5%)	189 (3.3%)	41 (4.2%)
Surgery	37 (6.1%)	189 (4.7%) [‡]	1931 (7.5%)	868 (15%) [‡]	249 (25%) [‡]
Immobility ≥4 days	101 (17%)	606 (15%) [‡]	4568 (18%)	1236 (21%) [‡]	212 (22%) [‡]
Estrogen therapy	17 (2.8%) [‡]	91 (2.3%) [‡]	1396 (5.4%)	455 (7.8%) [‡]	50 (5.1%)
Pregnancy or puerperium	2 (0.3%)	9 (0.2%) [†]	148 (0.58%)	99 (1.7%) [‡]	30 (3.0%) [‡]
Long-term travel	10 (1.6%)	89 (2.2%) [*]	727 (2.8%)	129 (2.2%) [†]	8 (0.81%) [‡]
None of the above	312 (51%) [†]	2499 (62%) [‡]	14,445 (56%)	2450 (42%) [‡]	313 (32%) [‡]
Underlying Conditions					
Chronic liver disease	20 (3.3%) [‡]	38 (0.95%) [‡]	107 (0.42%)	29 (0.50%)	9 (0.91%) [*]
Chronic heart failure	38 (6.2%)	267 (6.7%)	1725 (6.7%)	384 (6.6%)	74 (7.5%)
Chronic lung disease	74 (12%)	532 (13%) [†]	2978 (12%)	640 (11%)	109 (11%)
Recent major bleeding	17 (2.8%) [‡]	35 (0.87%)	219 (0.86%)	113 (1.9%) [‡]	49 (5.0%) [‡]
CrCl levels <30 mL/min	49 (8.0%) [‡]	272 (6.8%) [‡]	1152 (4.5%)	266 (4.6%)	55 (5.6%)
Anemia	260 (43%) [‡]	923 (23%)	5727 (22%)	2332 (40%) [‡]	603 (61%) [‡]

Comparisons between patients with abnormal platelet count versus those with normal counts: ^{*} $P < 0.05$; [†] $P < 0.01$; [‡] $P < 0.001$. CrCl = creatinine clearance levels, VTE = venous thromboembolism.

TABLE 2. Treatment and Clinical Outcome (Expressed as Number of Events/100 Patient-Years), According to Platelet Count at Baseline

	<100,000	100,000–150,000	150,000–300,000	300,000–450,000	>450,000
Patients, N	611	4006	25,598	5801	984
Initial Therapy					
Unfractionated heparin	61 (10%)	364 (9.1%) [†]	1996 (7.8%)	508 (8.8%)*	89 (9.0%)
LMWH	510 (83%) [‡]	3528 (88%)*	22,858 (89%)	5105 (88%) [†]	873 (89%)
LMWH doses (IU/kg/d)	177 ± 38*	180 ± 37	181 ± 37	181 ± 38	182 ± 39
DOACs	1 (0.16%)	0	10 (0.04%)	3 (0.05%)	0
Fondaparinux	14 (2.3%)	58 (1.4%)	459 (1.8%)	111 (1.9%)	12 (1.2%)
Thrombolytics	5 (0.82%)	34 (0.85%)*	139 (0.54%)	25 (0.43%)	2 (0.20%)
Vena cava filter	24 (3.9%) [‡]	53 (1.3%)	358 (1.4%)	89 (1.5%)	26 (2.6%) [†]
VKAs Therapy					
Duration (mean days ± SD)	275 ± 305	304 ± 363	301 ± 351	281 ± 322 [‡]	283 ± 319
Duration (median days)	189	199	195	190	189
% of time INR levels <2.0	30%	27%	28%	30% [†]	32% [†]
% of time INR levels 2.0–3.0	48%	52%	51%	50%	47%*
% of time INR levels >3.0	22%	21%	21%	20%	21%
Events During Therapy					
PE recurrences	1.52 (0.66–3.01) 7	0.84 (0.57–1.20) 28	1.11 (0.97–1.26) 234	1.20 (0.91–1.56) 54	1.19 (0.58–2.18) 9
DVT recurrences	2.85 (1.58–4.75)* 13	1.90 (1.47–2.41) 63	1.45 (1.30–1.62) 306	1.71 (1.35–2.12) 76	2.01 (1.17–3.24) 15
VTE recurrences	4.20 (2.60–6.43)*	2.76 (2.24–3.38)	2.57 (2.36–2.80)	2.91 (2.44–3.45)	3.27 (2.15–4.79)
Major bleeding	4.77 (3.06–7.10) [†] 22 (3.6%)	2.65 (2.14–3.25) 88 (2.1%)	2.41 (2.21–2.62) 509 (1.9%)	2.79 (2.33–3.32) 125 (2.1%)	4.93 (3.52–6.72) [‡] 37 (3.7%)
All-cause death	12.3 (9.38–16) [‡] 57	4.93 (4.22–5.73) [‡] 166	3.60 (3.36–3.87) 768	5.25 (4.61–5.95) [‡] 237	5.32 (3.86–7.14)* 41
Fatal PE recurrences	0.22 (0.01–1.06) 1	0.15 (0.05–0.33) 5	0.16 (0.11–0.22) 34	0.18 (0.08–0.34) 8	–
Fatal bleeding	1.51 (0.66–2.98) [†] 6 (0.98%)	0.18 (0.07–0.37) 7 (0.17%)	0.36 (0.28–0.44) 76 (0.29%)	0.44 (0.28–0.67) 20 (0.34%)	0.65 (0.24–1.44) 5 (0.5%)

Comparisons between patients with abnormal platelet count versus those with normal counts: * $P < 0.05$; [†] $P < 0.01$; [‡] $P < 0.001$.

DOACs = direct oral anticoagulants, DVT = deep vein thrombosis, INR = international normalized ratio, IU = international units, LMWH = low molecular weight heparin, PE = pulmonary embolism, SD = standard deviation, VKAs = vitamin K antagonists, VTE = venous thromboembolism.

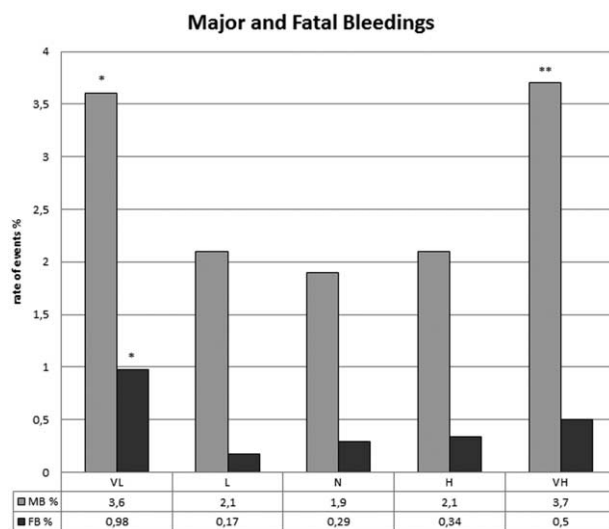


FIGURE 1. Rate of major bleeding and fatal bleeding according to platelet count subpopulations: H = high, L = low, N = normal, VH = very high, VL = very low. * $P < 0.01$; ** $P < 0.001$.

though in other studies intracranial hemorrhage was the major cause of death associated with VKA treatment.¹²

In patients with very low PIC, we found a higher rate of active and advanced cancer, and most studies reported a higher incidence of hemorrhagic complications in patients with malignancy during the course of oral anticoagulant therapy.¹³ These findings could explain the higher rate of fatal bleeds in this subgroup. The first period of anticoagulation is associated with a higher rate of bleeding, probably because of the presence of occult lesions unmasked at the beginning of anticoagulant therapy, and to a less adequate dose adjustment in that period.¹³ In our cohort, the timing of bleeding did not differ significantly among subgroups, but we observed that in patients with abnormal PIC, over 40% of bleeds occurred within the first month after VKA therapy was started, and in patients with very low PIC the rate was 54%. Finally, there were no differences in the duration of VKA treatment or INR values at the time of hemorrhage. Overtherapeutic INR levels (higher than 3.0) were most often represented, both in very low and very high PIC subgroups, as previously reported.^{14,15}

Several studies have analyzed the relationship between PIC and outcome, but they assumed this relationship to be linear and divided the continuous PIC value arbitrarily at specific cut

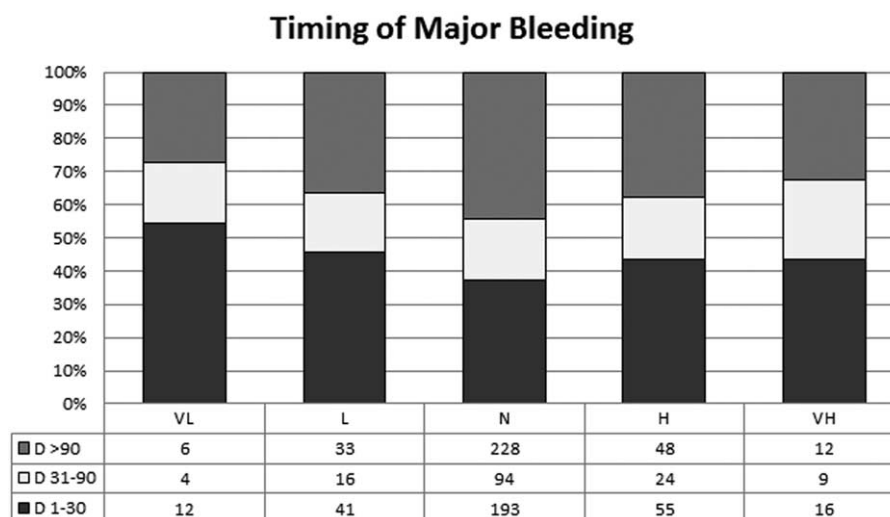


FIGURE 2. Rate of bleeding according to timing and platelet count subpopulations. H = high, L = low, N = normal, VH = very high, VL = very low. * $P < 0.01$; ** $P < 0.001$.

TABLE 3. Major Bleeding During the Course of Anticoagulation With Vitamin K Antagonist Drugs, According to Platelet Count at Baseline

	<100,000	100,000–150,000	150,000–300,000	300,000–450,000	>450,000
Major bleeding, N	22	88	509	125	37
Time Course of Bleeding,					
First 30 days	12 (54%)	41 (47%)	193 (38%)	55 (44%)	16 (43%)
From day 31 to day 90	4 (18%)	16 (18%)	94 (18%)	24 (19%)	9 (24%)
From day 91 on	6 (27%)	33 (37%)	228 (45%)	48 (38%)	12 (32%)
INR Levels at Bleeding					
<2.0	3 (14%)	29 (33%)	150 (29%)	35 (28%)	6 (16%)
2.0–3.0	7 (32%)	28 (32%)	115 (23%)	44 (35%) [†]	8 (22%)
>3.0	9 (41%)	21 (24%)	160 (31%)	35 (28%)	15 (40%)
Not available	3 (14%)	10 (11%)	84 (16%)	11 (8.8%)*	8 (22%)
Sites of Major Bleeding					
Gastrointestinal	8 (36%)	32 (36%)	170 (33%)	45 (36%)	12 (32%)
Intracranial	6 (27%)	16 (18%)	121 (24%)	23 (18%)	5 (13%)
Hematoma	2 (9.1%)	19 (22%)	103 (20%)	24 (19%)	8 (22%)
Retroperitoneal	1 (4.5%)	6 (6.8%)	37 (7.3%)	10 (8.0%)	3 (8.1%)
Urinary	1 (4.5%)	8 (9.1%)	29 (5.7%)	9 (7.2%)	0
Menorrhagia	0	0	14 (2.7%)	5 (4.0%)	4 (11%)*
Hemoptysis	2 (9.1%)*	0	7 (1.4%)	2 (1.6%)	0
Epistaxis	1 (4.5%)	0	8 (1.6%)	1 (0.80%)	0
Hemothorax	0	1 (1.1%)	5 (0.98%)	1 (0.80%)	1 (2.7%)
Hemopericardium	0	1 (1.1%)	2 (0.39%)	3 (2.4%)	0
Other	1 (4.5%)	5 (5.7%)	21 (4.1%)	5 (4.0%)	4 (11%)
30-Day Outcome					
Recurrent PE	0	3 (3.4%)	6 (1.2%)	0	0
Recurrent DVT	0	2 (2.3%)	14 (2.7%)	1 (0.80%)	0
Major rebleeding	1 (4.5%)	5 (5.7%)	16 (3.1%)	2 (1.6%)	1 (2.7%)
Overall death	6 (27%)	12 (14%)	102 (20%)	26 (21%)	6 (16%)
Fatal PE	0	0	2 (0.39%)	0	0
Fatal bleeding	6 (27%)	7 (7.9%)	76 (15%)	20 (16%)	5 (13%)

Comparisons between patients with abnormal platelet count versus those with normal counts: * $P < 0.05$; [†] $P < 0.01$; [‡] $P < 0.001$.

DVT = deep vein thrombosis, INR = international normalized ratio, PE = pulmonary embolism.

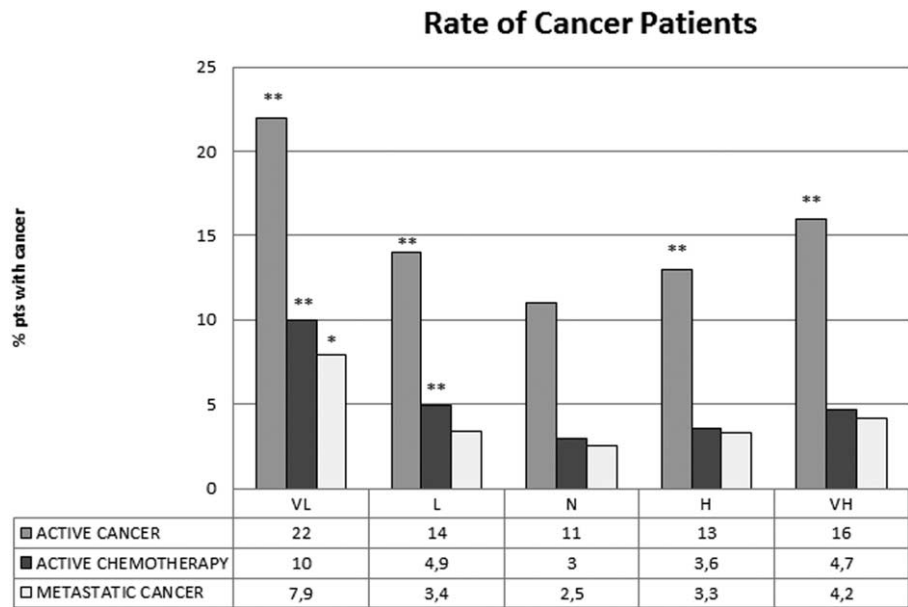


FIGURE 3. Rate of active or metastatic cancer and active chemotherapy according to platelet count subpopulations. H = high, L = low, N = normal, VH = very high, VL = very low. **P* < 0.01; ***P* < 0.001.

points.^{16,17} In 2013, RIETE investigators showed that a PIC lower than 100,000/ μ L is an independent predictor for fatal bleeding in patients on anticoagulant therapy for acute VTE, and it represents an item of the RIETE score for fatal bleeding.⁵ Furthermore, a number of studies reported the influence of increased PIC on the rate of symptomatic VTE and outcome in cancer patients,^{19,20} whereas a previous study in patients with essential thrombocytopenia found a U-shaped curve for the correlation between PIC and major bleeding (MB).²¹ Consistent with our results, the previous findings from RIETE investigators reported a statistically significant increased risk of MB in patients with low or high PIC and treated with different anticoagulant drugs for acute VTE,⁹ but our findings do not confirm a statistically significant higher rate of fatal bleeding in very

high PIC subgroup. Furthermore, our study showed that altered PIC at baseline was associated with important comorbidities, such as severe renal impairment, active cancer, recent bleeding complication, and anemia (Table 1). Thus, it is difficult to declare whether an altered PIC at baseline should be considered a risk factor for bleeding complications and mortality, or if these poor outcomes could be influenced by many comorbidities and a greater frailty in a patient presenting acute VTE and abnormal PIC at baseline.

Our study has some limitations. Firstly, the study design does not allow to prove the causality of relationship between MB and altered PIC. Secondly, concerning the platelets count's monitoring, because of a lack in prospective values of PIC after the index event. We have no data about PIC at the time of

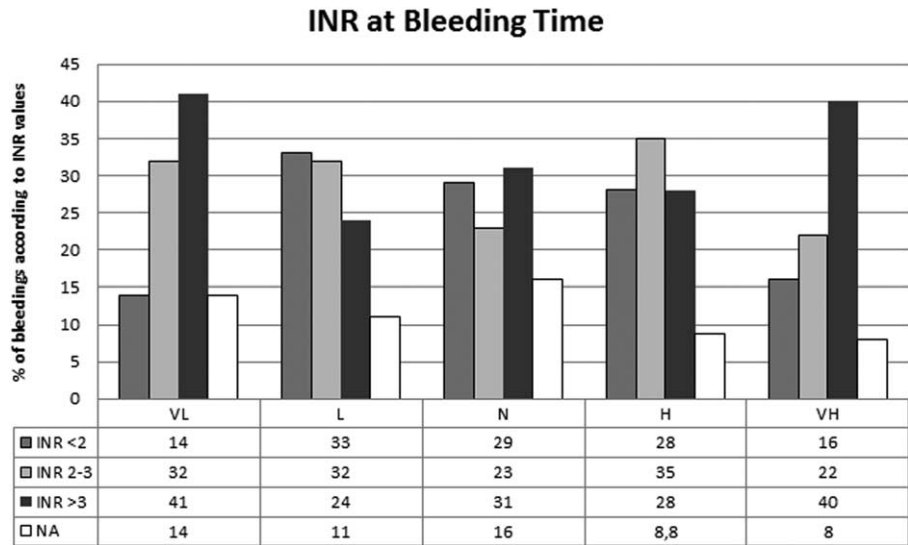


FIGURE 4. International normalized ratio at time of bleeding according to platelet count subpopulations. H = high, L = low, N = normal, NA = not available, VH = very high, VL = very low. **P* < 0.01; ***P* < 0.001.

bleeding. In our database, we have no information about the causes of abnormal PIC, probably because of cancer or chemotherapy in thrombocytopenic patients, and secondary to infection, inflammation, iron deficiency, tissue damage, hemolysis, severe exercise, malignancy, or other causes¹¹ in most patients with thrombocytosis.

Moreover, previous studies showed that the presence of extreme thrombocytosis might be associated with acquired von Willebrand syndrome causing an increased risk of bleeding,^{22,23} but this hypothesis cannot be confirmed for all patients reported in the RIETE registry because they are selected after a recent VTE and not for chronic platelets' disorders. Furthermore, we have no data on the presence of liver cirrhosis, which could cause thrombocytopenia and potentiates the response to VKA therapy by impairing coagulation and making INR control difficult,¹¹ because in our cohort we recorded generically chronic liver diseases. And lastly, on the anticoagulation side, we have only partial data on INR at bleeding time (Fig. 4) that is well known to be less predictive for hemorrhages than the time in therapeutic range used to evaluate the intensity of anticoagulation.²⁴

CONCLUSIONS

In summary, in patients with a recent VTE recorded in the RIETE registry, we found a nonlinear, U-shaped, relationship between PIC at baseline and major bleeding in patients on long-term therapy with VKA for acute VTE. Patients with consistently abnormal PIC had a number of comorbidities, such as metastatic cancer, renal insufficiency, chronic liver disease, anemia, recent major bleeding, and a greater mortality, thus suggesting that a very low or very high PIC at baseline might be a sign of greater frailty. Our findings may be of help to identify patients who require closer surveillance on risk of bleeding, but further dedicated studies are needed to evaluate the causality of these relationships.

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ADDENDUM

M. Giorgi-Pierfranceschi, P. Di Micco, and M. Monreal contributed to concept and design of the study, analysis and interpretation of data, and writing the contents. C. Cattabiani and A. Guida contributed to revising the intellectual content; all authors contributed to patients' enrolment and approved the final version of this article.

APPENDIX

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