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REPORTS OF ORIGINAL INVESTIGATIONS

Thrombocytopenia in the critically ill: prevalence, incidence, risk factors, and clinical outcomes

La thrombocytopénie chez les personnes gravement malades: prévalence, incidence, facteurs de risque et pronostics cliniques

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Abstract

Purpose *The aim of this cohort study was to describe the prevalence, incidence, and risk factors for thrombocytopenia in the intensive care unit (ICU) and to evaluate the impact of thrombocytopenia on mortality with further comparisons amongst major diagnostic categories.*

Methods *Patients admitted to the ICU from 1997-2011 for cardiac, medical, surgical, and trauma conditions were included. The presence of a platelet count* $< 100 \times 10^9 \cdot L^{-1}$ *on admission day or its appearance during ICU stay were considered as prevalent and incident thrombocytopenia, respectively. Risk factors for thrombocytopenia and the influence of thrombocytopenia on mortality were also analyzed.*

Results *This study included 20,696 patients. Prevalent and incident thrombocytopenia occurred in 13.3% and 7.8% of patients, respectively, with associated mortality rates of 14.3% and 24.7%, respectively, compared with 10.2% in the group with normal platelet count ($P < 0.001$). After adjustments, thrombocytopenia remained associated with an increased risk of mortality (odds ratio 1.25; 95% confidence interval 1.20 to 1.31; $P < 0.001$). The greatest impact of thrombocytopenia on mortality was observed in the cancer, respiratory, digestive, genitourinary, and infectious diagnostic categories. Independent risk factors included age, female sex, admission platelet counts and hemoglobin, mechanical ventilation, days of hospitalization prior to ICU admission, liver cirrhosis, hypersplenism, coronary bypass grafting, intra-aortic balloon pump placement, acute hepatitis, septic shock, and pulmonary embolism or deep vein thrombosis.*

Conclusions *Thrombocytopenia in the ICU is associated with an independent risk of mortality that varies greatly depending on diagnostic admission category.*

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Résumé

Objectif *L'objectif de cette étude de cohorte était de décrire la prévalence, l'incidence et les facteurs de risque de thrombocytopénie à l'unité des soins intensifs (USI) et d'évaluer son impact sur la mortalité en la comparant à d'autres catégories diagnostiques majeures.*

Méthode *Les patients admis à l'USI entre 1997 et 2011 pour un problème cardiaque, médical, chirurgical ou traumatique ont été inclus dans l'étude. La prévalence de thrombocytopénie était basée sur la présence d'une numération plaquettaire* $< 100 \times 10^9 \cdot L^{-1}$ *le jour de l'admission et son incidence obtenue à partir de la fréquence de son apparition pendant le séjour à l'USI. Les facteurs de risque de thrombocytopénie et l'influence de thrombocytopénie sur la mortalité ont également été analysés.*

Résultats *Cette étude a inclus 20 696 patients. La prévalence et l'incidence de thrombocytopénie étaient de 13,3 % et 7,8 %, respectivement, avec des taux de mortalité associée de 14,3 % et 24,7 %, respectivement, par rapport à 10,2 % dans le groupe présentant une numération plaquettaire normale (*$P < 0{,}001$*). Après ajustements, la thrombocytopénie est restée associée à un risque accru de mortalité (rapport de cotes 1,25; intervalle de confiance 95 % 1,20 à 1,31;* $P < 0{,}001$*). L'impact le plus important de la thrombocytopénie sur la mortalité a été observé dans les catégories diagnostiques suivantes: oncologique, respiratoire, digestive, génito-urinaire et infectieuse. Les facteurs de risque indépendants comprenaient l'âge, le sexe féminin, les numérations plaquettaires et d'hémoglobineà l'admission, la ventilation mécanique, les jours d'hospitalisation avant l'admission à l'USI, la cirrhose du foie, l'hypersplénisme, le pontage aorto-coronarien, le placement d'un ballonnet intra-aortique, l'hépatite aiguë, le choc septique, et l'embolie pulmonaire ou la thrombose veineuse profonde.*

Conclusion *La thrombocytopénie à l'USI est associée à un risque indépendant de mortalité qui varie grandement selon la catégorie diagnostique à l'admission.*

In the critically ill, thrombocytopenia is the most common coagulation abnormality.[1] Depending on its definition (platelet count $< 100 \times 10^9 \cdot L^{-1}$ or $< 150 \times 10^9 \cdot L^{-1}$) and the category of patients in which it was studied, the prevalence and incidence of thrombocytopenia varied from 8.3-76.6% and from 13-44%, respectively.[2] Intensive care unit (ICU)-acquired thrombocytopenia has been associated with an increased risk of bleeding, blood product transfusion, progression towards multi-organ failure, and longer length of stay[3-6]; however, ICU-thrombocytopenia has been inconsistently identified as an independent risk factor for mortality.[5,7-10] Studies published to date have included selected patient populations, have been underpowered, and have evaluated and identified a limited number of risk factors.[2-4,9,11-15] In addition, these studies have failed to evaluate the relative importance of thrombocytopenia among different diagnostic categories.[3,4,9,11-15] The relation between thrombocytopenia and bleeding has also been reported inconsistently.[2]

By using a very large and heterogeneous cohort of cardiac, medical, and surgical critically ill patients, this study aimed to evaluate the prevalence, incidence, and risk factors for thrombocytopenia and to evaluate its impact on bleeding, length of stay, and mortality in the critically ill, with further comparisons amongst major diagnostic categories.

Methods

The Research Ethics Committee of the Centre Hospitalier Universitaire de Sherbrooke (CHUS) approved the study (12/2008) and waived the need for informed consent. This was a retrospective study conducted using data from the Centre informatisé de recherche évaluative en services et soins de santé (CIRESSS). The CHUS implemented a patient-oriented hospital information system (ARIANE; Per-Sé technologies, Georgia) in 1990. This single operational database includes all transactions of admission, diagnostics, therapeutics, and interventions.[16] The CIRESSS research-purpose data warehouse of the CHUS is linked to the ARIANE system and updated every 24 hr. The database also incorporates MEDECHO data (Système de maintenance et d'exploitation des données pour l'étude de la clientèle hospitalière) required by the Quebec Ministry of Health. The data collected include demographics, detailed information on all primary and secondary diagnoses using International Classification of Diseases ninth revision (ICD-9) codes before 2006 and tenth revision ICD-10 codes after 2006, procedures using Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures before 2006 and the Canadian Classification of Health Interventions after 2006, and biochemical and clinical data.[16] This database includes data on all admissions at the main site (Fleurimont) since 1997. Data from a second (Hotel-Dieu) site have been collected since 2001. The CIRESSS was used in previously published studies.[17-20] Although we did not formally validate data included in the database, diagnostic and procedures codes included in CIRESSS are those used for the MEDECHO database. The MEDECHO database was recently evaluated for the 14 comorbidities included in the Charlson comorbidity index and showed reliable coding.[21]

Study population

The study was conducted at the Centre Hospitalier Universitaire de Sherbrooke (CHUS), a tertiary care teaching hospital on two sites in Sherbrooke, Quebec, Canada. There are two ICU units at a first site, a mixed medical/coronary unit and a surgical/trauma unit (16- and 14-bed capacity, respectively). There is also a general ICU with medical, coronary, and surgical patients at a second site (14-bed capacity). The patient population was composed of all patients aged 18 yr and older admitted for more than 48 hr. The hospital database enabled the inclusion of patients admitted to the first site from 1997-2011 and the second site from 2001-2011. We further selected patients who had at least one platelet count measured within the first 24 hr of admission. For patients with multiple ICU admissions during the study period, only the most recent admission was retained in order to capture mortality.

Data collection

We extracted all platelet counts and defined thrombocytopenia as at least one platelet count $< 100 \times 10^9 \cdot L^{-1}$ during the ICU stay. We further defined moderate and severe thrombocytopenia as at least one platelet count of $50\text{-}100 \times 10^9 \cdot L^{-1}$ or $< 50 \times 10^9 \cdot L^{-1}$, respectively. Thrombocytopenia was considered present on admission if it was already present or occurred during the first day of ICU admission, and it was then labelled "prevalent thrombocytopenia". Thrombocytopenia acquired in the ICU was defined as thrombocytopenia occurring in the days following ICU-admission and was considered "incident thrombocytopenia". We identified factors associated with thrombocytopenia to be evaluated after a literature review of published studies[3,9,11,13-15,22,23] and overviews (Appendix 1).[24,25]

Admission diagnoses were classified into 14 categories based on ICD-9 and ICD-10 codes (Table E1; available as electronic supplementary material). The predicted outcome of patients at admission was assessed with the Charlson comorbidity index,[26] which was calculated using ICD-9 (1997-2006) and ICD-10 (2006-2011) codes at admission as previously described.[27-29] The Charlson score has been shown to correlate with APACHE II scores and mortality in critically ill patients and is a reasonable alternative when acute illness scores are not systematically calculated.[30,31]

The presence of comorbidities and illnesses associated with thrombocytopenia were identified using ICD-9 and ICD-10 codes (Table E2; available as electronic supplementary material). Severe bleeding was defined as the presence of selected bleeding conditions during the index hospitalization (Table E3; available as electronic supplementary material).[32] In the case of heparin-induced thrombocytopenia (HIT), it was defined as a positive PF4/heparin ELISA test.

We also used the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures before 2006 and the Canadian Classification of Health Interventions after 2006 to consider the following interventions associated with thrombocytopenia if they were performed or started prior to the onset of thrombocytopenia: hemodialysis, extracorporeal circulation, coronary bypass grafting, intra-aortic balloon pump placement, splenectomy, and blood transfusion (Table E2; available as electronic supplementary material). Blood transfusion was further defined as the patient having received at least one unit of packed red blood cells during the ICU stay. In patients without thrombocytopenia, interventions were considered if they occurred during the ICU stay.

Statistical analysis

We expressed continuous data as means (standard deviation) or as medians [25th and 75th percentiles] for continuous data according to distribution, and we expressed categorical data as percentages. Lengths of stay in the ICU were compared with the log-rank test. We used the Chi square test to compare major bleeding and mortality between patients with prevalent or incident thrombocytopenia and those without.

To select variables to be included in a multivariable model, we first used univariable logistic regression to analyze risk factors for thrombocytopenia in patients who developed *incident* thrombocytopenia while in the ICU.

The following risk factors were evaluated: 1) patient demographics and admission characteristics (age, sex, admission unit, Charlson comorbidity score, days of hospitalization prior to ICU admission, and admission platelet, hemoglobin, and leukocyte counts), 2) pre-existing comorbidities (alcoholism, liver cirrhosis, hypersplenism, rheumatoid disease, chronic renal failure, and hematologic and non-hematologic cancer), 3) acquired risk factors (acute hepatitis, deep vein thrombosis and pulmonary embolism, diagnosis of lupus, gastrointestinal bleeding, and sepsis during the ICU stay), and 4) procedures associated with thrombocytopenia (coronary artery bypass grafting, extracorporeal circulation, hemodialysis, intra-aortic balloon pump, mechanical ventilation, blood transfusions, splenectomy).[2] In order to evaluate risk factors for ICU-acquired thrombocytopenia in patients who were not suffering from diseases highly associated with thrombocytopenia, we evaluated risk factors in a model excluding patients suffering from the following diseases highly associated with thrombocytopenia: disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, microangiopathies, heparin-induced thrombocytopenia,

aplastic anemia and other bone marrow failures, and secondary thrombocytopenia (includes post-transfusion, dilutional, drug-induced, extracorporeal circulation-induced, and massive blood transfusion and platelet alloimmunization-induced thrombocytopenia).[33] Multivariable logistic regression was used for this analysis. Since univariable analyses were used to screen variables rather than to test a specific hypothesis, all factors with a P value < 0.2 in the univariable analysis were included in the multivariable logistic regression model and reduced using a backward elimination procedure. Variables were selected for removal by using a P value of 0.05 as the significance level. The discriminative power of the logistic equation was estimated with the c statistic, and the adequacy was tested for goodness of fit with the Hosmer-Lemeshow statistic (ten groups). Conformity with the linear gradient of each continuous variable was checked. Following this analysis, admission platelet counts were categorized. Multicollinearity between variables in the models was verified using variance inflation factors, and influential cases were verified.

The independent effect of thrombocytopenia on mortality was evaluated using a multivariable regression model that included the admission diagnostic categories: age, sex, admission unit, length of ICU stay, length of stay before ICU admission, number of ICU stays, mechanical ventilation, sepsis, major bleeding, and Charlson comorbidity scores. Adjusted mortality was also calculated in each diagnostic category. Finally, the independent effect of thrombocytopenia on major bleeding was evaluated in a multivariable analysis adjusting for age, sex, admission unit, Charlson comorbidity scores, mechanical ventilation, extracorporeal circulation, dialysis, sepsis, and moderate to severe liver dysfunction. All reported P values are two-sided. Statistical analysis was performed with PASW® version 18.0 (SPSS Inc., Chicago, Il, USA).

Results

During the study period, 20,775 patients were identified as eligible for inclusion in the study. Seventy-nine patients had incomplete data and were excluded from the study (Figure); thus, 20,696 cardiac, medical, surgical, or trauma critically ill patients were included in the study. Prevalent and incident thrombocytopenia occurred in 13.3% and 7.8% of patients, respectively, and thrombocytopenia was severe in 3.5% and 1.0% of prevalent and incident cases, respectively. In patients with incident thrombocytopenia, thrombocytopenia developed from one to 60 days following ICU admission with a median [25^{th}-75^{th} percentile] of 2.2 [1.3-3.3] days after ICU admission.

Patients with prevalent and incident thrombocytopenia were slightly older and spent more days in hospital prior to ICU admission than those who didn't develop thrombocytopenia (Table 1). Patients with prevalent and incident thrombocytopenia were more likely to have been given mechanical ventilation. The Charlson comorbidity index was slightly lower in patients with prevalent thrombocytopenia and slightly higher in patients with incident thrombocytopenia compared with patients without thrombocytopenia. Compared with patients without thrombocytopenia, those with prevalent thrombocytopenia were more often admitted for valvular, vascular, infectious, and hematological diseases, whereas those with incident thrombocytopenia were more often admitted for vascular, valvular, genitourinary, and infectious diseases.

From the univariable analysis, we identified 24 variables for inclusion in the multivariable analysis (Table 2). Independent risk factors for ICU-acquired thrombocytopenia included age, female sex, admission to the surgical and medical units, admission platelet counts, admission hemoglobin, mechanical ventilation, length of hospital stay prior to ICU admission, liver cirrhosis, hypersplenism, coronary bypass grafting, intra-aortic balloon pump placement, acute hepatitis, septic shock, pulmonary embolism, and deep vein thrombosis (Table 3). The discriminative power of the model was excellent (c-statistic = 0.83), but the Hosmer-Lemeshow test suggested that the model was not well calibrated ($Khi^2 = 47.7$; $P < 0.001$). The lack of fit occurred predominately in the first and last three deciles (Appendix 2).

The incidence of positive heparin platelet factor 4 antibodies associated with thrombocytopenia in the prevalent and incident cases was 0.3% (nine cases) and 1.5% (24 cases), respectively. Thrombocytopenia was classified as secondary thrombocytopenia in 2.9% (80 cases) and 4.2% (68 cases) of prevalent and incident cases, respectively.

Prevalent and incident thrombocytopenia were both associated with prolonged ICU length of stay (median [25^{th}-75^{th} percentile]) (4.0 [2.9-6.8] days and 6.1 [3.8-11.2] days, respectively) compared with patients without thrombocytopenia (3.4 [2.6-5.2] days; $P < 0.001$ for both comparisons). Major bleeding during the index hospitalization was also more frequent in patients with prevalent or incident thrombocytopenia when compared with patients without thrombocytopenia (20.3% *vs* 19.3% *vs* 12.5%, respectively; $P < 0.001$ for both comparisons). The association between thrombocytopenia (prevalent or incident) and major bleeding remained significant after adjustment for age, sex, admission unit, Charlson comorbidity scores, mechanical ventilation, extracorporeal circulation, dialysis, sepsis, and moderate to severe liver dysfunction [adjusted

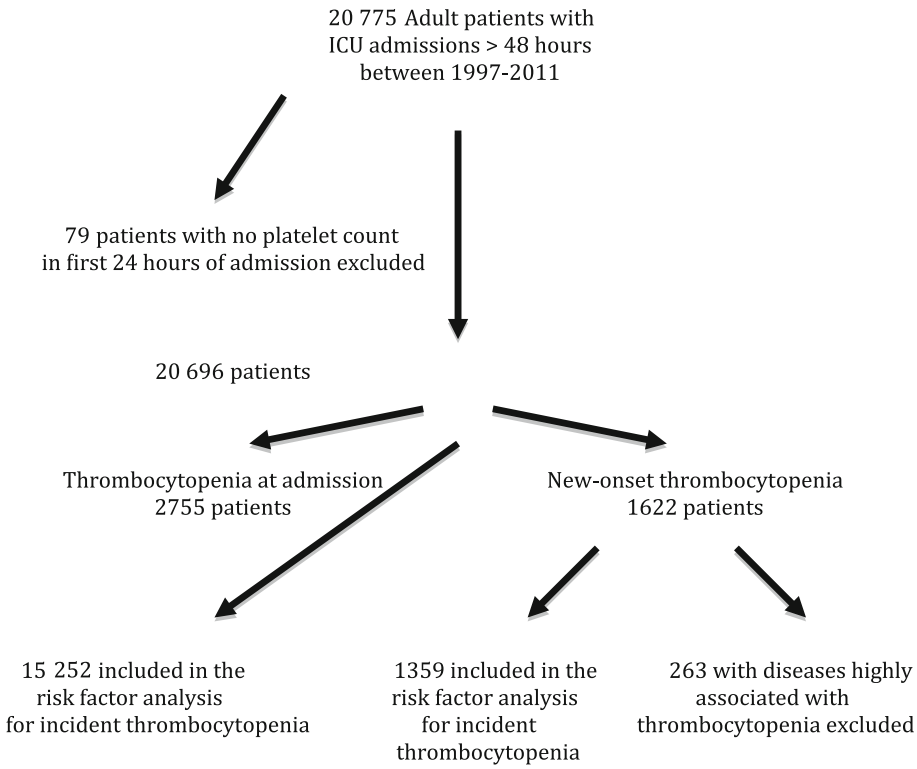

Figure Study flow chart.
ICU = intensive care unit

odds ratio (aOR) 1.32; 95% confidence interval (CI) 1.20 to 1.46; $P < 0.001$].

Prevalent and incident thrombocytopenia were associated with mortality rates of 14.3% and 24.7%, respectively, compared with 10.2% in patients without thrombocytopenia ($P < 0.001$ for both comparisons). Moderate and severe thrombocytopenia were associated with mortality rates of 13.9% and 33.5%, respectively ($P < 0.001$ for both comparisons). Severe thrombocytopenia was associated with mortality rates of 29.7% and 44.5% in patients with prevalent and incident thrombocytopenia, respectively ($P < 0.001$ for both comparisons). After adjusting for admission categories, age, sex, admission unit, length of ICU stay, length of stay before ICU admission, number of ICU stays, sepsis, major bleeding, and Charlson scores, thrombocytopenia remained associated with an increased risk of mortality (aOR 1.25; 95% CI 1.20 to 1.31; $P < 0.001$).

The greatest impact of thrombocytopenia on mortality was observed in the cancer, digestive, genitourinary, respiratory, vascular, infectious, trauma/injury, and circulatory/cardiac diagnoses (Table 4).

Discussion

In this study of thrombocytopenia in critically ill cardiac, medical, surgical, and trauma patients, we found that 13.3% of patients had at least one platelet count $< 100 \times 10^9 \cdot L^{-1}$ on ICU admission day and that an additional 7.8% developed thrombocytopenia later in the ICU stay. Severe thrombocytopenia was relatively rare but more frequent on admission than during the ICU stay. Previous studies have reported different results concerning the epidemiology of thrombocytopenia in the ICU, with a reported *prevalence* of thrombocytopenia as high as 20.0%, 23.4%, and 27.1% using the same threshold of platelet count.[8,13,22] Dissimilar patient populations and greater severity of disease than were found in our study may account for this difference. On the other hand, the *incidence* of thrombocytopenia in previous studies is similar to our findings. One study in a surgical ICU population reported an incidence of 13.0%.[12] Studies using a more inclusive definition of thrombocytopenia (platelets $< 150 \times 10^9 \cdot L^{-1}$) have reported an incidence varying from 14.3-44.1%.[3,5,8] Thrombocytopenia was associated with an increase in length of stay and bleeding events, and the association with major bleeding remained positive after multivariable adjustment. Previous studies in critically ill patients have reported an association between thrombocytopenia and bleeding events but have not adjusted for disease severity.[2] Our study used an inclusive definition of bleeding and could not evaluate the onset of bleeding in relation to thrombocytopenia because of the limits of ICD coding; however, in prevalent cases and in a majority of incident cases, thrombocytopenia occurred early in the ICU stay.

Table 1 Characteristics of the 20,696 study patients

	No thrombocytopenia ($n = 16,319$)	Prevalent ($n = 2,755$)	Incident ($n = 1,622$)
Age, yr (SD)	64.5 (15.3)	65.1 (14.2)	66.4 (13.8)
Male sex	60.8%	62.4%	64.4%
Median days hospitalized before ICU admission [25^{th}-75^{th} percentile]	1.0 [0-2.0]	1.0 [1.0-7.0]	1.0 [0-6.0]
Median number of ICU admissions [25^{th}-75^{th} percentile]	1.0 [0-2.0]	1.0 [1.0-7.0]	1.0 [0-6.0]
Median Charlson score [25^{th}-75^{th} percentile]	2.0 [1.0-4.0]	2.0 [1.0-4.0]	2.0 [1.0-4.0]
Platelet count admission day ($\times 10^9 \cdot L^{-1}$) (SD)	253 (97)	142 (77)	193 (76)
Hemoglobin admission day ($\times 10^6 \cdot L^{-1}$) (SD)	122 (24)	111 (25)	119 (25)
Leukocyte count admission day ($\times 10^6 \cdot L^{-1}$) (SD)	11.5 (6.5)	8.9 (10.2)	11.8 (9.1)
Medical/Coronary ICU	47.9%	26.9%	51.1%
Surgical ICU	28.0%	63.8%	38.0%
Mixed unit	21.9%	9.0%	10.4%
Mechanical ventilation	25.7%	58.3%	56.1%
Admission diagnostics categories			
Cancer	8.8%	7.3%	5.1%
Circulatory/Cardiac	43.1%	31.6%	38.2%
Digestive	7.5%	7.2%	8.7%
Genitourinary	2.1%	1.9%	3.1%
Hematological	0.2%	1.2%	0.4%
Infectious	2.1%	3.5%	4.0%
Musculoskeletal	1.5%	1.0%	1.5%
Neurological	7.2%	2.2%	4.4%
Respiratory	8.9%	3.8%	5.9%
Trauma/Injury	7.8%	6.4%	9.1%
Valvular	2.1%	21.4%	7.4%
Vascular	6.2%	11.1%	10.2%
Other	2.2%	1.2%	1.7%

ICU = intensive care unit; SD = standard deviation

After adjusting for disease severity, admission categories, and comorbidities, thrombocytopenia remained independently associated with an increased risk of in-hospital mortality (OR 1.25; 95% CI 1.20 to 1.31; $P < 0.001$). This finding confirms the independent association reported in other studies.[5,8,23] These studies reported odds ratios greater than ours for hospital or ICU mortality, which varied from 2.20-3.10. This difference may be due to differences in patient populations, as our study also included cardiac ICU patients. It remains unclear whether this effect on mortality is due to disease severity and possible residual confounding from unknown factors or is related to the essential role platelets play in many disease processes.[34] A growing body of evidence suggests that platelets might not only be executors of thrombosis but might also be important actors in the immune response.[34,35]

Critically ill patients are a heterogeneous patient population in which the impact of thrombocytopenia may vary widely depending on the associated diseases. We observed that thrombocytopenia had the greatest impact on mortality after adjustments in patients admitted for cancer, genitourinary, digestive, respiratory, vascular, and infectious diagnoses. In other diagnostic categories, such as neurological and musculoskeletal diseases, the impact of thrombocytopenia on mortality seems less important. Accordingly, thrombocytopenia may be linked to advanced stages of diseases, such as cancer or liver cirrhosis, and to more severe presentations of diseases, such as urinary tract and respiratory infections. Thrombocytopenia may also be associated with an increased risk of complications, such as bleeding or secondary infections, in these identified diagnostic categories more than in others. The increased risk of mortality associated with thrombocytopenia in cancer patients, specifically, may also be due to an association with recent chemotherapy or more advanced cancer. In our study, cancer in patients admitted to the ICU had the greatest impact on mortality associated with thrombocytopenia. These findings are corroborated by a recent study

Table 2 Univariable analysis of risk factors for ICU-acquired thrombocytopenia ($n = 16{,}636$; #events = 1,359)

Variables	OR (95% CI)	*P* value
Demographic and admission characteristics		
Age	1.010 (1.006 to 1.014)	< 0.001
Sex (female)	0.83 (0.74 to 0.93)	0.002
Medical ICU admission	1.05 (0.94 to 1.17)	0.39
Surgical ICU admission	1.74 (1.55 to 1.95)	< 0.001
Mixed ICU	0.38 (0.31 to 0.46)	< 0.001
Charlson comorbidity score	1.03 (1.00 to 1.05)	0.02
Days of hospitalization prior to ICU admission	1.02 (1.01 to 1.02)	< 0.001
Admission platelet counts	0.989 (0.988 to 0.990)	< 0.001
Admission hemoglobin	0.994 (0.992 to 0.996)	< 0.001
Admission leukocyte counts	1.005 (0.997 to 1.012)	0.24
Pre-existing comorbidities		
Alcoholism	1.42 (1.06 to 1.92)	0.02
Liver cirrhosis	2.46 (1.74 to 3.50)	< 0.001
Hypersplenism	8.45 (1.89 to 37.8)	0.005
Rheumatoid disease	0.92 (0.64 to 1.32)	0.64
Chronic renal failure	1.16 (0.92 to 1.47)	0.21
Hematologic cancer	1.60 (0.94 to 2.71)	0.08
Non-hematologic cancer	0.70 (0.53 to 0.94)	0.02
Acquired risk factors		
Acute hepatitis	2.22 (1.37 to 3.60)	0.001
Deep vein thrombosis and pulmonary embolism	1.33 (1.06 to 1.68)	0.02
Diagnosis of lupus	2.51 (1.16 to 5.40)	0.02
Gastrointestinal bleeding	2.77 (1.71 to 4.48)	< 0.001
Sepsis	2.44 (1.96 to 3.04)	< 0.001
Procedures		
Coronary artery bypass grafting	4.02 (3.49 to 4.64)	< 0.001
Extracorporeal circulation	3.75 (3.24 to 4.34)	< 0.001
Hemodialysis	1.32 (1.02 to 1.72)	0.04
Intra-aortic balloon pump	3.75 (3.07 to 4.58)	< 0.001
Mechanical ventilation	2.47 (2.19 to 2.78)	< 0.001
Blood transfusions	4.15 (3.71 to 4.65)	< 0.001
Splenectomy	2.69 (0.41 to 17.61)	0.30

OR = odds ratio;
CI = confidence interval;
ICU = intensive care unit

of metastatic cancer patients admitted to ICU that identified thrombocytopenia (OR 26.2) as an important predictor of mortality.[36] Hence, patients admitted within these diagnostic categories may represent potential subgroups for interventional trials of strategies with the objective of modifying the impact of thrombocytopenia and conditions leading to thrombocytopenia-related mortality.

The purpose of this study was to verify independent risk factors for thrombocytopenia, such as admitting platelet counts, sepsis, and intra-aortic balloon pump, which had been described in previous studies.[2-4,9,13,37] Given the large sample size and important number of candidate factors, new factors were identified in this study which had not been previously described, including history of liver cirrhosis, admission hemoglobin, and new pulmonary embolism or deep vein thrombosis. The hospital admission unit was also an important factor, as admission to the surgical ICU and, to a lesser extent, the medical ICU was associated with an increased risk of thrombocytopenia. Invasive surgery and severity of disease may have accounted for these findings. In order to evaluate risk factors for ICU-acquired thrombocytopenia in patients who were not suffering from diseases highly associated with thrombocytopenia, we chose to exclude patients suffering from disseminated intravascular coagulation, thrombotic microvascular disorders, and myelodysplasia.

Our model showed excellent discriminative power, but calibration was non-optimal. It remains uncertain how much of the lack of fit is due to the model and how much is due to the sensitivity of the Hosmer-Lemeshow test to large

Table 3 Multivariable analysis of risk factors for ICU-acquired thrombocytopenia ($n = 16{,}621$, #events 1,359)

Variables	Adjusted OR (95% CI)	*P* value
Age (per yr)	1.007 (1.002 to 1.012)	0.002
Female sex	1.18 (1.03 to 1.35)	0.02
Admission unit		
Medical ICU admission	1.58 (1.27 to 1.95)	< 0.001
Surgical ICU admission	1.69 (1.35 to 2.12)	0.001
Mixed ICU	1.00	
Days of hospitalization prior to ICU admission	1.012 (1.007 to 1.016)	< 0.001
Mechanical ventilation	1.95 (1.71 to 2.30)	< 0.001
Admitting platelet count		
100-149 $\times 10^9 \cdot L^{-1}$	24.57 (15.94 to 37.88)	< 0.001
150-199 $\times 10^9 \cdot L^{-1}$	6.72 (4.38 to 10.30)	< 0.001
200-249 $\times 10^9 \cdot L^{-1}$	3.26 (2.12 to 5.03)	< 0.001
250-299 $\times 10^9 \cdot L^{-1}$	2.52 (1.61 to 3.93)	< 0.001
300-349 $\times 10^9 \cdot L^{-1}$	1.56 (0.94 to 2.59)	0.09
350-399 $\times 10^9 \cdot L^{-1}$	1.48 (0.82 to 2.67)	0.19
$> 400 \times 10^9 \cdot L^{-1}$	1.00	
Admitting hemoglobin (per $g \cdot L^{-1}$)	1.006 (1.003 to 1.009)	< 0.001
Liver cirrhosis	2.01 (1.34 to 3.05)	0.001
Hypersplenism	6.65 (1.17 to 37.73)	0.03
Blood transfusion	3.06 (2.66 to 3.52)	< 0.001
Intra-aortic balloon pump	2.47 (1.93 to 3.15)	< 0.001
Coronary bypass grafting	2.83 (2.37 to 3.37)	< 0.001
Septic shock	2.60 (2.03 to 3.33)	< 0.001
Acute hepatitis	2.21 (1.27 to 3.85)	< 0.001
Pulmonary embolism and deep vein thrombosis	1.53 (1.19 to 1.98)	0.001

OR = odds ration;
CI = confidence interval;
ICU = intensive care unit

sample sizes.[38] Although heparin-induced thrombocytopenia is frequently suspected in critically ill patients with thrombocytopenia, the incidence of heparin platelet factor 4 antibodies was relatively low in patients with thrombocytopenia in our cohort. This finding could be explained by underdiagnosis, or it could represent an institutional variability in requests for heparin platelet factor 4 antibodies. The use of the PF4/heparin ELISA test, which has a limited specificity to define heparin-induced thrombocytopenia, may also have identified false positive cases. Nevertheless, previous studies of medical surgical critical care patients have reported a similar incidence of heparin-induced thrombocytopenia.[39,40]

Even though this study includes a large sample size and a considerable number of variables were analyzed, it has some limitations. The retrospective design limits the information that can be obtained concerning possible etiologies for the thrombocytopenia. The use of ICD and CCDATC codes to classify diagnostic categories and identify risk factors also has a number of limits. Certain consumptive causes of thrombocytopenia, such as drug-induced thrombocytopenia, were not evaluated. Information bias secondary to misclassification is a concern but would most likely be non-differential. The retrospective design also limited the available data concerning Glasgow coma scales, thus precluding the use of severity of illness scores, such as the APACHE II score and other population-specific scores. In addition, due to the problems associated with automated variable selection procedures, some of the newly identified predictors may be spurious or their effects may be overestimated and would need to be confirmed in other studies.[41]

In conclusion, thrombocytopenia, defined as a platelet count $< 100 \times 10^9 \cdot L^{-1}$ is common both upon admission and during ICU stay in medical, surgical, and trauma ICU patients. Prevalent thrombocytopenia and incident thrombocytopenia are both associated with prolonged ICU length of stay and major bleeding. In addition, thrombocytopenia is associated with an independent risk of mortality. The greatest impact of thrombocytopenia on mortality was observed in the cancer, genitourinary, digestive, vascular, infectious, and respiratory diagnostic categories. Independent predictors of thrombocytopenia included age, female sex, age, admission platelet counts, admission hemoglobin,

Table 4 Comparative hospital mortality in patients with and without thrombocytopenia according to admission diagnostic category

Admission diagnosis (n =20,252, #events 2,405)	Hospital mortality		Crude OR; P value (95%CI)	Adjusted OR; P value (95%CI)
	No thrombocytopenia	Thrombocytopenia		
Hematological (67)	10.7%	15.4%	1.51; $P = 0.58$(0.35 to 6.66)	0.49; $P = 0.53$(0.05 to 4.53)
Circulatory (8,538)	7.1%	12.1%	1.79; $P < 0.001$(1.50 to 2.15)	1.54; $P < 0.001$ (1.23 to 1.91)
Valvular (1,051)	7.6%	8.5%	1.12; $P = 0.63$ (0.70 to 1.82)	1.74; $P = 0.06$ (0.98 to 3.10)
Digestive (1,566)	11.1%	29.7%	3.39; $P < 0.001$ (2.53 to 5.54)	2.52; $P < 0.001$ (1.83 to 3.48)
Genitourinary (449)	11.0%	27.5%	3.08; $P < 0.001$ (1.78 to 5.33)	2.42; $P = 0.006$ (1.29 to 4.54)
Vascular (1,483)	7.5%	15.9%	2.32; $P < 0.001$ (1.65 to 3.27)	2.07; $P < 0.001$ (1.38 to 3.11)
Cancer (1,725)	11.2%	39.7%	5.21; $P < 0.001$ (3.90 to 6.96)	3.71; $P < 0.001$ (2.65 to 5.19)
Central nervous system (1,310)	18.8%	26.7%	1.57; $P = 0.03$ (1.04 to 2.38)	1.25; $P = 0.335$ (0.79 to 1.97)
Musculoskeletal (300)	10.1%	21.2%	2.39; $P = 0.03$ (1.09 to 5.24)	1.08; $P = 0.89$ (0.39-2.96)
Trauma/Injury (1,595)	8.7%	16.4%	2.05; $P < 0.001$ (1.44 to 2.92)	1.65; $P = 0.01$ (1.11 to 2.45)
Respiratory (1,655)	18.3%	35.6%	2.47; $P < 0.001$ (1.80 to 3.39)	2.56; $P < 0.001$ (1.80 to 3.66)
Infectious (513)	15.7%	30.9%	2.40; $P < 0.001$ (1.55 to 3.73)	2.05; $P = 0.004$ (1.25 to 3.37)

OR = odds ratio; CI = confidence interval

mechanical ventilation, length of hospital stay prior to ICU admission, liver cirrhosis, hypersplenism, coronary bypass grafting, intra-aortic balloon pump placement, acute hepatitis, septic shock, pulmonary embolism, and deep vein thrombosis.

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Appendix 1: Search strategy for identification of risk factors

MEDLINE search terms used to identify studies evaluating thrombocytopenia risk factor

1. critical care.mp. or exp Critical Care/
2. intensive care unit.mp. or Intensive Care Units/
3. critical illness.mp. or Critical Illness/
4. 1 or 2 or 3
5. exp Thrombocytopenia/ or thrombocytopenia.mp.
6. blood platelet.mp. or Blood Platelets/
7. thrombocyte.mp
8. 5 or 6 or 7
9. 4 and 8

Bibliographies of relevant citations and reviews were also searched.

Appendix 2: Hosmer-Lemeshow goodness of fit test C-statistic results

Subgroups (n/10)	Thrombocytopenia = NON CASES		Thrombocytopenia = CASES		Total
	Observations	Expected	Observations	Expected	
1	1,648	1,646,295	14	15,705	1,662
2	1,647	1,636,389	15	25,611	1,662
3	1,641	1,627,261	21	34,739	1,662
4	1,637	1,619,181	25	42,819	1,662
5	1,621	1,607,667	41	54,333	1,662
6	1,584	1,584,912	78	77,088	1,662
7	1,559	1,562,493	103	99,507	1,662
8	1,465	1,503,398	197	158,602	1,662
9	1,350	1,402,056	312	259,944	1,662
10	1,110	1,072,349	553	590,651	1,663

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