Medical Research Archives

ESMED
European Society of Medicine

OPEN ACCESS

Published: December 31, 2022

Citation: Bou-ouhrich Y and Charra B, 2022. Thrombocytopenia in Critical Care Unit: Risk Factors, Etiologies, and Management, Medical Research Archives, [online] 10(12). https://doi.org/10.18103/mra.v10i12.3465

DOI
https://doi.org/10.18103/mra.v10i12.3465

ISSN: 2375-1924

RESEARCH ARTICLE

Thrombocytopenia in Critical Care Unit: Risk Factors, Etiologies, and Management

Yassine Bou-ouhrich[1], **Boubaker Charra***

[1]Department of Intensive Care Medicine, Ibn Rochd University Hospital, Faculty of medicine and Pharmacy of Casablanca, Hassan 2 University, Casablanca, Morocco.

*Correspondence
Boubaker Charra
Head of the medical intensive care department, Ibn Rochd university hospital,Hassan 2 university, Casablanca, Morocco.
boubaker.ch68@gmail.com

ABSTRACT

Introduction: Thrombocytopenia is a platelet count below 150,000/mm3. It is a frequent abnormality in critically ill patients.

Methods: We conducted a retrospective study which included 603 patients admitted to the medical intensive care unit in the Ibn Rochd university hospital of Casablanca over a two years period, from January 1, 2018 to December 31, 2019. The aim of the study is to point out the incidence, risk factors, etiologies, therapeutic modalities, as well as the morbidity and mortality related to thrombocytopenia in critical care.

Results: During the study period, and out of these 603 patients, 168 patients had thrombocytopenia, that is an incidence of 27.8%; 38 patients among them were admitted with an already ongoing thrombocytopenia. Sepsis, Acute respiratory distress syndrome, renal failure, hemodialysis, and liver dysfunction were risk factors of thrombocytopenia and predictors of mortality. Thrombocytopenia was a factor of increased mortality, the percentage of death was higher in the thrombocytopenic group compared with the non-thrombocytopenic group with a rate of 42.26%. However, it was not an independent factor of mortality.

Conclusion: Sepsis is the major factor incriminated in the occurrence of thrombocytopenia in critically ill patients. Therapeutic management including platelet transfusion should depend on the etiology of thrombocytopenia along with the associated hemorrhagic risk.

Keywords: Thrombocytopenia, Intensive care, Sepsis, Platelet transfusion, Mortality.

Introduction

Thrombocytopenia is a common hematologic disorder among patients admitted to the intensive care unit (ICU). In adults, the prevalence of thrombocytopenia at the time of ICU admission ranges from 8.3% to 67.6% while thrombocytopenia developing during ICU hospitalization varies from 14% to 44%.[1,2] Variability in these estimates reflects differences in patient populations (e.g. age, severity of illness, diagnoses), ICU characteristics (e.g. medical, surgical, cardiac), and the threshold for defining thrombocytopenia (e.g. platelet count of <150 × 109/L, <100 × 109/L, and sometimes <50 × 109/L).[1,3]

The diagnosis is relatively straightforward owing to the frequent prescription of blood counts in critically ill patients. However, false thrombocytopenia due to in vitro platelet agglutination (especially when the sample is taken on Ethylene Diamine Tetra Acetic acid) should always be ruled out by a blood smear examination. Clinical manifestations of thrombocytopenia are variable, and its occurrence can sometimes constitute a hematological emergency, particularly when there is a hemorrhagic syndrome.

Although thrombocytopenia has several possible origins, risk factors commonly associated with ICU-acquired thrombocytopenia, in multivariate analyses, include severity of illness, organ dysfunction, sepsis, acute respiratory distress syndrome (ARDS), renal failure, vasopressor use, and transfusion.[1,4-6]

Its pejorative prognostic value has been highlighted by several studies since it is associated with increased bleeding and transfusion risks as well as increased ICU length of stay and need for organ support.[1,2,6,7] In the PROTECT trial, a large randomized trial of thromboprophylaxis in patients admitted to medical-surgical ICUs, both moderate and severe thrombocytopenia were associated with increased ICU and hospital mortality.[8]

The purpose of this paper is to pinpoint the incidence of thrombocytopenia in intensive care unit, its risk factors, etiologies, the several therapeutic modalities, as well as its impact on the overall prognosis in critically ill patients.

Patient and Methods

Patient

-Type and duration of study:

This is a retrospective study which included all patients who presented a thrombocytopenia in the medical intensive care unit of the Ibn Rochd University Hospital of Casablanca over a two years period, from January 1, 2018 to December 31, 2019. We checked the records of all hospitalized patients during the study period. Patients were divided into two arms (***Figure S1***): group with thrombocytopenia and a group without thrombocytopenia or control group. The patients in the thrombocytopenia group were also divided into 2 subgroups: group with thrombocytopenia acquired in the intensive care unit and a group admitted with thrombocytopenia.

-Inclusion criteria:

-Age ≥ 18 years.

-All patients with thrombocytopenia defined by a platelet count of less than 150,000/mm3, managed in the intensive care unit after eliminating false thrombocytopenia by a blood smear.

-Exclusion criteria:

-All patients with unworkable medical records.

-Patients with previous platelet disorders, hematological malignancies, and patients undergoing chemotherapy.

Methods

-Pre-analytical phase:

This stage allows the elimination of false thrombocytopenia before starting the data collection in order to improve the quality of the results. The quality of the pre-analytical phase in cellular hematology is conditioned by two types of constants: some are not specific and concern biological examinations in general. These are parameters related to traceability, such as identification of the sample, the collector, the place, and the method of sampling. Others are specific and relate to the quality of the biological sample itself as its suitability for the analyses that are to be carried out. To ensure the reality of thrombocytopenia, any low platelet count should be systematically checked on the slide along with completing with sodium citrate sampling to replace Ethylenediamine tetra-acetic acid (EDTA) which may be responsible for platelet aggregation.

-Sample size

Among the patients admitted to the unit during the study period, all thrombocytopenia cases were included in the study including both those who were admitted with thrombocytopenia and those who developed thrombocytopenia during their hospital stay.

-Data collection:

The following data were collected for each patient recruited: epidemiological data, reason for admission, severity scores: IGS II (simplified gravity index II), SOFA (Sequential organ failure assessment), APACHE II (Acute Physiology And Chronic Health Evaluation II), Clinical data: Skin signs, mucosal hemorrhage, presence of hepatomegaly and/or splenomegaly. Associated factors: septic state; invasive monitoring: urinary catheterization, arterial catheter, central venous catheter, dialysis catheter. Biological workup (cellular blood count, hemostasis, liver workup, renal workup). Date of onset of thrombocytopenia in relation to admission, cause of thrombocytopenia, treatment of thrombocytopenia, factors associated with thrombocytopenia, and evolution of thrombocytopenia.

-Statistical analysis:

The statistical study was carried out using SPSS 25 software. The results are expressed as percentages for qualitative variables and as mean ± standard deviation for quantitative variables. This is a comparative study between thrombocytopenic and non-thrombocytopenic patients. The variable of interest is mortality in thrombocytopenic patients. Multivariate analyses were also performed to explain the mortality according to the different variables (clinical data, paraclinical data, severity scores, and therapeutic modalities). The tests used were: Student's t test for comparison of two means and the Chi-square test for the comparison of two percentages. The comparison is considered significant when the p value is less than 0.05.

Results

Descriptive study

- ***Incidence :***

During the study period, 603 patients were admitted to the medical intensive care unit and included in the study. 168 cases of thrombocytopenia were recorded with an overall incidence of 27.8% in two years (***figure S2***). Among these 168 patients, 38 patients (22.61%) were admitted with thrombocytopenia while 130 patients (77.38%) acquired thrombocytopenia during their ICU stay.

- ***Distribution by age :***

In the thrombocytopenic group, the mean age was 44 ± 13 years with extremes ranging from 18 to 91.

In the control group, the average age was 46 ± 15 years with extremes ranging from 18 to 92 years. (***Figure S3***)

- ***Distribution by sex :***

In the thrombocytopenic group: 91 men (54.16%) were accounted for 77 women (45.83%) with a sex ratio of 1.18. (**Figure S4**)

In the control group: 229 men (52.64%) were accounted for 206 women (47.35%) with a sex ratio of 1.11.

There was a male predominance in both groups.

- ***Diagnosis upon admission :***

The reasons for hospitalization most associated with the occurrence of thrombocytopenia were: infectious diseases especially leptospirosis, digestive hemorrhage, liver cirrhosis, and septic shock.

The admission diagnoses are reported in ***Table 1***:

Table 1: Distribution of patients according to the admission diagnosis in the two study groups.

	Thrombocytopenic group N (%)	**Control group N (%**
Complicated diabetes: •Diabetic ketoacidosis •Hyperosmotic coma	17(10.12%) •16 •1	98 (22.53%) •95 •3
Neurosurgery/neurology: •Stroke •Hemorrhagic stroke •Apyretic consciousness impairment •Febrile consciousness impairment •Status epilepticus •Guillain barre syndrome	38 (22.62%) •6 •5 •10 •7 •8 •2	101 (23.22%) •10 •4 •38 •16 •14 •19

Abdominal pathologies : •Acute pancreatitis •hepatobiliary pathologies •Digestive Hemorrhage	20 (11.91%) •10 •4 •6	16 (3.68%) •8 •5 •3
Respiratory diseases: •Respiratory failure •COPD •Acute severe asthma •Acute pneumonia	28 (16.67%) •14 •4 •6 •4	81 (18.62%) •47 •9 •16 •9
Gastro-enterology: •Cirrhosis •Ulcer •Fulminant hepatitis •Hemorrhagic recto-colitis	8 (4.76%) •5 •1 •1 •1	5 (1.15%) •3 •1 •1 •0
Infectious diseases: •Leptospirosis/ suspicion of leptospirosis •Meningitis •Meningoencephalitis	25 (14.88%) •17 •5 •3	23 (5.29%) •7 •11 •5
Electrolyte disorders: •Hypokalemia •Hyponatremia •Hypercalcemia	8 (4.76%) •7 •1 •--	44 (10.11%) •36 •6 •2
Trauma : •Polytrauma •Traumatic brain injury	6 (3.57%) •2 •4	15 (3.45%) •4 •11
Others: •Neuro-tuberculosis •Myasthenia gravis flare •Severe anemia •Intoxication •Post-operative care •Pulmonary embolism •Septic shock •Cardiogenic shock	18 (10.71%) •1 •1 •2 •1 •3 •2 •6 •2	52 (11.95%) •1 •6 •5 •13 •9 •4 •5 •9
Total	168 (100%)	435 00%)

- ***History of patients :***

Regarding the thrombocytopenia group: Toxic habits came first and were found in 57 patients. In second place, came general pathologies such as diabetes followed by respiratory and cardiac diseases. General pathologies, especially diabetes, were in first place for the control group with 195 patients. The list of patient histories is provided in ***Table S1***.

- ***Severity score upon admission :***

Three scores were used to assess severity: IGS II, APACHE II, and the SOFA score.

IGS II score upon admission: In the thrombocytopenic group, the mean IGS II on admission was 27± 3 with extremes ranging from 14 to 56. In the control group, the mean IGS II was 18±2 with extremes ranging from 9 to 42. The IGS II score on admission was higher in the thrombocytopenic group than in the control group (**Figure S5**).

SOFA and **APACHE II** scores: SOFA and APACHE II severity scores were higher in thrombocytopenic patients compared with control group. The mean of the assessed scores in each group is represented in ***Table S2***.

- ***Physical examination :***

Clinical symptoms presented by patients in each study group are outlined in ***table 2***.

Table 2: Clinical symptoms in each study group.

Clinical signs	Thrombopenic group	Control group	P value
Purpura	13 (7.73%)	3 (0.68%)	P<0.0001
Petechiae	11 (6.54%)	4 (0.91%)	P=0.0002
Ecchymosis	19 (11.3%)	7 (1.60%)	P<0.0001
Epistaxis	11 (6.54%)	5 (1,14%)	P=0.0002
Digestive hemorrhage	17 (10.11%)	6 (1.37%)	P<0.0001
Gingival bleeding	16 (9.52%)	5 (1.14%)	P<0.0001
Intra alveolaire hemorrhage	21 (12.5%)	4 (0.91%)	P<0.0001
Splenomegaly	6 (3.57%)	4 (0.91%)	P > 0.05
Hepatomegaly	3 (1.78%)	5 (1.14%)	P > 0.05

The association between thrombocytopenia and mucocutaneous signs was significant for a platelet count lower than 50,000 /mm³ with a hemorrhagic risk inversely proportional to the platelet levels (***Figure S6***).

- ***Biology :***

-In the thrombocytopenia group, the mean platelet count was 98500 +- 31600 /mm3 with low levels around 6000/mm3. In 10% of the cases, the count was less than 20,000/mm3; and in 4.16%, it was less than 10,000/mm3 (***Figure S7***).

Abnormalities in hemostasis was observed in 74 patients (44.84%) in the thrombocytopenia group compared to 52 patients (11.95%) in the control group (***Table S3***). The disturbance of the hemostasis balance was strongly associated with thrombocytopenia. Liver abnormalities were more frequent in thrombocytopenic patients.

Regarding the group with thrombocytopenia acquired in the ICU, thrombocytopenia was observed in 59% of patients on day 2 of hospitalization while it appeared after day 2 of hospitalization in 41%. The mean time of onset was 4 days±6 days after admission.

- ***Etiologies of thrombocytopenia :***

Of the 168 patients identified, sepsis appeared to be the major cause of thrombocytopenia in 88 patients (52.38%), followed by ARDS in 23 patients (13.6%). Leptospirosis occupied the third position in 17 patients (10. 11%). Then massive fluid filling detected in 15 patients (8.92%) and massive transfusion and liver diseases in 6 patients (3.57%). Auto immune origin was found in four patients (2.23%) who were followed for lupus. Disseminated intravascular coagulopathy (DIC) was found in three patients (1.78%). A case of splenomegaly was also recorded. The drug-induced origin was difficult to prove due to the polymedication and the association with other clinical conditions in particular sepsis, which could have potentially been involved in the appearance of thrombocytopenia. It was mainly related to heparin in four patients and imipenem in one patient. This was actually suspected clinically due to the delay in the onset of thrombocytopenia and the improvement in platelet count after the discontinuation of the incriminated drug. Sepsis, ARDS, and leptospirosis were therefore the most common causes of thrombocytopenia in the study population. (***Figure S8***)

-In the thrombocytopenia group, 88 patients (52.38%) had sepsis compared with 85 patients (19.54%) in the control group. The lower the platelet count, the more severe the sepsis, the more likely it was that sepsis was associated with thrombocytopenia (***Figure 1***).

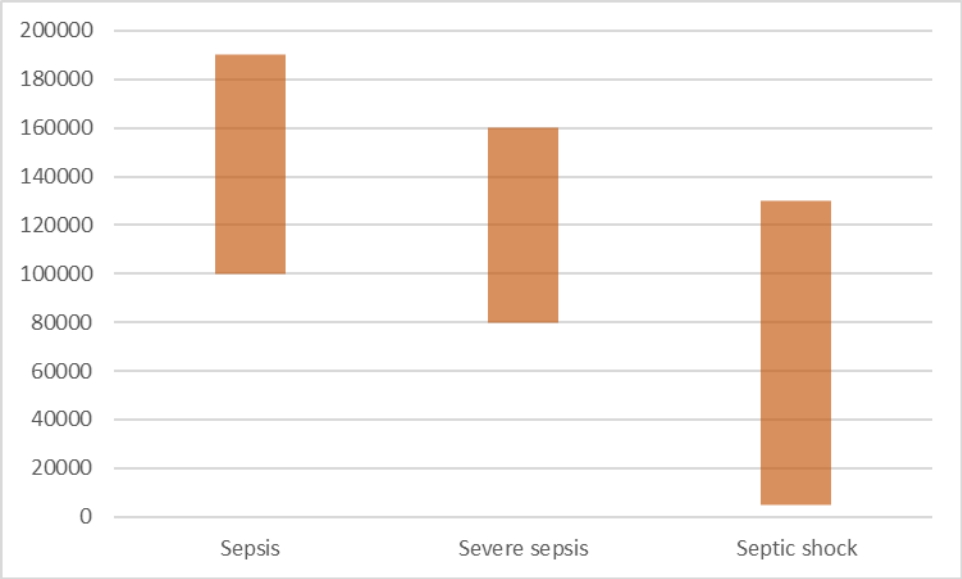

Figure 1: Platelet count depending on severity of sepsis.

ARDS could be considered as one of the incriminated factors in the development of thrombocytopenia as well (P<0.05).39 patients (23.21%) developed ARDS in the thrombocytopenia group versus 68 patients (15.63%) in the control group.

Other factors that may be related to thrombocytopenia are presented in ***Table S4***.

- ***Management :***

Forty-five of the thrombocytopenic patients, of which 16 belonged to the group of patients admitted with thrombocytopenia, were transfused with platelet concentrate with an average of 8 +/- 6 platelet units per patient. Treatment was mainly etiologic, especially in cases of sepsis, ARDS, or bleeding. Therapeutic management was identical between patients admitted with thrombocytopenia and those with thrombocytopenia acquired during their ICU stay. This would have eliminated any possible performance bias. Transfusion was relatively more frequent in the thrombocytopenia group than in the control group. Indeed, 23% and 28% of patients in the thrombocytopenia group were transfused with fresh frozen plasma and red blood cells respectively. Approximately 7% and 15% of the control patients received fresh frozen plasma and red blood cells respectively. Blood transfusion may therefore be a factor associated with the development of thrombocytopenia.

- ***Evolution :***

The prognosis of patients admitted with thrombocytopenia was poorer than those whose thrombocytopenia was acquired during their ICU stay with a mortality rate of 60.52%. (***Table 3***)

Table 3: Evolution of thrombocytopenic patients.

	Patients with acquired thrombocytopenia during ICU stay.	**Patients admitted with thrombocytopenia**
Mortality	48(36.92%)	23(60.53%)
Transfer to other wards	51(39.23%)	11(28.95%)
Recovery	31(23.85%)	4(10.52%)
Total	130(100%)	38(100%]

Regarding the control group, the average length of stay was 8± 7 days with extremes ranging from 3 to 48 days. For the thrombocytopenia group, the average length of stay was 12± 8 days for patients admitted with thrombocytopenia and 9± 6 days for patients with ICU acquired thrombocytopenia with extremes ranging from 3 to 54 days. The length of stay was therefore slightly longer for patients admitted with thrombocytopenia. Among the 168 thrombocytopenic patients, 71 patients died with a mortality rate of about 42.26%. Among these 71

patients who died:48 patients (36.92%) were in the group with thrombocytopenia acquired during ICU stay while 23 patients (60.52%) were in the group admitted with thrombocytopenia.

Thrombocytopenia at admission was therefore a factor of mortality. Regarding the control group and among the 435 patients, there were 143 deaths with a mortality rate of 32.87%. (***Figures S9 and S10***)

The causes of death in thrombocytopenic patients are reported in the ***Table 4***.

Table 4: The causes of death in thrombocytopenic patients.

Cause of death	Number of patients (%)
Septic shock	42 (59.15%)
Hemorrhagic shock	5(7.04%)
ARDS/alveolar hemorrhage	14 (19.7%)
Decompensated cirrhosis	4 (5.63%)
Liver failure	3(4.22%)
Multiorgan failure	2 (2.81%)
Cardiogenic shock	1 (1.40%)

In order to identify the factors associated with the development of thrombocytopenia and its impact on mortality, multivariate analyses were performed according to different parameters: reasons for hospitalization, clinical data, paraclinical data, severity scores, and therapeutic data (***Table S5***). The main predictors of mortality in thrombocytopenic patients were: septic shock, hemorrhagic shock, ARDS, renal failure, liver failure, use of vasoactive drugs, and hemodialysis (***Table S6***). Following the results of the performed statistical analyses, thrombocytopenia was a factor of excess mortality and not an independent factor of mortality.

Discussion

Thrombocytopenia is a common abnormality in critically ill patients.[9] It is an independent factor of morbidity, mortality, and prolongation of ICU length of stay.[10-13] The lower the platelet count, the higher the mortality.[14] However, more than the absolute value of the platelet count, it is the kinetics of the decrease that seems to be a determining prognostic element.[11]

The diagnosis of thrombocytopenia is based upon a platelet count < 150,000/mm3. The severity of thrombocytopenia is generally classified as mild, moderate, severe, and profound when the platelet count is < 150,000, 100,000, 50,000, and 20,000/mm3, respectively.[15] Below a platelet count of 50,000/mm3, there is often a clinical hemorrhagic syndrome (mucocutaneous purpura) whereas above 50,000/mm3, the clinical expression is variable with usually a well-tolerated thrombocytopenia.[13] It actually seems that the risk of spontaneous bleeding does not increase significantly until a platelet count of less than 10,000/mm3 or 5,000/mm3.[16] Moreover, Beyond the actual platelet count, associated comorbidities must be taken into account to assess the potential risk of bleeding, such as fever, sepsis, high blood pressure, renal and/or liver failure.

Several studies have helped to understand the mechanisms and pathways involved in the occurrence of thrombocytopenia. It can be either a peripheral thrombocytopenia due to destruction, consumption, or sequestration of platelets; or central thrombocytopenia due to insufficient production.[15] In intensive care, thrombocytopenia is in most cases peripheral with a multifactorial origin, including sepsis, spoliation, transfusion, acute respiratory distress syndrome, the presence of invasive intravascular catheters,[17] as well as the use of heparin.

Indeed, only sepsis is accepted by most studies as a major risk factor of thrombocytopenia.[18] It accounts for roughly 50% of all thrombocytopenias in critically ill patients, yet the mechanisms underlying thrombocytopenia in sepsis are poorly understood.[19,20] Nonetheless, several pathological processes are likely to contribute to thrombocytopenia in sepsis. Sepsis is a well-recognized trigger of disseminated intravascular coagulation (DIC), largely driven by the upregulation of tissue factor expression on monocytes and other cells in response to inflammatory mediators such as endotoxin.[21] Even in

the absence of overt DIC, markers of coagulation activation (e.g. thrombin-antithrombin complexes, prothrombin fragment 1.2) are increased. Moreover, the use of low-molecular- weight heparin for venous thromboprophylaxis has been shown to be associated with lower risk of moderate thrombocytopenia (hazard ratio, 0.62; 95% confidence interval, 0.47-0.84).[6] Data from published randomized trials indicate the potential for heparin to improve clinical outcomes in sepsis.[22] Hemophagocytosis (HPS) has also been shown to be incriminated in sepsis-related thrombocytopenia.[21] Unfortunately, high-quality evidence to inform the optimal management of sepsis-associated HPS in adult patients is lacking. However, available recommended therapies target T cells (steroids, cyclosporine) and macrophages (etoposide).[23] Intravenous immunoglobulins (IVIG) to support defective humoral immunity and reduce systematic inflammation have also been suggested.[23] ADAMTS13 depletion has also been incriminated in sepsis-related thrombocytopenia and microvascular injury and its possible contribution should lead to consideration of future trials evaluating plasma exchange or infusion of recombinant ADAMTS13.[21,24] Complement activation has a role to play as well and developing complement inhibitors such as eculizumab should elucidate the complement's contribution to the thrombocytopenia and other sepsis-related disorders.[21] Antiplatelets auto-IgG have also been isolated in 30-40% of septic thrombocytopenia in both gram-positive cocci and gram-negative bacilli infections.[25] It is of note that thrombocytopenia may independently modify the host immune response to infection.[26]

Disseminated intravascular coagulation (DIC) is found in 10% to more than 60% of critically ill patients[27] and thrombocytopenia is present in approximately 88% of DIC cases, below 50,000/mm3 in roughly 50%. A low platelet count is strongly correlated with markers of thrombin formation because thrombin-induced platelet aggregation is the primary cause of platelet consumption.[28] Platelet transfusion is only indicated in cases of combined thrombocytopenia below 50,000/mm3 and bleeding risk factors (surgery, invasive procedure, associated thrombopathy) or in severe bleeding (complicated DIC).[27]

The sequestration of platelets in the lung is also well-documented during acute respiratory distress syndrome (ARDS) which may explain the link between ARDS and the development of thrombocytopenia.[5] Macrophagic activation syndrome (MAS) is a fairly common complication in intensive care with an early thrombocytopenia which is very often in the context of bi or profound pancytopenia.[29] Then come thrombotic microangiopathies, which include thrombotic thrombocytopenic purpura (TTP or Moschcowitz syndrome), hemolytic uremic syndrome (HUS), and HELLP syndrome in pregnant women (hemolysis, elevated liver enzymes, low platelet count).[30] Immunological thrombocytopenic purpura (ITP) whose incidence varies from 2 to 6.1 per 100,000 adults per year, all ages combined is featured by an immunological destruction of platelets resulting in thrombocytopenia with an increased risk of bleeding.[31-34] Idiosyncratic drug-induced thrombocytopenia is a minor etiology of thrombocytopenia in intensive care.[10,14] They may be related to an alteration in central platelet production (e.g. colchicine, tolbutamide, and thiazide diuretics),[35,36] to hyperconsumption due to thrombotic microangiopathy (e.g. ticlopidine, clopidogrel),[37,38] or to immunological destruction (e.g. heparin-induced thrombocytopenia).[39]

Post-transfusion purpura (PTT) is a rare cause of immune thrombocytopenia but should not be missed in patients with profound thrombocytopenia. It is related to a post-transfusion anti-HPA-1a alloimmunization.[5] Liberal fluid filling strategies with crystalloids and/or colloids following a blood loss may also lead to dilution thrombocytopenia depending on the extent of the loss.[40]

Thrombocytopenia due to platelet sequestration is usually seen in splenomegaly regardless of its origin,[41] and in perioperative hypothermia particularly during traumatic brain injuries. The use of invasive intravascular catheters is classically associated with the occurrence of thrombocytopenia in intensive care.[42,43] Likewise, in hemodialysis patients, it is estimated that a drop of about 15% in platelet count would be observed after each hemodialysis session by platelets consumption on the filter.[44] However, several case series have shown very low rates of bleeding complications related to the use of central lines despite the presence of thrombocytopenia and/or coagulopathy.[45]

Post-traumatic fat embolism is often complicated by thrombocytopenia, found in 37% of cases.[46] It is sometimes part of a disseminated intravascular coagulation (DIC) and is characterized by the absence of a decrease in fibrinogen.[47] Severe burns may also manifest thrombocytopenia which is

initially seen in patients as a transient occurrence during the first week after injury.[48] Subsequent decreases occur later in the course of treatment and are commonly due to sepsis, dilutional effects, and medication exposure.[48]

Last but not least, comes gravidic or gestational thrombocytopenia also known as incidental thrombocytopenia of pregnancy. It is the most common cause of thrombocytopenia in pregnant women, accounting for roughly 75% of all cases.[49] The reason for this decline is unknown, although it has been speculated that these changes may reflect dilution, decreased platelet production, or increased platelet turnover during pregnancy.[50] However, It can sometimes be part of a serious condition requiring specific management, such as pre-eclampsia, HELLP syndrome, thrombotic microangiopathies, auto-immune thrombocytopenic purpura, lupus, or the anti-phospholipid syndrome.[51]

The central origin of thrombocytopenia is rare in intensive care and is often associated with damage to other blood lines.[13] It may be an insufficiency in platelet production directly related to the underlying condition (hematological malignancies, medullary metastases, medullary aplasia) or following a myelotoxic treatment (chemotherapy, radiotherapy, immunosuppressants).

In the absence of any orientation, a situation which is rare in intensive care, an urgent myelogram, eventually completed by a bone marrow biopsy, should be performed if the platelet count is less than 80,000/mm3.[52]

The management strategy of thrombocytopenia in critically ill patients (corticosteroid therapy, immunoglobulin, platelet transfusion) must take into account the etiology of thrombocytopenia, platelet dysfunction, the risk of bleeding, the need for an invasive procedure, and the presence of comorbidities.[5] Treating the underlying cause of the critical illness is of paramount and likely to result in improved platelet counts. If thrombocytopenia is due to sepsis, an appropriate antimicrobial therapy, source control, and organ support are required.[53] If the thrombocytopenia is due to severe bleeding (e.g. trauma), hemostatic control is the priority. In the presence of mechanical circulatory support devices (e.g. intra-aortic balloon pumps), device-related thrombocytopenia may persist and may be further influenced by an underlying cardiogenic shock and/or multiorgan failure. Although uncertainty exists whether extracorporeal membrane oxygenation (ECMO) is independently associated with thrombocytopenia, the conditions associated with the need for ECMO certainly are.[54] Thrombocytopenia is consistently associated with increased risks of bleeding, transfusion, and death. The effectiveness of platelet transfusion to stop bleeding, to reduce transfusion of other blood products, or to improve clinical outcomes is uncertain,though.[1,6,55] Indeed, platelet transfusion may be associated with harm, including increased incidence of nosocomial infection and transfusion-related acute lung injury (TRALI).[56-58] In the context of massive transfusion, treatment of bleeding with a 1:1:1 or a 1:2:1 ratio of red cells, plasma, and platelets is supported by clinical studies and widely recommended in clinical guidelines to prevent severe thrombocytopenia or hemodilution of coagulation factors.[21]

Overall, in ICU patients with severe bleeding, current guidelines recommend that platelet transfusion be considered if the platelet count is $<50 \times 109/L$ or if significant platelet dysfunction is suspected or confirmed.[58] Regarding prophylactic platelet transfusion, the American Association of Blood Banks (AABB) and the Society for Critical Care Medicine (SCCM) 2016 Surviving Sepsis Guidelines recommend prophylactic platelet transfusion below a threshold of $10 \times 109/L$.[53,58] However, Post-transfusion platelet increments and the durability of platelet increases are known to be attenuated in ICU patients. In observational studies, the median increase in platelet count per platelet transfusion was $15 \times 109/L$.[59] Periprocedural platelet transfusion is also recommended to minimize bleeding during placement of an elective central venous catheter if the platelet is $<20 \times 10/L$.[58,60]

Finally, It should be emphasized that major hemorrhage is a recognized consequence of critical illness with multiple organ failure regardless of the platelet count.

Limitations of the study:

-The retrospective nature of the study.

-The patients included in the study had a different initial severity.

-The polymedication and the association with other clinical conditions like sepsis, which can also be incriminated in the occurrence of thrombocytopenia, made it difficult to individualize the thrombocytopenic role of the treatments used in intensive care.

- The study was carried out in a medical intensive care unit; the drawn conclusions may therefore not be valid in peri-operative intensive care units.

Conclusion

Thrombocytopenia is a frequent abnormality in intensive care. It is classically associated with an increased mortality. Sepsis is the major factor incriminated in the occurrence of thrombocytopenia in critically ill patients. Therapeutic management should depend on the etiology of thrombocytopenia. Platelet transfusion must also take into account the severity, the mechanism, the need for an invasive procedure, as well as the hemorrhagic risk associated with thrombocytopenia.

Added value/recommendations:

-The etiological diagnosis is an essential element in the management of thrombocytopenic patients.
-A level of 20,000/mm3, with or without clinical manifestations, can be considered as a threshold for platelet transfusion.
-The therapeutic management of patients admitted with thrombocytopenia and those who have acquired it in the intensive care unit does not differ.
-The prognosis is poorer for patients admitted with thrombocytopenia, especially below a threshold of 50,000/mm3.

Statements and Declarations

Funding: The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interests: The authors have no relevant financial interests to disclose.

Data availability: The datasets generated and analyzed during the study are available from the corresponding author upon reasonable request.

Ethics approval: This is an observational study. The Research Ethics Committee has confirmed that no ethical approval is required.

Consent to publish: The manuscript contains no individual personal details, images, nor videos.

CRediT author statement: **Pr Boubaker Charra**: Conceptualization, Methodology, Resources, Supervision, Project administration,and Validation. **Dr Yassine Bou-ouhrich**: Methodology, Investigation, formal analysis, Writing Original Draft, Writing Review&Editing, visualization.

Acknowledgements: We thank the staff of the medical intensive care unit of the Ibn Rochd University Hospital for their contribution to the study.

Disclosure of Conflicts of interest: The authors declare no conflict of interest.

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SUPPLEMENTARY MATERIALS

SUPPLEMENTARY FIGURES

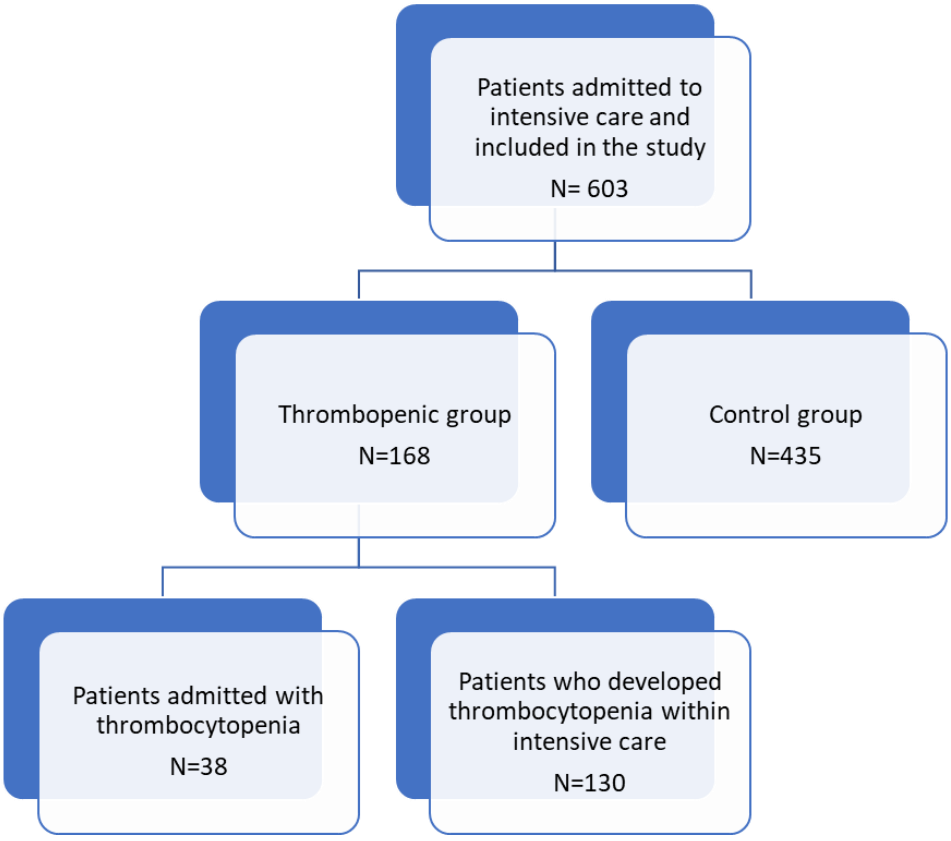

Figure S1: Distribution of patients during the study period.

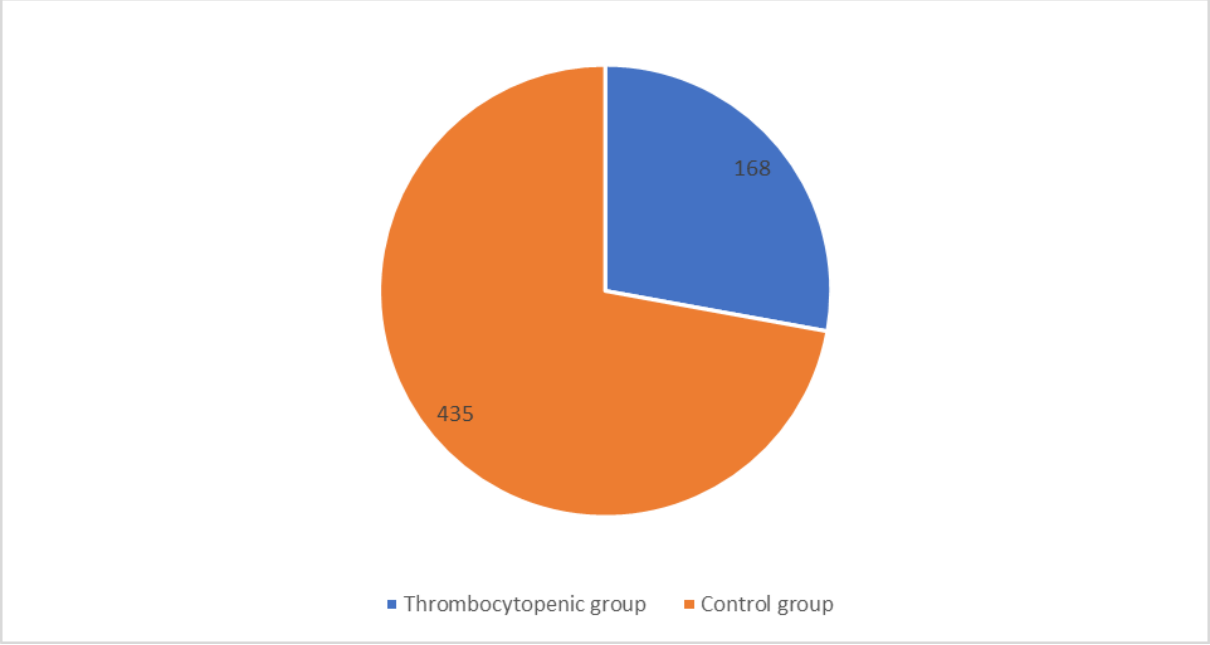

Figure S2: Distribution of patients between the two study groups.

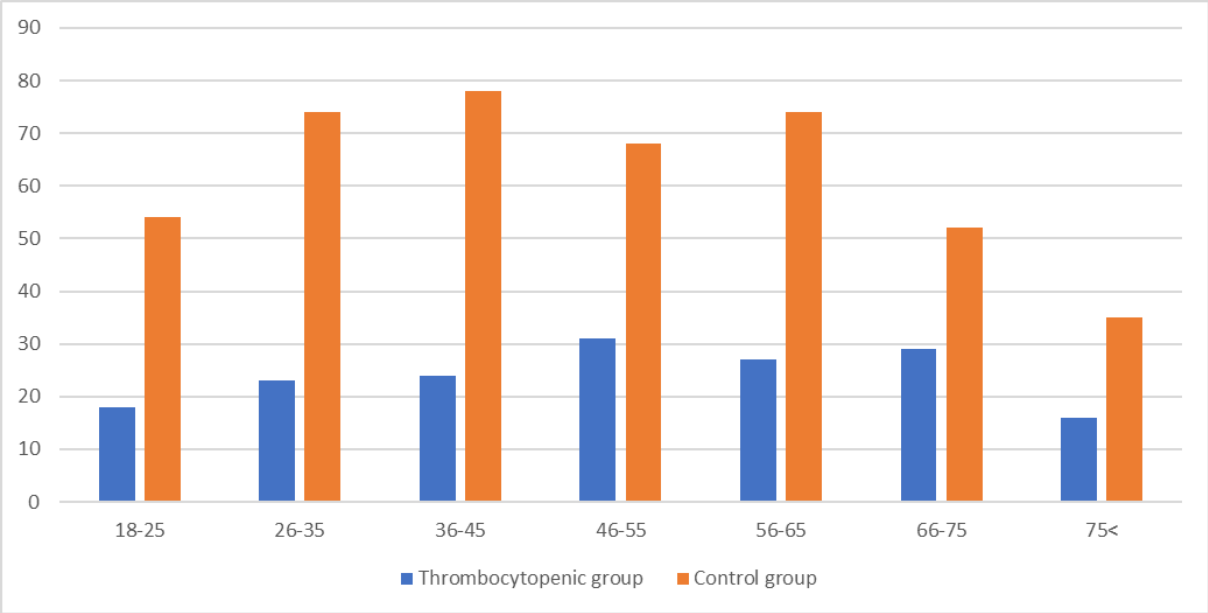

Figure S3: Distribution of patients by age brackets within the two study arms.

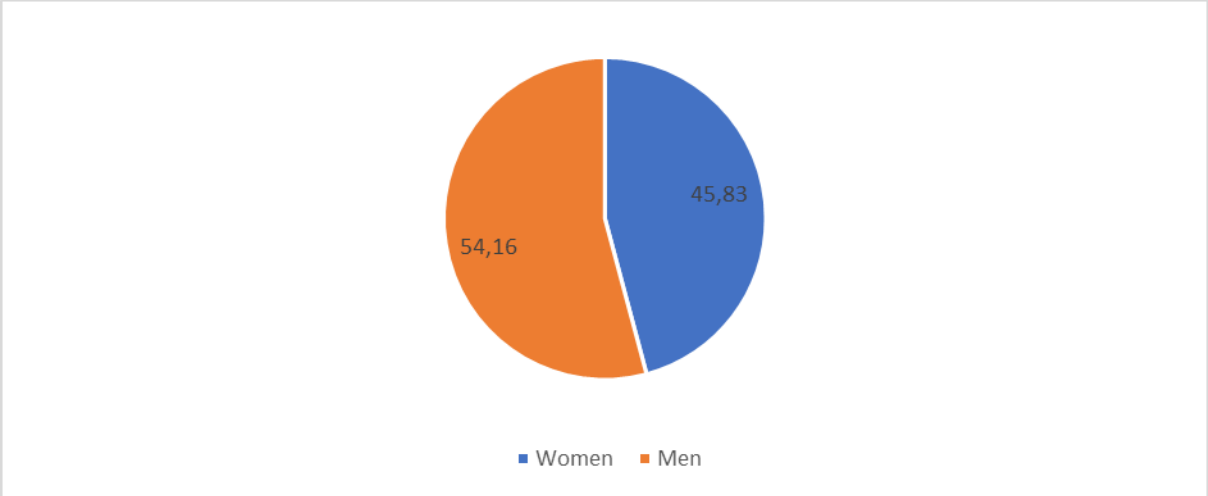

Figure S4: Distribution of patients within the thrombocytopenic group depending on the sex.

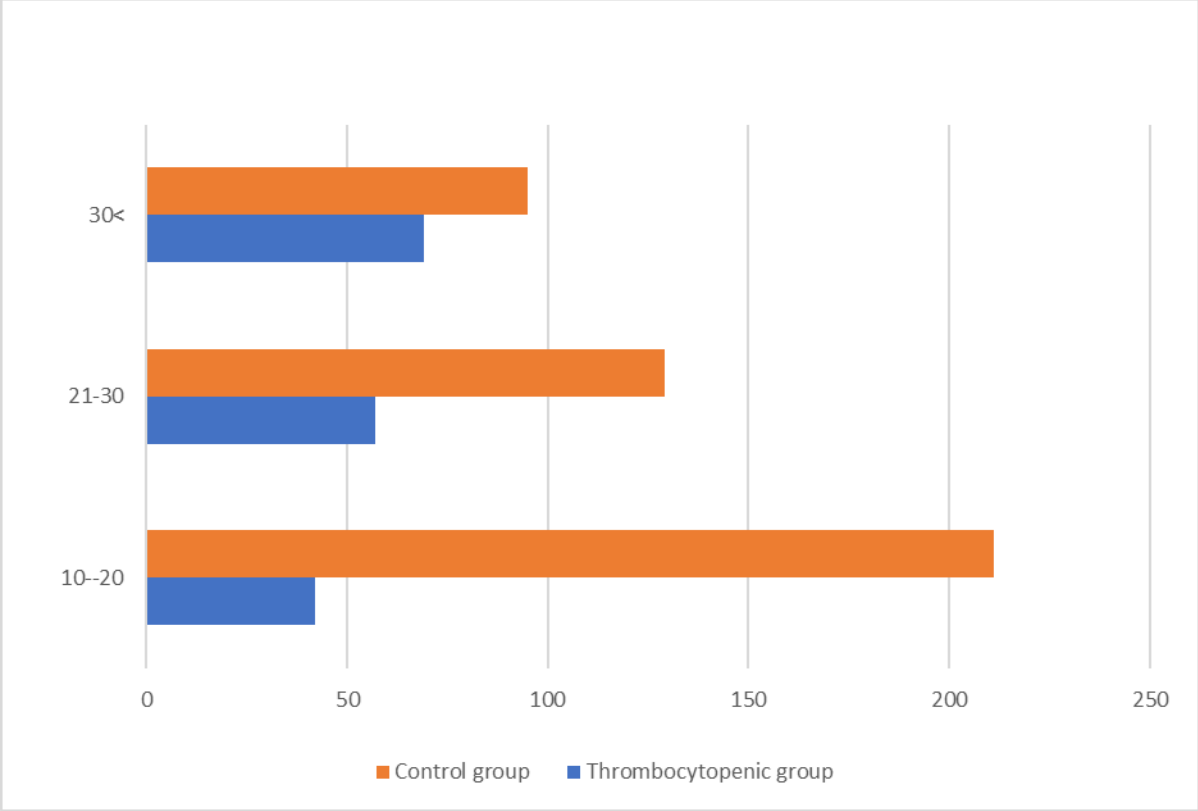

Figure S5: Distribution of groups by IGS scores.

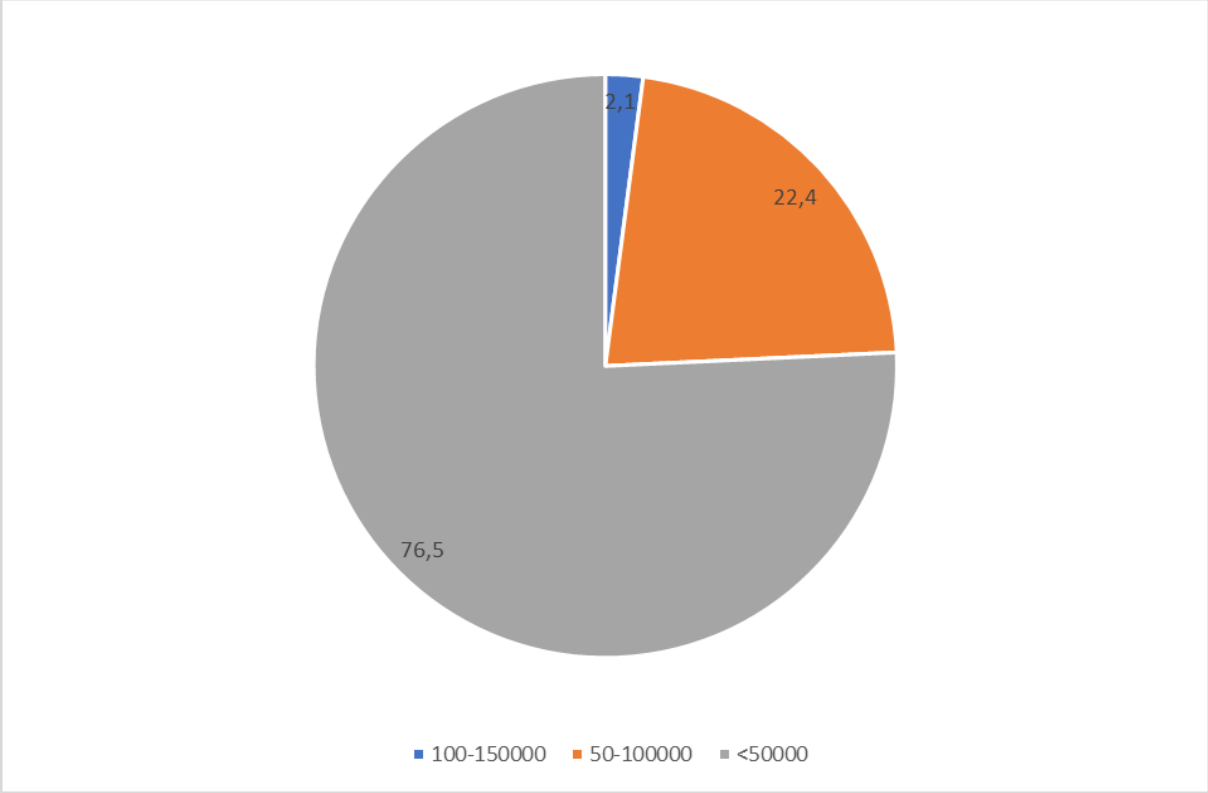

Figure S6: Incidence of hemorrhagic syndrome depending on the platelet count within the thrombocytopenia group.

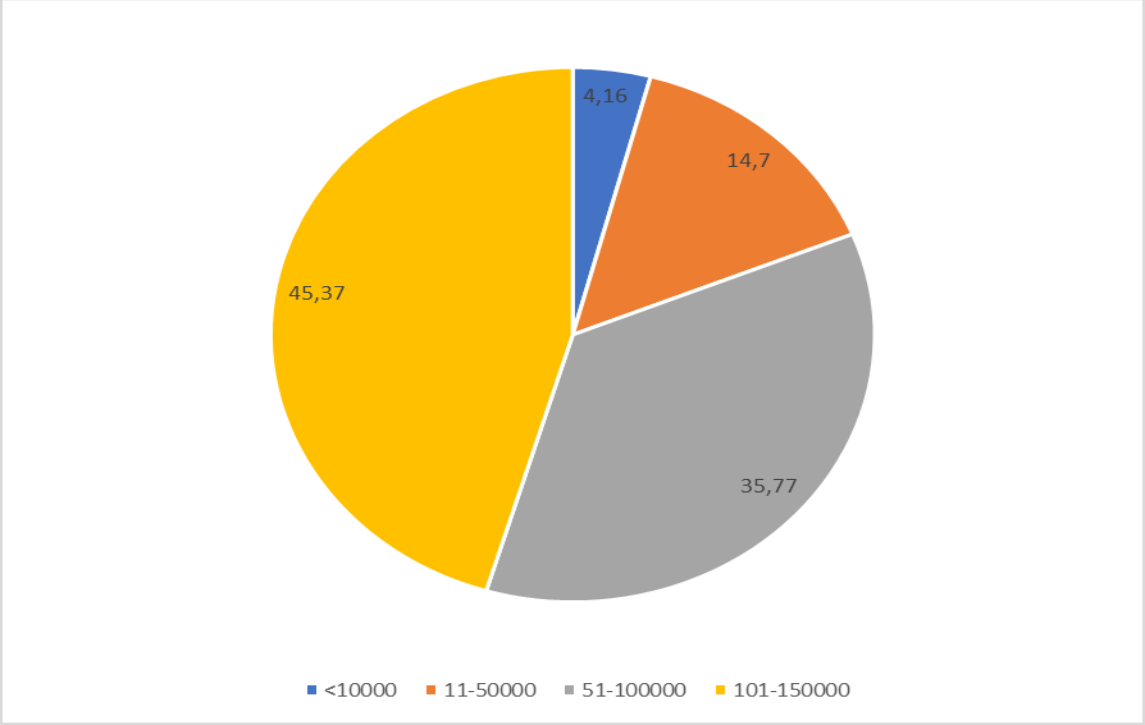

Figure S7: Distribution of patients within thrombocytopenia group depending on platelet count.

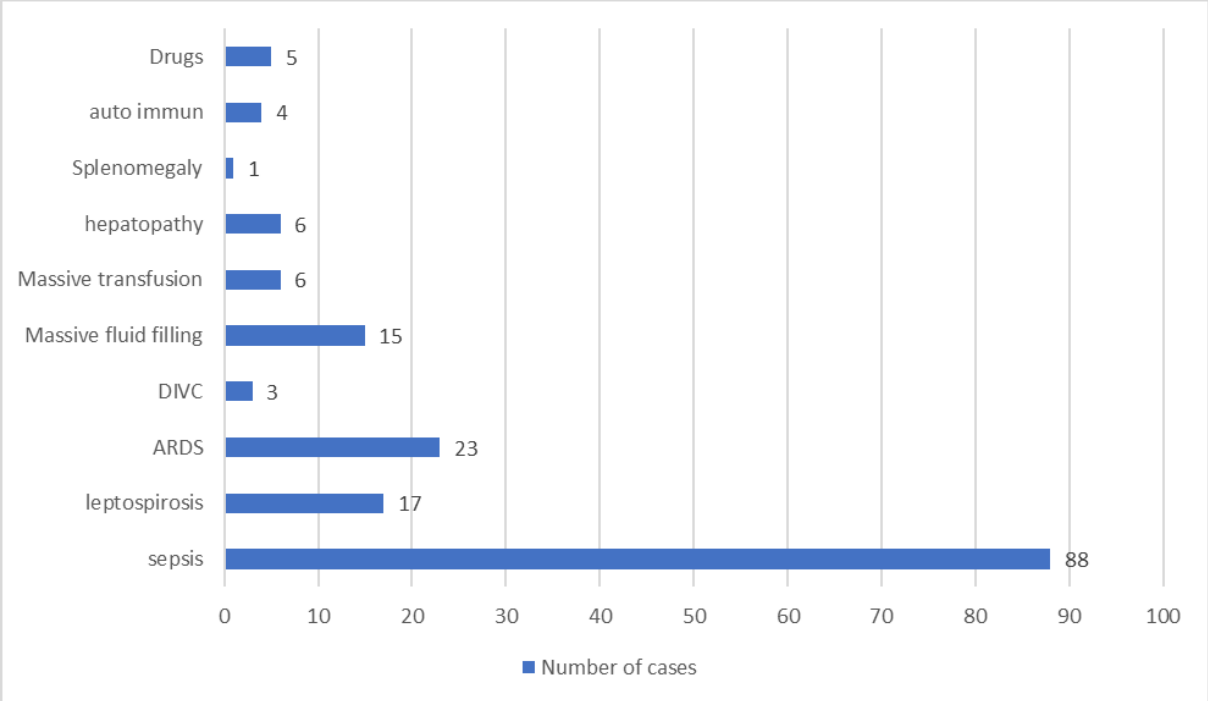

Figure S8: Main causes of thrombocytopenia.

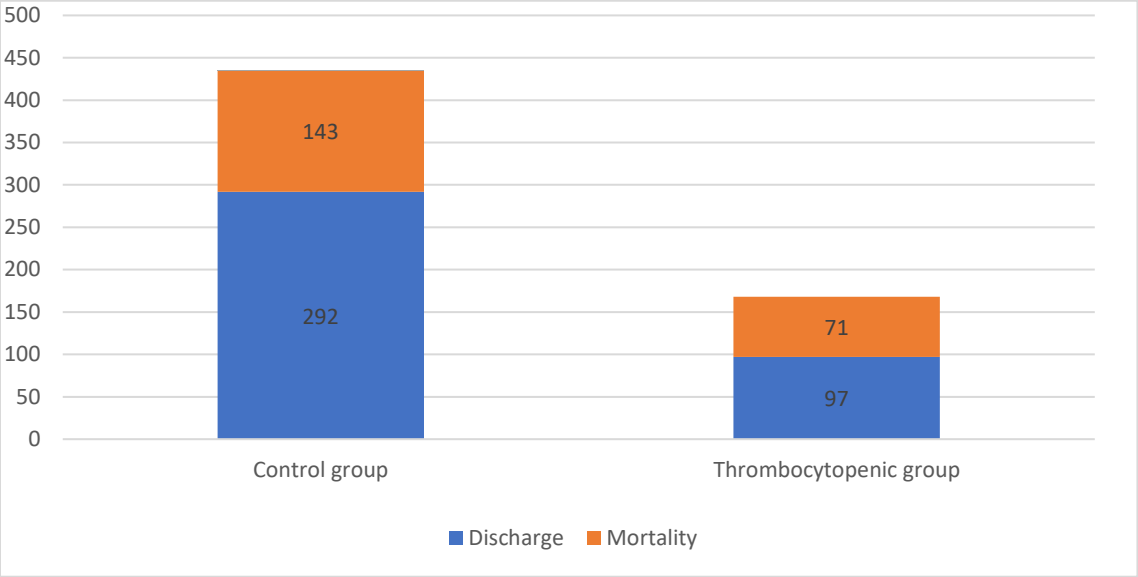

Figure S9: Evolution of patients in both groups.

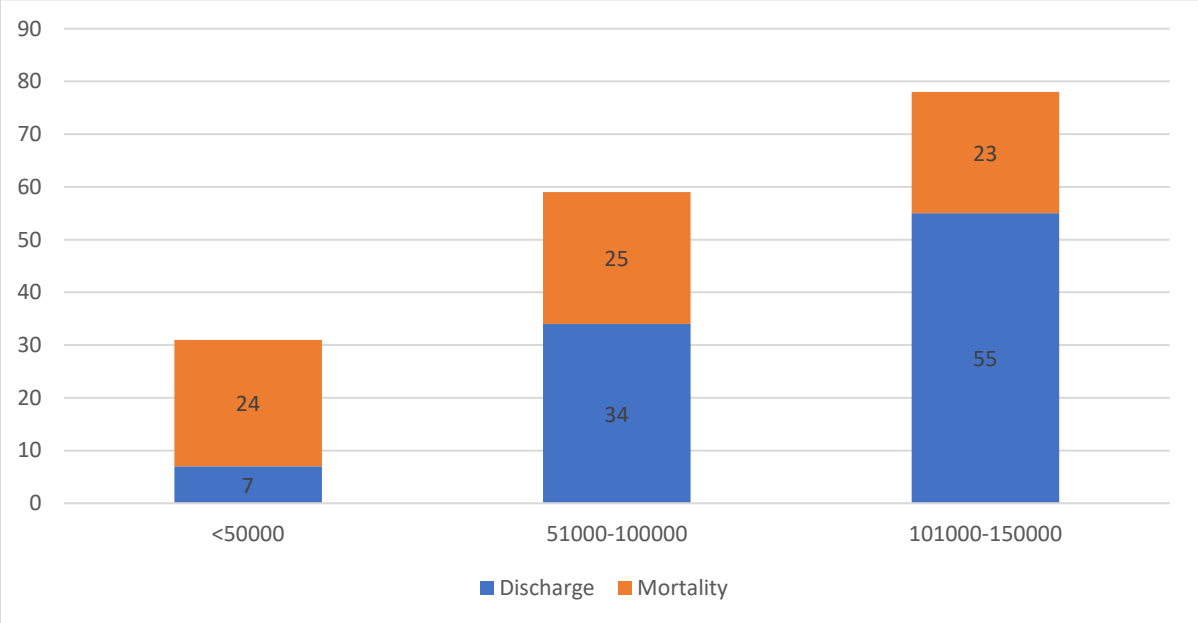

Figure S10: Evolution of thrombocytopenic patients depending on platelet count.

SUPPLEMENTARY TABLES

Table S1: Medical history of patients in the two groups.

History	Thrombopenic group (N)	Control group (N)
General pathologies:		
•High blood pressure	17	34
•Diabetes	26	132
•Epilepsy	4	13
•Chronic kidney failure	9	16
Toxic habits :		
•Smoking	44	61
•Alcohol	13	23
Cardiac diseases :	9	21
Liver diseases:		
•B/C hepatitis	6	8
•Cirrhosis	5	3
•Others	1	2
Ulcer disease	3	2
Respiratory diseases:		
•COPD	4	8
•Asthma	7	13
•Tuberculosis	2	5
Others:		
•Vasculitis	1	1
•Parkinson disease	1	--
•Lateral sclerosis	1	1
•Scleroderma	1	--
•Psychiatric illness	2	3
•Œsophagitis	1	--
•Behçet	1	--

Table S2: The average severity scores in each study group.

Scores	Thrombopenic group	Control group	P value
IGS II	27± 3	18± 2	P=0.002
SOFA	13,1 ± 2	9,6 ± 1.8	P =0,001
APACHE II	27,2 ± 3,2	13,3 ± 3,4	P=0,001

Table S3: Biological workup.

	Thrombopenic group	Control group	P value
Prothrombin ratio	74% +/-20%	87%+/-21%	P<0.0001
Partial thromboplastin time	34"+ /-8"	29"+/-5	P<0.0001
Fibrinogen	4.7 g/l	4.5g/l	P > 0.05
Hemoglobin (g/dl)	11.2	12.02	P > 0.05
White blood cells count (/mm3)	11.190 ± 4870	14.700 ± 5900	P > 0.05
Urea (g/l)	0.94g /l	0.7g /l	P=0.002
Creatinine (mg/l)	22.34mg/l	19.74mg/l	P > 0.05
Bilirubin « mg/l »	18±12	15±25	P > 0.05
ASAT « IU/L »	115(±87)	60(±55)	P<0.0001
ALAT « IU/L »	80(±69)	42(±39)	P<0.001

Table S4: Other factors potentially related to thrombocytopenia.

	Thrombopenic group N (%)	Control group N (%)	P value
Kidney failure	42 (25%)	59 (13,5%)	P=0.007
Liver failure	12 (7%)	2 (0,45%)	P=0.00097
Hemodialysis	32 (19%)	13 (29,8%)	P=0.00068
Mechanical ventilation	61 (36,3%)	49 (11,2%)	> 0.05
Use of vasopressors	65 (38,6%)	30 (6,8%)	P=0.0001

Table S5: Main factors associated with thrombocytopenia.

Parameters	**Thrombopenic group N= 168**	**Control group N=435**	**P value**
Age	44 ±13	46 ±15	> 0.05
Sexe :			
-Male :	91 (54.16%)	229(52.64%)	> 0.05
-Female :	77(45.83%)	206(47.35%)	> 0.05
Reason for admission:			
-Leptospirosis	17(10.11%)	1(0.22%)	P < 0.0001
-Cirrhosis	5(2.97%)	3(0.68%)	P= 0.0278
-Septic shock	6(3.57%)	5(1.14%)	P=0.0464
-Hemorrhagic syndrome	6(3.57%)	3(0.68%)	P=0.0222
Clinical status:			
-Hemorrhagic syndrome	21 (12.5%)	9(2.06%)	P < 0.0001
-Sepsis /Septic shock	88(52.38%)	85(19.54%)	P < 0.0001
-Hypoxia/ARDS	39(23.21%)	68(15.63%)	P < 0.0001
Gravity scores:			
-IGS II	27+/-3	18+/-2	P=0.02
-Apache II	25.2+/-4.2	15.3+/-2.4	P=0.003
-SOFA	14.2+/-1.9	7 ,6+/-1.8	P=0.009
Biology:			
-Hemoglobin (g/dl)	11.2	12.02	> 0.05
-White blood cells	11.190+/-4870	14.700+/-5900	> 0.05
-Prothrombin ratio	74%+/-20%	87%+/-21	< 0.0001
-Partial thromboplastin time	34"+/-8	29"+/-5	< 0.0001
-Fibrinogen(g/l)	4.7	4.5	> 0.05
-ASAT(IU/l)	115+/-87	60+/-55	P < 0.0001
-ALAT(IU/l)	80+/-69	42+/-39	P < 0.001
-Urea (g/l)	1.94	0.7	P=0.002
-Creatinine (mg/)	32.34	19.74	> 0.05
Renal failure	42	59	P=0.007
Liver dysfunction	12	2	P=0.00097
Management:			
•Transfusion by:			--
-Fresh frozen plasma	39(23.21%)	31(7.12%)	
-Red blood cells	48(28.57%)	65(14.94%)	
-Platelets units	45(26.78%)	0	
•Vasopressors	77	42	P=0.000104
•Hemodialysis	32	13	P=0.000068
•Mechanical ventilation	61	49	P> 0.05

Table S6: predictive factors of mortality in thrombocytopenic patients.

Parameters	Surviving patients	Non surviving patients	P
Admission reason:			
-Septic shock	1	5	P=0.0383
-Leptospirosis	10	7	P> 0.05
-Hemorrhagic shock	1	5	P=0.0383
Gravity score:			
-IGS II	23+/-2	28+/-3	P> 0.05
-APACHE II	21+/-3	26+/-2	P> 0.05
-SOF	12.1+/-1.2	15.3+/-1.5	P> 0.05
Clinical status:			
-Hemorrhagic syndrome	7	14	P=0.015
-Hypoxia/ARDS	15	24	P=0.005
Biology:			
-Renal failure	13	29	P<0.0001
-Liver failure	3	9	P=0.0171
Management:			
-Transfusion by platelets units	15	31	P<0.0001
-Vasopressors	13	64	P<0.0001
-Hemodialysis	9	23	P=0.0001