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RESEARCH ARTICLE

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Platelet transfusions and thrombocytopenia in intensive care units: Protocol for an international inception cohort study (PLOT-ICU)

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Abstract

Introduction: Thrombocytopenia is frequent in intensive care unit (ICU) patients and has been associated with worse outcome. Platelet transfusions are often used in the management of ICU patients with severe thrombocytopenia. However, the reported frequencies of thrombocytopenia and platelet transfusion practices in the ICU vary

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considerably. Therefore, we aim to provide contemporary epidemiological data on thrombocytopenia and platelet transfusion practices in the ICU.

Methods: We will conduct an international inception cohort, including at least 1000 acutely admitted adult ICU patients. Routinely available data will be collected at baseline (ICU admission), and daily during ICU stay up to a maximum of 90 days. The primary outcome will be the number of patients with thrombocytopenia (a recorded platelet count < 150×10^9/L) at baseline and/or during ICU stay. Secondary outcomes include mortality, days alive and out of hospital, days alive without life-support, the number of patients with at least one bleeding episode, at least one thromboembolic event and at least one platelet transfusion in the ICU, the number of platelet transfusions and the indications for transfusion. The primary and secondary outcomes will be presented descriptively. In addition, we will assess risk factors for developing thrombocytopenia during ICU stay and the association between thrombocytopenia at baseline and 90-day mortality using logistic regression analyses.

Conclusion: The outlined international PLOT-ICU cohort study will provide contemporary epidemiological data on the burden and clinical significance of thrombocytopenia in adult ICU patients and describe the current platelet transfusion practice.

KEYWORDS
intensive care unit, platelet transfusion, thrombocytopenia

1 | BACKGROUND

Thrombocytopenia, typically defined as a platelet count of less than 150×10^9/L, is a common condition in the intensive care unit (ICU).[1–3] Its prevalence and incidence vary across different studies from 21 to 77% and from 8 to 56 cases per 100 admissions, respectively,[4] likely depending on the case-mix and the definition of thrombocytopenia used in each study.[5–8] Thrombocytopenia is frequent in critically ill patients with an underlying haematological malignancy[9] but patients with sepsis and septic shock are also particularly at risk[10–12] with reported incidences as high as 55%.[11] The cause of thrombocytopenia in critically ill patients is often multifactorial[9] and may be a marker of illness severity and/or a consequence of critical illness.[6] Several risk factors for thrombocytopenia have been proposed and it has been associated with increased rates of bleeding, transfusion requirements, length of hospital stay and mortality.[4] However, uncertainty exists as the current evidence mainly consists of small single-centre observational studies, some with methodological issues, low external validity and conflicting results.[4]

Platelet transfusions are frequently used to prevent bleeding in critically ill patients with severe thrombocytopenia.[13] However, the evidence base is sparse and primarily based on observational data and extrapolation from trials in patients with haematological malignancies and hypoproliferative thrombocytopenia.[14–16] Furthermore, surveys among ICU physicians indicate considerable variation in clinical practice.[13,17] Transfusion with platelets has several undesirable effects that, although rare, include potentially life-threatening reactions such as anaphylaxis, transfusion-transmitted infections and transfusion-related acute lung injury.[18] Moreover, platelet transfusions has been associated with ICU-acquired infections in observational studies[19–21] and harm from platelet transfusions has been observed in trials conducted in critically ill preterm infants[22] and in patients with intracerebral haemorrhage.[23]

Thus, there is uncertainty about the clinical significance of thrombocytopenia and its risk factors in ICU patients and the current platelet transfusion practice is unknown. To move forward, contemporary data with high external validity are needed including data describing the number of patients with thrombocytopenia in the ICU, risk factors for thrombocytopenia, the current platelet transfusion practice and outcomes of thrombocytopenic ICU patients.

1.1 | Objectives

This protocol describes the primary analyses of the PLOT-ICU cohort data. Studies with more exploratory analyses are planned and will be described and reported separately.

With this study, we aim to assess the number of patients with thrombocytopenia among acutely admitted adult ICU patients and evaluate risk factors for thrombocytopenia in a contemporary international cohort. In addition, we will report the outcomes of adult ICU patients with thrombocytopenia and describe the current use of platelet transfusions in the ICU. We hypothesise that thrombocytopenia is common, that specific risk factors exist, that thrombocytopenia is associated with worse outcome, and that the current platelet transfusion practice is variable.

1.2 | Research questions

1. How many acutely admitted adult ICU patients are thrombocytopenic at baseline and/or during ICU stay?
2. What are the risk factors for developing thrombocytopenia during ICU stay in acutely admitted adult ICU patients?
3. What is the outcome of acutely admitted adult ICU patients with thrombocytopenia?
4. What is the current practice for the use of platelet transfusions in acutely admitted adult ICU patients?

2 | METHODS

2.1 | Study design and setting

We will conduct an international inception cohort study with prospective data collection in general ICUs located in Europe and North America. We aim to enrol at least 1000 patients from 40 to 50 participating ICUs (planned sites are listed in Supplement S2). Patients will be included during inception periods of 14 consecutive days with a 90-day follow-up period. An overview of the study is presented in Figure 1. The steering committee will oversee the study and the management committee will handle the study on a day-to-day basis (Supplement S3).

2.2 | Approvals

Approvals from all required authorities in participating countries will be obtained by the national or local investigator as appropriate before study initiation. If required by local or national regulations, informed consent will be obtained from patients or surrogates by local investigators as appropriate.

2.3 | Inclusion criteria

All adult (age ≥ 18 years) patients acutely admitted to the ICU during the 14 days inception periods will be eligible for inclusion. The local investigator or his/her delegate will actively screen all eligible patients. Patients already admitted to the ICU at the start of the inception periods will not be screened. Patients transferred directly from a non-participating ICU are considered eligible if they meet the inclusion criteria.

2.4 | Exclusion criteria

Patients that meet one or more of the following criteria will be excluded from the study:

1. Previously included in the PLOT-ICU study.
2. Elective open-heart surgery during current hospital admission.
3. Informed consent unobtainable as per local or national regulations.

2.5 | Study timeline and closure

The PLOT-ICU cohort study was initiated on May 15th, 2021, and is currently actively recruiting. As per June 22nd, 2022, 954 patients have been enrolled. We will close the study when the follow-up

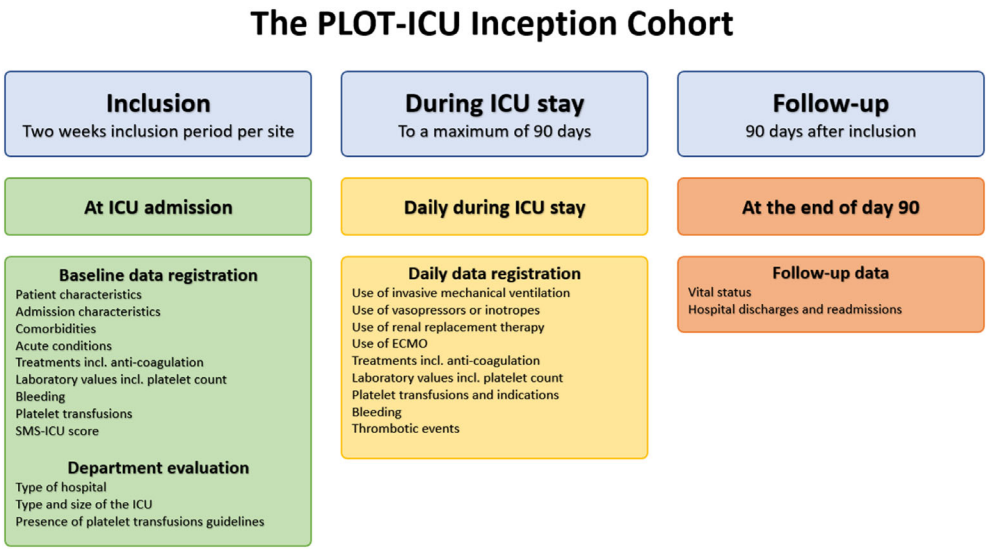

FIGURE 1 Study overview. Patients will be included during a 14-day inception period chosen by the local investigator. During this period, all acutely admitted adult patients will be screened for inclusion at ICU admission. Eligible patients will be followed daily during their intensive care unit stay (and subsequent stays if readmitted to a participating ICU) until day 90 after which the follow-up will be completed. Baseline variables are registered at inclusion, and daily registrations are performed for each day in the ICU to a maximum of 90 days. Follow-up variables are registered at the end of day 90. ECMO, extra corporeal membrane oxygenation; ICU, intensive care unit; SMS-ICU, simplified mortality score in the intensive care unit

period has ended at all sites and after a minimum of 1000 patients has been enrolled. We expect the inclusion and follow-up period to be completed by the end of July and October 2022, respectively.

2.6 | Outcome measures

2.6.1 | Classification of thrombocytopenia

Patients with 'thrombocytopenia at baseline' will be defined as patients with at least one recorded platelet count below 150×10^9/L within 24 h prior to ICU admission. Patients with 'thrombocytopenia during ICU stay' will be defined as patients with at least one recorded platelet count below 150×10^9/L during ICU stay without pre-existing thrombocytopenia at baseline. Patients with 'any thrombocytopenia' will be defined as patients with at least one recorded platelet count below 150×10^9/L at baseline and/or during ICU stay.

2.6.2 | Primary outcome

The primary outcome is the number of patients with 'any thrombocytopenia' in the ICU, which is a composite outcome consisting of the number of patients with 'thrombocytopenia at baseline' and the number of patients with 'thrombocytopenia during ICU stay' as defined above.

2.6.3 | Secondary outcomes

The secondary outcomes include:

1. The number of patients with 'any thrombocytopenia', 'thrombocytopenia at baseline' and 'thrombocytopenia during ICU stay' categorised into the following subclasses according to the nadir platelet count:
   a. Mild: 100 to 149×10^9/L
   b. Moderate: 50 to 99×10^9/L
   c. Severe: 20 to 49×10^9/L
   d. Very severe: < 20×10^9/L
2. Death within 90-days of ICU admission.
3. Days alive and out of hospital within 90-days of ICU admission.
4. Days alive without the use of life-support within 90-days of ICU admission.
5. Number of patients with at least one bleeding episode in the ICU according to the World Health Organisation (WHO) classification[24] (Supplement S5) graded into minor, mild, severe and debilitating bleeding according to the worst graded episode.
6. Number of patients with at least one new thrombotic event in the ICU (Supplement S6).
7. Number of patients that received at least one platelet transfusion during ICU stay, the number of units and volumes transfused and indications (prophylactic, pre-procedural, therapeutic).

The outcomes are further detailed in Supplement S4.

2.7 | Data collection and management

The local investigator or his/her delegate will collect routinely registered data from the medical and laboratory records. Baseline data will be collected at ICU admission and will include patient and admission characteristics, comorbidities, laboratory values including platelet count, treatments, acute conditions including sepsis and septic shock,[25] bleeding, platelet transfusions, and the Simplified Mortality Score in the Intensive Care Unit (SMS-ICU)[26,27] (further details and definitions of baseline variables are provided in Supplement S7 and S14). Daily data will be collected during ICU stay at the participating ICUs to a maximum of 90 days, and will include the use of life-support, treatments, laboratory values including platelet counts, bleeding episodes graded according to the WHO classification (Supplement S5), thrombotic events (Supplement S6), and platelet transfusions (further details and definitions of variables registered daily during ICU stay are provided in Supplement S8–S10). Data on discharges and readmissions from the ICU will also be registered (see Supplement S11). The 90-day follow-up data will be collected by assessing medical records, national registers, or by phone call as appropriate according to local or national regulations and will include vital status and hospital discharges and readmissions (details and definitions of follow-up variables are provided in Supplement S12). Lastly, we will collect data on participating sites including type of hospital, type and size of the ICU, and the presence of general or specific guidelines regarding platelet transfusions (see Supplement S13 for details). The local investigator or his/her delegate will be responsible for data accuracy and ensure the completeness of data after the follow-up period has ended.

The study data will be collected and managed using the REDCap electronic data capture tool hosted at the Capital Region of Denmark.[28,29] REDCap is a secure, web-based software platform that supports data capture for research studies and includes data-validation tools and audit trials. All included patients will be assigned a unique study identification (ID) number and data will be handled in accordance with all applicable regulations. Each investigator or his/her delegates will be assigned a personal login with access to enter and read data for patients enrolled at their site only. A detailed manual describing all aspects related to data-entry and management will be provided to the local investigators and educational meetings with members of the core research team will be encouraged prior to initiation of the study at each site.

2.8 | Statistical methods

2.8.1 | Sample size justification

Assuming a frequency of 'any thrombocytopenia' in the ICU of 20%[4,30] a sample size of minimum 1000 patients is necessary to determine the frequency with a 95% confidence interval of 18%–23%.

2.8.2 | Population to be analysed

We plan to analyse all enrolled patients.

TABLE 1 Baseline data

	All patients	Patients without thrombocytopenia (n = XXX)	Patients with any thrombocytopenia[a] (n = XXX)	Patients with thrombocytopenia at baseline[b] (n = XXX)	Patients with thrombocytopenia during ICU stay[c] (n = XXX)	Patients with missing values (n = XX)
Age, years	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	*n* (%)
Female gender	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Source of admission[d]						
- Emergency department	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Hospital ward	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Operating or recovery room	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Another ICU	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Surgery[d]	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Elective	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Acute	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Main reason for ICU admission[d]						
- Neurological condition	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Respiratory failure	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Circulatory failure	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Renal failure	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Lever failure	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Metabolic condition	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Multiple trauma	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Burn injury	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Severe haemorrhage	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Other	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Acute conditions[d]						
- Sepsis	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Septic shock	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Acute liver failure	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- COVID-19	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
SMS-ICU[e]	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	*n* (%)
Comorbid conditions[d]						
- Pulmonary disease	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Heart disease	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Chronic liver failure	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Chronic renal failure	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Solid tumour cancer	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Metastatic cancer	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Haematological malignancy	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Non-malignant haematological emergency	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Chronic spleen enlargement	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Immune deficiency	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Coagulation disorder	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Previous thrombo-embolism[f]	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)

TABLE 1 (Continued)

	All patients	Patients without thrombocytopenia (n = XXX)	Patients with any thrombocytopenia[a] (n = XXX)	Patients with thrombocytopenia at baseline[b] (n = XXX)	Patients with thrombocytopenia during ICU stay[c] (n = XXX)	Patients with missing values (n = XX)
Treatments[d]						
- HSCT	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Chemotherapy	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Non-chemotherapy drugs affecting platelets	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Anticoagulating therapy	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
- Platelet inhibitors	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Laboratory values[d]						
- Habitual platelet count	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	*n* (%)[g]
- Platelet count at ICU admission	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	*n* (%)
- WBC count	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	*n* (%)
- INR > 1.5	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Any WHO bleeding[h]	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Patients transfused with platelets[d]	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)

Abbreviations: HCST, haematopoietic stem cell transplantation; ICU, intensive care unit; INR, international normalised ratio; WBC, white blood cell; WHO, World Health Organization.
[a]Patients with at least one recorded platelet count below 150 × 10^9/L at baseline and/or during ICU stay.
[b]Patients with at least one recorded platelet count below 150 × 10^9/L within 24 h prior to ICU admission.
[c]Patients with at least one recorded platelet count < 150 × 10^9/L during ICU stay without pre-existing thrombocytopenia at baseline.
[d]Definitions of baseline variables are available in Supplement S7.
[e]Details on the SMS-ICU score are available in Supplement S14.
[f]Definitions of thrombo-embolic events are available in Supplement S6.
[g]Number of habitual platelet counts estimated.
[h]WHO classification is available in Supplement S5.

TABLE 2 Number of patients with thrombocytopenia

	Thrombocytopenia at baseline[a]	Thrombocytopenia during ICU stay[b]	Any thrombocytopenia[c]
Overall: <150 × 10^9/L	*n* (%)	*n* (%)	*n* (%)
Subclasses			
- Mild: 100–149 × 10^9/L	*n* (%)	*n* (%)	*n* (%)
- Moderate: 50–99 × 10^9/L	*n* (%)	*n* (%)	*n* (%)
- Severe: 20–49 × 10^9/L	*n* (%)	*n* (%)	*n* (%)
- Very severe: <20 × 10^9/L	*n* (%)	*n* (%)	*n* (%)

Abbreviation: ICU, intensive care unit.
[a]Patients with at least one recorded platelet count < 150 × 10^9/L and within the specified subclasses within 24 h prior to ICU admission.
[b]Patients with at least one recorded platelet count < 150 × 10^9/L and within the specified subclasses according the nadir platelet count during ICU stay without pre-existing thrombocytopenia at baseline.
[c]Patients with at least one recorded platelet count < 150 × 10^9/L at baseline and/or during the ICU stay and within the specified subclasses according the nadir platelet count.

2.8.3 | Baseline data

We will present baseline data as outlined in Table 1. Continuous variables will be presented as medians with interquartile ranges (IQR) and categorial variables as numbers and percentages.

2.8.4 | Number of patients with thrombocytopenia

We will report the number of patients with 'any thrombocytopenia', 'thrombocytopenia at baseline' and 'thrombocytopenia during ICU stay' and the number of patients within the subclasses

TABLE 3 Risk factors for development of thrombocytopenia during ICU stay

	Thrombocytopenia during ICU stay[a] (<150 × 10^9/L)		Severe thrombocytopenia during ICU stay[b] (<50 × 10^9/L)	
	Unadjusted OR (95% CI)	Adjusted[c] OR (95% CI)	Unadjusted OR (95% CI)	Adjusted[c] OR (95% CI)
Gender (female)	-	-	-	-
SMS-ICU[d]	-	-	-	-
Any WHO bleeding[e]	-	-	-	-
Haematological malignancy	-	-	-	-
Immune deficiency[f]	-	-	-	-
Liver failure[f]	-	-	-	-
Septic shock[f]	-	-	-	-

Abbreviations: ICU, intensive care unit; WHO, World Health Organization.
[a]Patients with at least one recorded platelet count < 150 × 10^9/L during ICU stay without pre-existing thrombocytopenia at baseline.
[b]Patients with at least one recorded platelet count < 50 × 10^9/L during ICU stay without pre-existing thrombocytopenia at baseline.
[c]Adjusted for the following baseline variables: gender, SMS-ICU, any WHO bleeding, haematological malignancy, immune deficiency, liver failure (acute and chronic) and septic shock.
[d]Details on SMS-ICU is available in Supplement S14.
[e]Definitions of the WHO classification is available in Supplement S5.
[f]Definitions of baseline variables are available in Supplement S7.

TABLE 4 Association between thrombocytopenia at baseline[a] and 90-day mortality

	Adjusted OR (95% CI)[b]
Overall (<150 × 10^9/L)	-
Severe (<50 × 10^9/L)	-

[a]Patients with a platelet count of less than 150 × 10^9/L and within the specified subclass within 24 h prior to ICU admission.
[b]Adjusted for gender, SMS-ICU, haematological malignancy, country and septic shock at ICU admission.

defined above for each category as numbers and percentages as outlined in Table 2.

2.8.5 | Risk factors for developing thrombocytopenia during the ICU stay

We will use multiple logistic regression analysis to assess baseline risk factors for developing thrombocytopenia (platelet count < 150 × 10^9/L) and severe thrombocytopenia (platelet count < 50 × 10^9/L) during the ICU stay in patients without thrombocytopenia at baseline. Based on a literature review[4] we will assess the following baseline variables: gender (f/m), SMS-ICU[26,27] (continuous scale from 0 to 42), any WHO bleeding (y/n), co-existing haematological malignancy (y/n), immune deficiency (non-AIDS related immune deficiencies requiring treatment with immunosuppressive drugs) (y/n), liver failure (acute or chronic) (y/n) and septic shock (y/n). The results will be presented as unadjusted and adjusted odds ratios (ORs) with 95% CIs for each risk factor as outlined in Table 3.

2.8.6 | The association between thrombocytopenia at baseline and 90-day mortality

We will use multiple logistic regression analysis to assess the association between thrombocytopenia (platelet count < 150 × 10^9/L) and severe thrombocytopenia (platelet count < 50 × 10^9/L) at baseline and 90-day mortality and we will present the results as adjusted ORs with 95% CIs as outlined in Table 4. The analyses will be adjusted for the following baseline variables: gender (f/m), SMS-ICU[26,27] (continuous scale from 0 to 42), haematologic malignancy (y/n), country and septic shock (y/n).

2.8.7 | Descriptive data

We will report results for the following secondary outcomes descriptively stratified on patients with 'any thrombocytopenia' (overall and within the subclasses defined above), 'thrombocytopenia at baseline' and 'thrombocytopenia during ICU stay':

- Death within 90 days of ICU admission.
- Days alive and out of hospital within 90 days of ICU admission.
- Days alive without the use of life-support within 90-days of ICU admission
- Number of patients with at least one bleeding episode according to the WHO classification within 90 days of ICU admission.
- Number of patients with at least one new thromboembolic event within 90 days of ICU admission.
- Number of patients transfused with platelets, number of units and volume (ml) transfused per patient and indications.

TABLE 5 Secondary outcomes

	No thrombocytopenia (n = xxx)	Any thrombocytopenia[a] (n = xxx)					Thrombocytopenia at baseline[b]	Thrombocytopenia during ICU stay[c]
		<150 (n = xxx)	100–149 (n = xxx)	50–99 (n = xxx)	20–49 (n = xxx)	<20 (n = xxx)		
Death, n (%)	-	-	-	-	-	-	-	-
Days alive and out of hospital, median (IQR)	-	-	-	-	-	-	-	-
Days alive without life-support, median (IQR)	-	-	-	-	-	-	-	-
WHO bleeding 1–4,[d] *n (%)*	-	-	-	-	-	-	-	-
- Grade 1, *n (%)*	-	-	-	-	-	-	-	-
- Grade 2, *n (%)*	-	-	-	-	-	-	-	-
- Grade 3, *n (%)*	-	-	-	-	-	-	-	-
- Grade 4, *n (%)*	-	-	-	-	-	-	-	-
Thrombotic events,[e] *n (%)*	-	-	-	-	-	-	-	-
Platelet transfusions								
- Patients transfused, *n (%)*[f]	-	-	-	-	-	-	-	-
- Units, median (IQR)[g]	-	-	-	-	-	-	-	-
- Volume (ml), median (IQR)[g]	-	-	-	-	-	-	-	-
- Indications[h]								
- Prophylactic (%)	-	-	-	-	-	-	-	-
- Pre-procedural (%)	-	-	-	-	-	-	-	-
- Therapeutic (%)	-	-	-	-	-	-	-	-

Abbreviation: WHO, World Health Organization.
[a]Patients with at least one recorded platelet count baseline or during the ICU stay below 150 × 10^9/L and within the specified subclasses according the nadir platelet count.
[b]Patients with at least one recorded platelet count below 150 × 10^9/L within 24 h prior to ICU admission.
[c]Patients with at least one recorded platelet count < 150 × 10^9/L during ICU stay without pre-existing thrombocytopenia at baseline.
[d]Number of patients with at least one WHO grade 1–4 bleeding episode and stratified according to the worst graded bleeding episode.
[e]Number of patients with at least one new thrombotic event in the ICU.
[f]Number of patient receiving at least one platelet transfusion in the ICU.
[g]Number of units and volume transfused in the ICU per patient.
[h]Definitions of the indications is available in Supplement S4.

Continuous variables will be presented as medians with IQRs and categorical variables as numbers and percentages. The results will be reported as outlined in Table 5.

2.9 | Handling of missing data

We will report missingness as numbers with percentages. For missing platelet counts, we will use logical imputation. As we classify thrombocytopenia based on at least one recorded platelet count, it follows that we will assume that patients with no available platelet counts (on baseline and during ICU stay) do not have thrombocytopenia as there has been no clinical reason to measure a platelet count. If a patient has no recorded platelet count on baseline, we will, however, assume that this value is equal to the first available platelet count in the ICU. If a patient has a recorded platelet count on baseline, but none during their ICU stay, we will assume that at least one platelet count during ICU (i.e., on the first ICU day) is equal to the baseline value.

For the analyses of risk factors for developing thrombocytopenia during ICU stay and the association between thrombocytopenia at baseline and mortality, we will handle remaining missingness as follows: if less than 5% of the patients have missing data for the variables included in an analysis, we will report complete case analyses (excluding patients with missing data) as the primary analysis.[31] If 5% or more of the patients have missing data, we will use multiple imputed data in said analysis assuming that data are 'missing at random' and create 25 imputed datesets.[31,32] If multiple imputation is used, we will report analyses on the imputed data as the primary analyses and perform corresponding complete case analyses as a sensitivity analysis.

Throughout the study, we will contact local investigators regarding missing data to reduce missingness. Any additional details on the handling of missing data will be reported in the manuscript.

3 | ADMINISTRATIVE ASPECTS

3.1 | Confidentiality

All data from the included patients will be held in strict confidence by the study sponsor, research staff and investigators. No data or information concerning the study will be released by any unauthorised third party, without prior written approval of the sponsoring institution. All reports that leave participating sites will be identified only by the unique study ID number to ensure confidentiality.

4 | PUBLICATION POLICY

We will submit the manuscript to an international peer-reviewed journal. The manuscript will be drafted by the study steering committee and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[33] All investigators will declare any conflicts of interests. Deviations from the protocol (if any) will be reported with reasoning in a supplement to the manuscript. Funding sources will not have any influence on the conduct, data handling, analyses, or reporting of the study results. Sub studies will be encouraged after a written protocol has been approved by the management committee and data transfer has been approved by relevant authorities.

4.1 | Authorship

Authorship will be granted to members of the steering committee, national and local investigators in accordance with the guidelines from the International Committee for Medical Journal Editors (ICMJE; http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). All other research personnel or persons contributing to the study will be acknowledged as 'PLOT-ICU cohort study collaborators' in a supplement to the manuscript.

5 | DISCUSSION

Thrombocytopenia is a common condition in the ICU[1–3] and has been associated with worse outcomes.[4] However, there is uncertainty about the clinical implications of thrombocytopenia in the ICU, as the evidence base has methodological issues and is conflicting.[4] Platelet transfusions are recommended to ICU patients with severe thrombocytopenia and risk of bleeding[16] but surveys have indicated variable clinical practise.[13,17] Therefore, contemporary prospective observational studies providing epidemiological data on the current burden of thrombocytopenia in the ICU, its risk factors and outcome, and platelet transfusion practices are warranted. The PLOT-ICU cohort will provide these data and assist in the planning of future randomised clinical trials within the area.

The strengths of the PLOT-ICU cohort study will include the international collaboration, predefined variables of interests and outcomes as well as the predefined statistical analysis plan. Further, the study will be reported according to the STROBE statement.[33] This will increase internal and external validity and transparency of the reported results. The study will also have important limitations. First, the assumption that patients without any recorded platelet count do not have thrombocytopenia may potentially lead to an underestimation of the number of patients with thrombocytopenia. Second, patients lost to follow-up, incomplete data collection and missing data may lower precision and introduce bias. Third, as thrombocytopenia in ICU patients often results from multiple causes[9] and as ICU patients constitute a heterogeneous population, it is impossible to adjust for all possible confounders which may increase the risk of residual confounding. Fourth, the number of patients with severe thrombocytopenia may be low which could reduce the statistical power in the risk factor analysis and increase the risk of type two errors. Fifth, we do not plan to adjust for multiple testing which may increase the risk of type one errors. Thus, the analyses of risk factors and the association between baseline thrombocytopenia and mortality will be interpreted as exploratory.

In conclusion, the PLOT-ICU cohort study will provide important epidemiological information about thrombocytopenia and platelet transfusion practices in acutely admitted adult ICU patients. The results will inform the planning of a future randomised clinical trial assessing the benefits and harms of platelet transfusions in adult ICU patients.

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CONFLICT OF INTEREST

The Department of Intensive Care 4131 at Rigshospitalet (CTA, MHM, AP, LR) has received funding for other projects from the Novo Nordisk Foundation, Pfizer, Ferring Pharmaceuticals and Fresenius Kabi and conducts contract research for AM-Pharma. PP had received honoraria for lectures and participation in advisory boards from Merck Sharp & Dohme, Sanofi, Gilead and Pfizer.

DATA AVAILABILITY STATEMENT

No data is included in this publication.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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