Electronic Supplementary Material (ESM)

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplement to:

Anthon CT, Pène F, Perner A et al. Thrombocytopenia and platelet transfusions in ICU patients: an international inception cohort study (PLOT-ICU)

Corresponding author:

Lene Russell, MD, PhD
E-mail: lene.russell@mail.dk

Contents

ESM 1. Additions and changes to the protocol

Additions	**Reason**
Confidence intervals for the primary outcome and secondary outcomes.	We chose to provide 95% confidence intervals for the primary and secondary outcomes to provide estimates for the uncertainty. These are presented in the main text, ESM 19 and 20.
Platelet count before platelets transfusions in the ICU.	To describe the current practice, we chose to present data on platelet counts before platelet transfusions used in the ICU (in-ICU) for each indication (prophylaxis, therapeutic, pre-procedural). These are presented as median and IQR for each indication in the main text. Further, we presented medians, IQRs and ranges for specific procedures in ESM 23. For each day with in-ICU platelet transfusions, we had the following platelet counts available for analysis: - The lowest platelet count. - A platelet count before prophylactic platelet transfusion. - A platelet count before therapeutic platelet transfusion. - A platelet count before pre-procedural platelet transfusion. If more than one transfusion was used for the same indication on the same day, the platelet count registered before transfusion for that indication corresponded to the highest platelet count before any of the platelet transfusions given for that indication. Therefore, we made the following assumption: - On days where ≥ 2 transfusions were used for the same indication, we assumed that the lowest platelet count registered on that day was the trigger for the first transfusion and that the platelet count registered before transfusions for the specific indication(s) was the trigger for the remaining transfusions.
Number of RBC transfusions during ICU stay.	To describe the outcomes of patients with thrombocytopenia, we chose to present data on RBC transfusions. Data are presented as the number of patients with at least one transfusion and as median (IQR) transfusions per patient. Results are presented in the main text.
Changes were made to the definition of “immune deficiency”.	We planned to examine the effect of “immunocompromised status” on thrombocytopenia. To include all immunocompromised patients (and not just patients with cancer), we asked investigators to collect data on whether patients were considered to have an immune deficiency defined as non-AIDS-related immune deficiencies (including solid organ transplant) or conditions

	requiring long-term (> 30 days) or high-dose (> 1 mg/kg/day) steroids, or any immunosuppressive drug for more than 30 days. However, the definition used above was insufficient and led to uncertainty about whether patients who had received chemotherapy were included or not in this group, thereby, the extent of overlap with patients with solid tumour cancer and haematological malignancy was uncertain. Therefore, we chose to only include patients with non-cancer-related immune deficiencies, thereby defining "immune deficiency" in the final analysis as "non-AIDS-, non-cancer-related immune deficiencies (including solid organ transplant) or conditions requiring long-term (> 30 days) or high-dose (> 1 mg/kg/day) steroids, or any immunosuppressive drug for more than 30 days".

Abbreviations: intensive care unit (ICU), interquartile range (IQR), red blood cell (RBC), acquired immune deficiency syndrome (AIDS).

ESM 2. Strengthening the reporting of observational studies in epidemiology (STROBE) checklist.

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	p.1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	p. 11
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	p. 13
Objectives	3	State specific objectives, including any prespecified hypotheses	p. 13
Methods			
Study design	4	Present key elements of study design early in the paper	p. 14
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	p. 14–15, ESM 4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	p. 14
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	p 15–16, ESM 6–12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	p 15–16, ESM 6–12
Bias	9	Describe any efforts to address potential sources of bias	p. 17
Study size	10	Explain how the study size was arrived at	p. 16–17
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	p. 17
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	p. 17

		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	p. 18, ESM 13
		(*d*) If applicable, explain how loss to follow-up was addressed	p. 18, ESM 13
		(*e*) Describe any sensitivity analyses	p. 18, ESM 25, 27
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	p. 19, ESM 14
		(b) Give reasons for non-participation at each stage	p. 19, ESM 14
		(c) Consider use of a flow diagram	ESM 14
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	p. 19, Table 1, ESM 16
		(b) Indicate number of participants with missing data for each variable of interest	Table 1, 2, ESM 16
		(c) Summarise follow-up time (eg, average and total amount)	p. 14
Outcome data	15*	Report numbers of outcome events or summary measures over time	p. 19 – 21, table 2, EMS 18
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	p. 17, p.21, Table 3, ESM 26
		(*b*) Report category boundaries when continuous variables were categorized	NA
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	p. 21, ESM 25, 27
Discussion			
Key results	18	Summarise key results with reference to study objectives	p. 22

Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	p. 23 - 24
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	p. 25
Generalisability	21	Discuss the generalisability (external validity) of the study results	p. 23–24
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	p. 9–10

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

ESM 3. Participating countries and national investigators

National investigator(s)	Country	Centre
Lene Russell (PI)	Denmark	Department of Intensive Care, Copenhagen University Hospital – Rigshospitalet, Copenhagen
Frédéric Pène	France	Médecine Intensive & Réanimation, Hôpital Cochin, Assistance Publique – Hôpitaux de Paris, Université Paris Cité, Paris
Kathryn Puxty	UK	Department of Intensive Care, Glasgow Royal Infirmary, Glasgow
Andreas Barratt-Due	Norway	Department of Anaesthesia and Intensive Care Medicine, Division of Emergencies and Critical Care, Rikshospitalet, Oslo University Hospital, Oslo
Andry Van De Louw	USA	Division of Pulmonary and Critical Care, Penn State University College of Medicine, Hershey, Pennsylvania
Pedro Castro	Spain	Medical Intensive Care Unit, Hospital Clinic of Barcelona, IDIBAPS, University of Barcelona, Barcelona
Pedro Povoa, Luis Coelho	Portugal	Department of Intensive Care, Sao Francisco Xavier Hospital, CHLO, Lisbon
Thomas Kander	Sweden	Department of Intensive and Perioperative Care, Skåne University Hospital, Lund
Matthias Kochanek	Germany	Department I of Internal Medicine, Faculty of Medicine and University Hospital Cologne, University of Cologne, Cologne
Johanna Hästbacka	Finland	Department of Perioperative and Intensive Care Medicine, University of Helsinki and Helsinki University Hospital, Helsinki

Abbreviations: principal investigator (PI), United States of America (USA), United Kingdom (UK).

ESM 4. Participating sites and investigators

Site investigator(s) and contributor(s)	Country	Department(s)	Inclusion period (both dates included)
Carl T. Anthon (SI) Lene Russell Anders Granholm Morten H. Møller Anders Perner	Denmark	Department of Intensive Care, Copenhagen University Hospital – Rigshospitalet, Copenhagen	14-05-21 to 27-05-21
Thomas Hildebrandt (SI)	Denmark	Departments of Intensive Care, Zealand University Hospital - Department of Intensive Care Roskilde - Department of Intensive Care Koege	25-05-21 to 07-06-21
Mette Krag (SI) Moritz K. G.Denneborg	Denmark	Department of Intensive Care, Holbaek Hospital, Holbaek	29-11-21 to 12-12-21
Niels Clausen (SI)	Denmark	Department of Anaesthesia and Intensive Care, Copenhagen University Hospital - Bispebjerg and Frederiksberg, Copenhagen	01-07-21 to 14-07-21
Morten H. Bestle (SI) Frederik H. Bestle	Denmark	Department of Anaesthesiology and Intensive Care, Copenhagen University Hospital - North Zealand, Hilleroed	07-09-21 to 20-09-21
Kristian Lorentzen (SI)	Denmark	Department of Intensive Care, Copenhagen University Hospital – Herlev and Gentofte, Herlev	04-10-21 to 17-10-21
Lene B. Nielsen (SI)	Denmark	Department of Anaesthesiology and Intensive Care, Odense University Hospital, Odense	13-09-21 to 26-09-21
Jo B. Andreasen (SI) Anne-Marie Bunzel Rine M. Siegumfeldt Stine R. Vestergaard Olav L. Schjørring	Denmark	Departments of Anaesthesia and Intensive Care, Aalborg University Hospital, Aalborg - Neurological Intensive Care Unit - General Intensive Care Unit - Thoracic Intensive Care Unit	24-09-21 to 07-10-21

Christine L. Hvas (SI) Maria Toppenberg	Denmark	Department of Anaesthesiology and Intensive Care, Aarhus University Hospital, Aarhus	01-01-22 to 14-01-22
Christian S. Juhl (SI)	Denmark	Department of Anaesthesiology, Copenhagen University Hospital – Amager and Hvidovre, Hvidovre	01-05-22 to 14-05-22
Andreas Barratt-Due (SI) Cecilie Christoffersen	Norway	Department of Anaesthesia and Intensive Care Medicine, Division of Emergencies and Critical Care, Rikshospitalet, Oslo University Hospital, Oslo	31-01-22 to 13-02-22
Aleksander R. Holten (SI)	Norway	Department of Acute Medicine, Oslo University Hospital, Oslo	22-11-21 to 05-12-21
Per Martin Bådstøløkken (SI)	Norway	Department of Intensive Care, Akershus University Hospital, Lorenskog	10-01-22 to 23-01-22
Reidar Kvåle (SI) Brit Sjøbø	Norway	Department of Anaesthesia and Intensive Care, Haukeland University Hospital, Bergen	22-11-21 to 05-12-21
Kristian Strand (SI)	Norway	Department of Intensive Care, Stavanger University Hospital, Stavanger	22-11-21 to 05-12-21
Pål Klepstad (SI)	Norway	Department of Intensive Care Medicine, St Olavs University Hospital, Trondheim	17-11-21 to 31-11-21
Frédéric Péne Edwige Péju (SI) Juliette Pelle Minh-Pierre Le Clara Vigneron Morgane Bertrix Paul Cirera Driss Laghlam Swann Bredin Marin Nathalie	France	Médecine Intensive & Réanimation, Hôpital Cochin, Assistance Publique – Hôpitaux de Paris, Université Paris Cité, Paris.	26-11-21 to 09-12-21
Damien Vimpere (SI)	France	Médecine Intensive & Réanimation, Hôpital Necker, Assistance Publique – Hôpitaux de Paris, Université Paris Cité, Paris	10-06-22 to 23-06-22
Sophie Meant (SI)	France	Service de Médecine Intensive-Réanimation (Département "R3S"), Hôpital Pitié-Salpêtrière,	27-02-22 to 12-03-22

		Assistance Publique – Hôpitaux de Paris, Sorbonne Université, Paris	
Guillaume Voiriot (SI) Manal K. Mecheri Alexandre Elabbadi Cyrielle Desnos	France	Service de Medecine Intensive Reanimation, Hôpital Tenon, Assistance Publique – Hôpitaux de Paris, Sorbonne Université, Paris	14-03-22 to 27-03-22
Julien Schmidt (SI)	France	Service de réanimation médico-chirurgicale, Hôpital Avicenne, Assistance Publique – Hôpitaux de Paris, Paris	13-03-22 to 26-03-22
Etienne Dufranc (SI) Brice Benelli	France	Service de Médecine Intensive Réanimation, Hôpitaux Universitaires Henri-Mondor, Assistance Publique–Hôpitaux de Paris, Paris	14-03-22 to 27-03-22
Fabrice Uhel (SI) Coralie Gernez Ingrid Thiry	France	Médecine Intensive Réanimation, Assistance Publique – Hôpitaux de Paris, Hôpital Louis Mourier, DMU ESPRIT, Paris	11-02-22 to 24-02-22
Hafid Ait-Oufella (SI) Louai Missri	France	Service de Médecine Intensive-Réanimation, Hôpital Saint-Antoine, Assistance Publique – Hôpitaux de Paris, Sorbonne Université, Paris	06-12-21 to 19-12-21
Elie Azoulay (SI) Antoine Lafarge Olfa Mghirbi	France	Médecine Intensive & Réanimation, Hôpital Saint-Louis, Assistance Publique – Hôpitaux de Paris, Université Paris Cité, Paris	06-12-21 to 19-12-21
Emmanuel Canet (SI) Amélie Seguin Charlotte Garret Florian Guillotin Gauthier Blonz Jean-Baptiste Lascarrou Jérémie Lemarie Luc Desmedt Maïté Agbakou Mathieu Carpentier Maëlle Martin Naïla Benkalfate Olivier Zambon Paul Decamps Pauline L. Wilquin Soraya Benguerfi	France	Médecine Intensive Réanimation, CHU de Nantes, Nantes, France; Université de Nantes, Nantes	17-01-22 to 30-01-22

Thomas Kander Linda Lundqvist (SI)	Sweden	Department of Intensive and Perioperative Care, Skåne University Hospital, Lund Department of Intensive and Perioperative Care, Skåne University Hospital, Malmö	16-04-22 to 29-04-22
Pedro Castro Sara Fernandez (SI)	Spain	Medical Intensive Care Unit, Hospital Clinic of Barcelona, University of Barcelona, Barcelona.	22-04-22 to 05-05-22
Cándido Diaz Lagares (SI) Vanessa Casares	Spain	Intensive Care Department, Vall d'Hebron Hospital Universitari, Vall d'Hebron, Barcelona.	18-07-22 to 31-07-22
Elisabet Cos Badia	Spain	Department of Intensive Care, Hospital General Granollers, Barcelona.	03-07-2022 to 16-07-22
Pedro Povoa Luis Coelho Maria T. Miranda (SI)	Portugal	Department of Intensive Care, Sao Francisco Xavier Hospital, CHLO, Lisbon	24-06-22 to 07-07-22
Carolina Costa (SI) Cristiana V. Gonçalves Nuno M. B. Jacinto Monica P. Anselmo	Portugal	Intensive Care Unit, Hospital Professor Doutor Fernando Fonseca, EPE, Amadora	08-05-22 to 21-05-22
Joao C. S. Torres (SI) Lia S. A. Lêdo (SI) Pedro M. S. Freire	Portugal	Departments of Intensive Care Medicine, Hospital Egas Moniz - CHLO, EPE, Lisbon - Department of intensive care unit 1 - Department of intensive care unit 2	20-06-22 to 03-07-22
Maria C. Paulino (SI)	Portugal	Department of Intensive Care, Hospital da Luz Lisboa, Lisbon	30-06-22 to 13-07-22
Carina Graça (SI) Claudia Lemos	Portugal	Department of Intensive Care, Hospital Central do Funchal, Funchal, Madeira Island	04-07-22 to 17-07-22
Andry Van de Louw (SI)	USA	Division of Pulmonary and Critical Care, Penn State University College of Medicine, Hershey, Pennsylvania	20-03-22 to 02-04-22
Sanjay Chawla (SI) Sheila Carr Natalie Remor Gloria Yang	USA	Critical Care Medicine Service, Department of Anesthesiology & Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York	02-05-22 to 15-05-22

Johanna Hästbacka (SI) Mirka Sivula Elina Lappi Leena Pettilä Jonna Heinonen Minttu Saario	Finland	Department of Perioperative and Intensive Care Medicine, University of Helsinki and Helsinki University Hospital, Helsinki	31-05-22 to 13-06-22
Kathryn Puxty (SI) Katherine Brown	UK	Department of Intensive Care, Glasgow Royal Infirmary, Glasgow	19-04-22 to 02-05-22
Christopher Wright (SI) John Gardner	UK	Critical Care Unit, Queen Elizabeth University Hospital, Glasgow	03-06-22 to 16-06-22
Victoria Metaxa (SI) Ahmed Khalil Ahmed Yehia Haney Salem Hesham Farahat Manu Sudevan Melissa Biggart Nirmeen Fatima Mohammed Elkhonezy	UK	Departments of Critical Care, King's College Hospital NHS Foundation Trust, London - Frank Stansil Critical Care Unit - Christine Brown Critical Care Unit - Jack Steinberg Critical Care Unit - Critical Care Unit A - Critical Care Unit B	13-06-22 to 26-06-22
Catherina Lueck (SI) Marius M. Hoeper	Germany	Interdisciplinary Intensive Care Unit, Hannover Medical School, Hannover	07-06-22 to 20-06-22
Asterios Tzalavras (SI)	Germany	Department of Hematology and Stem Cell Transplantation, University Hospital Essen, Essen	18-07-22 to 31-07-22

Abbreviations: site investigator (SI), United States of America (USA), United Kingdom (UK).

ESM 5. Steering Committee

Name	Affiliation
Elie Azoulay, MD PhD	Médecine Intensive & Réanimation, Hôpital Saint-Louis, Assistance Publique – Hôpitaux de Paris, Université Paris Cité, Paris, France.
Frédéric Pène, MD, PhD	Médecine Intensive & Réanimation, Hôpital Saint-Louis, Assistance Publique – Hôpitaux de Paris, Université Paris Cité, Paris, France.
Kathryn Puxty, MD, PhD	Department of Intensive Care, Glasgow Royal Infirmary, Glasgow, UK
Anders Perner, MD, PhD	Department of Intensive Care, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark. [a]
Lene Russell, MD, PhD	Department of Intensive Care, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark. [a]
Morten Hylander Møller, MD, PhD	Department of Intensive Care, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark. [a]
Carl Thomas Anthon, MD	Department of Intensive Care, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark. [a]

[a] Coordinating centre.

ESM 6. Site variables and definitions

Site characteristics

- **Type of hospital.**
  o University hospital.
  o Non-university hospital.
 	
- **Type of ICU.**
  o Medical ICU.
  o Surgical ICU.
  o Mixed ICU.
 	
- **Number of beds open for admission**.
  o < 10.
  o 10-19.
  o 20-29.
  o ≥ 30.
 	
- **Presence of a general guideline/protocol for platelet transfusions in the hospital.**
 	
- **Presence of a specific guideline/protocol for platelet transfusions in the ICU.**

ESM 7. Simplified Mortality Score for the Intensive Care Unit (SMS-ICU).

Variable	Points
Age	
≤ 39 years	0
40 – 59 years	5
60 – 79 years	10
≥ 80 years	13
Lowest systolic blood pressure	
≤ 49 mmHg	6
50 – 69 mmHg	5
70 – 89 mmHg	3
≥ 90 mmHg	0
Acute surgical admission	
No	3
Yes	0
Haematological malignancy or metastatic cancer	
No	0
Yes	7
Vasopressors/inotropes [a]	
No	0
Yes	4
Respiratory support [b]	
No	0
Yes	5
Renal replacement therapy [c]	
No	0
Yes	4
Total score	0-42 [d]

Total score and predicted 90-day mortality risk			
0	3.3%	22	40.1%
3	4.8%	23	43.4%
4	5.5%	24	46.7%
5	6.2%	25	50.1%
6	7.1%	26	53.5%
7	8.0%	27	56.9%
8	9.1%	28	60.2%
9	10.3%	29	63.4%
10	11.6%	30	66.4%
11	13.1%	31	69.4%
12	14.7%	32	72.2%
13	16.5%	33	74.8%
14	18.4%	34	77.3%
15	20.5%	35	79.6%
16	22.8%	36	81.7%
17	25.3%	37	83.7%
18	28.0%	38	85.4%
19	30.8%	39	87.0%
20	33.8%	41	89.8%
21	36.9%	42	91.0%

Reproduced from a previous paper [1].

[a] Continuous use of any vasopressor or inotrope.

[b] Use of respiratory support, including invasive or non-invasive respiratory support and continuous use of continuous positive airway pressure (CPAP). Intermittent use of CPAP is not considered respiratory support. For this study, we only collected data on the use of mechanical ventilation and did not consider non-invasive respiratory support and continuous CPAP.

[c] Use of renal replacement therapy includes any renal replacement therapy whether chronic or acute, including continuous renal replacement therapy and intermittent haemodialysis, including the days in between intermittent haemodialysis.

[d] Points assigned for the different variables in the score. It is not possible to obtain a total score of 1, 2 or 40 points. The worst value recorded during the first day in the ICU is used [1, 2].

ESM 8. Baseline variables and definitions

Patient and admission characteristics

- **Age (years).**
  Age at ICU admission.

- **Gender (male/female).**
  Genotypic gender of the patient.

- **ICU admission date (dd-mm-yyyy).**

- **Hospital admission date (dd-mm-yyyy).**
  Date of admission to the first hospital during the current hospitalization.

- **Source of ICU admission.**
  - Emergency department (any accident/emergency/casualty/acute department or directly from the pre-hospital setting via ambulance service or similar).
  - General ward.
  - Operating or recovery room (any surgical theatre, endoscopy and angiography suite or recovery facilities observing post-operative patients).
  - Another ICU.

- **Elective surgery.**
  Surgery planned 24 hours or more in advance during the current hospitalization but before ICU admission.

- **Emergency surgery.**
  Surgery planned less than 24 hours in advance during the current hospitalisation but before ICU admission.

- **Main reason for ICU admission.**
  - Neurological condition.
  - Respiratory failure.
  - Circulatory failure.
  - Renal failure.
  - Liver failure.
  - Metabolic condition.
  - Multiple trauma.
  - Traumatic brain injury.
  - Burn injury.
  - Severe haemorrhage.
  - Other.

Comorbidities

- **Chronic pulmonary disease.**
  Treatment at time of hospital admission with any relevant drug indicating chronic pulmonary disease (e.g., COPD, asthma) e.g., albuterol, levalbuterol, salmeterol, formoterol, arformoterol, indacaterol, vilanterol, olodaterol, tiotropium, aclidinium, umeclidinium, glycopyrronium, budesonide and fluticasone.

- **Ischaemic heart disease or heart failure.**
  Previous myocardial infarction, invasive intervention for coronary artery disease, stable or unstable angina, NYHA class 3 or 4 or measured LVEF < 40%.

- **Chronic renal failure.**
  Need for chronic renal support including continuous or intermittent renal replacement therapy or S-creatinine > 3.6 g/dL / 300 µmol/L before hospital admission.

- **Chronic liver failure.**
  Including any of the following: portal hypertension, cirrhosis (proven by biopsy, CT scan or ultrasound), history of variceal bleeding or hepatic encephalopathy.

- **Solid tumour cancer.**
  Presence of a solid non-haematological malignant tumour confirmed by surgery, CT scan or any other method.

- **Metastatic cancer.**
  Proven non-haematological metastasis by surgery, CT scan, or any other method.

- **Haematological malignancy.**
  Any of the following: acute lymphoblastic leukaemia, acute myelogenous leukaemia, chronic lymphocytic leukaemia, chronic myelogenous leukaemia, t-cell prolymphocytic leukaemia, b-cell prolymphocytic leukaemia, large granular lymphocytic leukaemia, lymphomas including Hodgkin's lymphoma and non-Hodgkin lymphoma (e.g., small lymphocytic lymphoma, lymphoblastic lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, mantle cell lymphoma, Hairy cell leukaemia, Marginal zone lymphoma, Burkitt's lymphoma, Post-transplant lymphoproliferative disorder, Waldenstöm's macroglobulinemia, natural killer- or T-cell lymphomas), multiple myeloma/plasma cell myeloma, myelodysplastic syndrome, other myeloproliferative neoplasms including chronic neutrophilic leukaemia, primary myelofibrosis and mast cell disease.

- **Non-malignant haematological emergency**.
  Any of the following: thrombotic thrombocytopenic purpura, atypical haemolytic uraemic syndrome, Shiga toxin-producing Escherichia coli haemolytic uraemic syndrome, primary-, secondary- or drug-induced autoimmune haemolytic anaemia, hemophagocytic lymphohistiocytosis, acute antiphospholipid syndrome.

- **Chronic spleen enlargement.**
  Craniocaudal length >13 cm diagnosed by CT scan, ultrasonography or MRI [3].

- **Immune deficiencies.**
  Any non-AIDS related immune deficiency requiring either long-term (> 30 days) or high-dose (> 1 mg/kg/day) steroids, or any immunosuppressive drug for more than 30 days.

- **Hereditary or acquired coagulation disorders.**
  Any of the following: haemophilia A or B, Von Willebrand's disease, inherited deficiencies of factors I (fibrinogen), II (prothrombin), V, VII, X, XI, and XIII, Glanzmann's thrombasthenia, Bernard-Soulier syndrome, Gray platelet syndrome (platelet alpha-granule deficiency), May-Hegglin anomaly, factor V Leiden, prothrombin gene mutation, inherited deficiencies of protein C, S or antithrombin, inherited increased levels of homocysteine, or fibrinogen or dysfibrinogenemia, antiphospholipid antibody syndrome, essential thrombocytosis.

- **History of thrombo-embolism.**
  Venous or arterial thrombo-embolisms as defined in ESM 12.

Treatments before ICU admission

- **Haematopoietic stem cell transplantation.**
  Includes both autologous and allogeneic stem cell transplantations within 1 year before ICU admission.

- **Treatment with chemotherapy.**
  Treatment with chemotherapy within 6 weeks before ICU admission. Includes treatment with any of the following: Bortezomib, Carboplatin, Cisplatin, Cyclophosphamide, Dacarbazine, Docetaxel, Doxirubicin, Etoposide, Fluorouracil, Gemcitabine, Hydroxycarbamide, Ibritumomab tiuxetan, Ifosfamide, Irinotecan, Leucovorin, Methotrexate, Oxaliplatin, Panobinostat, Temozolomide, Tamoxifen, Vincristine.

- **Treatment with drugs that may affect platelet count.**
  Treatment with any of the following drugs within 1 week prior to ICU admission: Piperacillin, Rituximab, Abciximab, Carbamazepine, Valproic acid, Interferon-alfa.

- **Treatment with anticoagulating agents.**
  Includes treatment with unfractionated heparin, low-molecular-weight heparin, new oral anticoagulant drugs, vitamin K-antagonists and intravenous direct thrombin inhibitors in any dose within 48 hours of ICU admission.

- **Treatment with platelet inhibitors.**
  Includes treatment with ADP-receptor inhibitors, acetylsalicylic acid, and dipyridamole within 48 hours of ICU admission.

Acute conditions

- **Acute liver failure at ICU admission.**
  Severe liver injury, potentially reversible in nature and with onset of hepatic encephalopathy within eight weeks of the first symptoms (i.e., jaundice) in the absence of pre-existing liver disease [4, 5].

- **Sepsis during the first 24 hours of ICU admission.**
  A suspected or confirmed site of infection or positive blood culture AND an acute change in total SOFA score ≥ 2 points consequent to the infection [6].

- **Septic shock during the first 24 hours of ICU admission.**
  A suspected or confirmed site of infection or positive blood culture AND ongoing infusion of vasopressor/inotrope agent to maintain a mean arterial blood pressure of 65 mmHg or above AND lactate of 2 mmol/L or above in any plasma sample [6].

- **Coronavirus disease 2019 (COVID 19).**
  Any sample from airway secretions or nasopharyngeal swab positive for COVID-19 at any time leading to or during current hospital admission before ICU admission.

Biochemistry

- **Habitual platelet count.**
  Highest platelet count within 6 months prior to current hospitalisation. If no value was available, the highest platelet count within 12 months prior to hospitalisations was used. If no platelet count within 12 months before hospitalisation was available, the habitual platelet count was estimated. Unit: cells $x10^9$/L.

- **Platelet count.**
  Latest platelet count within 24 hours prior to ICU admission. Unit: cells $x10^9$/L.

- **White blood cell count.**
  Latest white blood cell count within 24 hours prior to ICU admission. Unit: cells $x10^9$/L.

- **International normalised ratio.**
  Latest INR within 24 prior to ICU admission.

Bleeding
- **Bleeding event according to the WHO classification.** Any bleeding event according to the WHO classification (ESM 11) within 24 hours prior to ICU admission. Bleeding occurring during surgery only was not registered**.**
Platelet transfusions
- **Platelet transfusion.** Any platelet transfusion administered within 24 hours prior to ICU admission.
Simplified Mortality Score for the Intensive Care Unit[a]
- **Lowest measured systolic blood pressure.** Lowest systolic blood pressure (invasive or non-invasive) in the first 24 hours after ICU admission. Unit: millimetres of mercury (mmHg).

Only variables used in the present work are listed above. Additional details and variables were registered for subsequent studies. For full information on all baseline variables in the PLOT-ICU cohort, please refer to the published protocol [7].

[a] Variables for the SMS-ICU score not otherwise included in the baseline variables or daily variables.

Abbreviations: intensive care unit (ICU), chronic obstructive pulmonary disease (COPD), New York Heart Association (NYHA), left ventricular ejection fraction (LVEF), computed tomography (CT) scan, magnetic resonance imaging (MRI), acquired immune deficiency syndrome (AIDS), adenosine diphosphate (ADP), sequential organ failure (SOFA), international normalised ratio (INR), World Health Organization (WHO).

ESM 9. Daily variables and definitions

Date

- **Date of the dayform (dd-mm-yyyy).**

Life support

- **Infusion of vasopressors.**
  Any continuous treatment with norepinephrine, epinephrine, phenylephrine, vasopressin analogues, dopamine, dobutamine, milrinone or levosimendan.

- **Invasive mechanical ventilation.**
  Invasive mechanical ventilation is defined as the use of positive pressure ventilation using a ventilator via a cuffed tube (oral, nasal or tracheostomy). CPAP is not considered invasive mechanical ventilation.

- **Renal replacement therapy.**
  Any form of renal replacement therapy (e.g., dialysis, hemofiltration or hemodiafiltration) at any rate. Days between intermittent renal replacement therapy are included.

- **Extracorporeal membrane oxygenation.**
  Any form of extracorporeal membrane oxygenation.

Biochemistry [a]

- **Lowest platelet count.**
  Unit: cells $x10^9$/L.

Transfusions during surgery

- **Transfusion with platelets during surgery.**
  Any type of platelet transfusion in the operating room.
  If yes:
  - **Number of transfusions.**
    Total number of platelet transfusions.

  - **Volume.**
    Total volume transfused. Unit: millilitres.

- **Transfusion with RBCs during surgery.**
  Any RBC transfusion in the operating room.
  If yes:
  - **Number of transfusions.**
    Total number of RBC transfusions.

- **Volume.**
  Total volume transfused. Unit: millilitres.

Transfusions in the ICU (in-ICU transfusions)

- **Transfusion with platelets.**
  Any type of platelet transfusion in the ICU.
  If yes:
  - **Number of transfusions.**
    Total number of platelet transfusions.
  - **Volume.**
    Total volume transfused. Unit: millilitres.
  - **Indication for platelet transfusion.**
    - Prophylaxis
      Any non-procedural platelet transfusion administered in the ICU to patients to prevent or reduce the risk of bleeding).
    - Pre-procedural
      Any platelet transfusion administered in the ICU to prevent or reduce the risk of bleeding prior to an invasive procedure (e.g., central venous catheter or dialysis catheter placement/removal, lumbar puncture, epidural catheter placement/removal, biopsies, pigtail catheter placement/removal, chest tube placement/removal, CNS surgery (including placement of EVD or ICP device), percutaneous dilatational tracheostomy, or surgery of any type).
    - Therapeutic
      Any platelet transfusion administered in the ICU *specifically* due to bleeding.
  - **Platelet count prior to transfusion.**
    Latest platelet count prior to transfusion for each indication. Unit: cells $x10^9$/L. If there were multiple transfusions for the same indication on the same day, only the highest platelet count prior to any of the transfusions for that indication was registered.

- **Transfusion with RBCs.**
  Any RBC transfusion in the ICU.
  If yes:
  - **Number of transfusions.**
    Total number of RBC transfusions.
  - **Volume.**
    Total volume transfused. Unit: millilitres.

Bleeding in the ICU

- **Bleeding event according to the WHO classification.**
  Any bleeding event according to the WHO classification (ESM 11) in the ICU. Bleeding occurring only during surgery was not registered.
  If yes:
    - **Bleeding grade according to the WHO classification.**
        - Grade 1 – Minor blood loss.
        - Grade 2 – Mild blood loss.
        - Grade 3 – Severe blood loss.
        - Grade 4 – Debilitating blood loss.

Thrombosis

- **New thrombotic event.**
  Any new (not previously registered) venous or arterial thrombosis (ESM 12)

Discharge/readmission

- **Discharge from the ICU.**
  Discharge from the ICU including death.
  If yes:
    - **Patient discharged to:**
        - General ward.
        - ICU participating in the PLOT-ICU study.
        - ICU not participating in the PLOT-ICU study.
        - Home or rehabilitation unit outside the hospital.
        - Dead.

- **Readmission to the ICU.**
  Patients who have been discharged from a participating ICU and readmitted to a participating ICU during the 90-day follow-up period.

Only variables used in the present work are listed above. Additional details and variables were registered for subsequent studies. For full information on all daily variables in the PLOT-ICU cohort, please refer to the published protocol [7].

[a] The timespan of the dayform corresponded to calendar days, i.e., 00:00 to 23:59. The timespan on the dayforms was shorter on days of ICU admission, discharge and death. If no biochemistry was obtained within the timespan of the first ICU day (from ICU admission to 23:59), biochemistry obtained on the day of ICU admission was registered. For the second ICU day and onwards, if no biochemistry was obtained within the time span of the dayforms, biochemistry obtained +/- 3 hours outside the timespan of the dayform was used unless already used in another dayform.

Abbreviations: continuous positive airway pressure (CPAP), intensive care unit (ICU), red blood cell (RBC), central nervous system (CNS), extra-ventricular drain (EVD), intracranial pressure monitoring (ICP), World Health Organization (WHO).

ESM 10. Follow-up variables and definitions

Vital status

- **Death within 90 days after inclusion.**
  Death from any cause within the 90-day follow-up period.
  If yes:
    - **Date of death (dd-mm-yyyy).**

Hospital discharge(s) / readmission(s)

- **Discharge from the hospital alive within 90 days after inclusion.**
  Discharge alive from the index hospitalisation (the hospitalisation where the patient was included in the PLOT-ICU study).
  If yes:
    - **Date of index hospital discharge (dd-mm-yyyy).**

    - **Additional hospitalisations within 90 days after inclusion.**
      Any hospitalisation after discharge from the index hospitalisation within the 90-day follow-up period.
      If yes:

        - **Dates of additional hospital admissions and discharges (dd-mm-yyyy).**

ESM 11. Modified World Health Organization bleeding classification.

Modified World Health Organization bleeding classification
Grade 1: Minor Blood Loss – Petechiae (<2 mm in size). – Purpura (< 2.5 cm diameter/1 inch). – Subconjunctival bleeding. – Upper airways: Oropharyngeal bleeding, epistaxis <30 minutes, not requiring packing. – Abnormal vaginal bleeding (non-menstrual; < 2 pads/day).
Grade 2: Mild Blood Loss – Retinal bleeding without visual impairment. – Profuse epistaxis or oropharyngeal bleeding >30 minutes or requiring packing. – Haemoptysis, blood in broncho-pulmonary lavage, blood in the tracheal tube (intubated patients). – Haematemesis, blood in nasogastric aspirates, melaena or haematochezia. – Haematuria. – Abnormal vaginal bleeding (>2 pads/day). – Diffuse petechia/purpura, multiple haematomas or ecchymoses, each >2.5 cm or any one >10 cm. – Musculoskeletal bleeding, soft tissue bleeding and bleeding in cavity fluids evident macroscopically. – Abnormal bleeding from invasive- or procedure sites.
Grade 3: Severe Blood Loss – CNS bleeding visible on imaging study but without neurological symptoms or clinical consequences. – Any bleeding requiring up to two RBC transfusions within 24 hours of onset including epistaxis, oropharyngeal bleeding, haemoptysis, melaena, haematemesis, haematuria, haematochezia, vaginal bleeding, musculoskeletal bleeding, soft tissue bleeding and bleeding from invasive- or procedure sites.

Grade 4: Debilitating Blood Loss

- Debilitating or life-threatening bleeding; including any bleeding requiring either more than two units of RBC, intubation and mechanical ventilation or surgical intervention (including coiling) within 24 hours after onset.
- Non-fatal CNS bleeding resulting in neurological symptoms.
- Retinal bleeding with visual impairment.
- Fatal bleeding from any source.

The World Health Organization (WHO) bleeding classification has been used in modified versions to grade bleeding events in large multicentre trials assessing platelet transfusions in patients with haematological malignancy and hypo-proliferative thrombocytopenia [8–11]. We used specific descriptors for each grade as previously used in these trials and adopted the classification to the intensive care unit setting.

Abbreviations: central nervous system (CNS), packed red blood cells (RBC), computed tomography scan (CT).

ESM 12. Outcome measures

Primary outcome
Number of patients with any thrombocytopenia Definition: patients with at least one recorded platelet count <150x10^9/L at ICU admission and/or during ICU stay.
Secondary outcomes
Number of patients with any thrombocytopenia, baseline thrombocytopenia and ICU thrombocytopenia categorised in severity subclasses Definition: the number of patients with baseline thrombocytopenia, ICU thrombocytopenia, and any thrombocytopenia classified as mild (100–149x10^9/L), moderate (50–99x10^9/L), severe (20–49x10^9/L), very severe (<20x10^9/L) based on the platelet count at ICU admission, and the nadir platelet count during ICU stay and overall, for baseline-, ICU-, and any thrombocytopenia, respectively.
90-day mortality Definition: death from any cause within 90 days from ICU admission.
Days alive and out of hospital Definition: the total number of days spent in hospital subtracted from the total study period of 90 days; i.e., if a patient is discharged 15 days after the index hospital admission and then readmitted to the hospital for a period of 10 days before the second discharge, the total number of days alive and out of hospital was calculated as 90 – 15 – 10 days. Patients that died within 90 days of ICU admission were assigned zero days alive and out of hospital.
Days alive without the use of life-support Definition: the total number of days alive without the use of invasive mechanical ventilation, continuous infusion of vasopressors or inotropic agents, renal replacement therapy (including days between intermittent haemodialysis) and extracorporeal membrane oxygenation. The total number of days alive without the use of life-support was calculated as the total number of days with the use of life-support subtracted from the total number of days alive during the study period of 90 days. Patients that died within 90 days from ICU admission were assigned zero days alive without the use of life-support.
The number of patients with at least one bleeding event in the ICU graded according to the WHO classification Definition: the number of patients with at least one bleeding event in the ICU and graded into grade 1, grade 2, grade 3 and grade 4 bleedings (ESM 11). Each patient was only counted

once, and the highest-graded bleeding event took priority. Bleeding occurring only during surgery was not registered as a bleeding event.

The number of patients with at least one thrombotic event in the ICU

Definition: the number of patients with at least one thrombotic event in the ICU including any of the following (each patient will only be counted once):

- Peripheral arterial thrombosis.
  Defined as limb-threatening ischemia which is confirmed by limb haemodynamic or imaging and leads to an acute vascular intervention (i.e., pharmacologic, peripheral arterial surgery/reconstruction, peripheral angioplasty/stent, or amputation) within 30 days of onset of symptoms. In the absence of confirmation by limb haemodynamic or imaging, absent pedal pulses are acceptable as hemodynamic criteria for acute limb ischemia [12].
- Acute coronary thrombosis.
  Defined as ST-elevation myocardial infarction with imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology and/or identification of a coronary thrombus by angiography including intracoronary imaging or by autopsy [13].
- Acute mesenteric ischemia.
  Defined as a thrombus visible on a CT scan or surgical findings/autopsy findings consistent with acute mesenteric ischaemia [14].
- Acute ischemic stroke.
  Defined as clinical symptoms in combination with relevant findings on a CT scan, or sign of thrombosis on CT angiography, MRI or MR angiography [15].
- Central vein thrombosis
  Defined as a thrombosis visible on CT scan, venography or ultrasonography of central veins including the caval vein, and subclavian- and jugular veins as well as portal vein thrombosis and acute mesenteric venous thrombosis [16–18].
- Pulmonary embolus
  Defined as a thrombus visible on multidetector-row CT pulmonary angiogram in combination with clinical symptoms [19].
- Peripheral venous thrombosis
  Defined as a thrombosis visible on a CT scan or ultrasonography in any peripheral veins. When ultrasound is used, any partial or incompressible venous segment in common femoral, proximal, middle, and distal superficial femoral, and popliteal veins and the venous trifurcation is classified as a deep-vein thrombosis [20].
- Cerebral vein thrombosis
  Defined as a thrombus in the cerebral veins detected by MRI and MRI venography [15].

The number of patients receiving at least one platelet transfusion during ICU stay

Definition: the number of patients that received at least one platelet transfusion administered in the ICU or during surgery while admitted to the ICU.

The number of transfusions and volumes transfused per patient during ICU stay
Definition: the number of platelet transfusions and the total volume (mL) transfused in the ICU and during surgery while admitted to the ICU.

Indications for in-ICU platelet transfusions
The number of patients receiving at least one transfusion administered in the ICU for each indication below:

- *Pre-procedural:* any platelet transfusion administered in the ICU to prevent or reduce the risk of bleeding before an invasive procedure (e.g., central venous catheter or dialysis catheter placement/removal, lumbar puncture, epidural catheter placement/removal, biopsies, pigtail catheter placement/removal, chest tube placement/removal, CNS surgery (including placement of EVD or ICP device), percutaneous dilatational tracheostomy, or surgery of any type).
- *Prophylactic:* any non-procedural platelet transfusion administered in the ICU to prevent or reduce the risk of bleeding.
- *Therapeutic:* any platelet transfusion administered in the ICU specifically due to bleeding.

Process variables (added post hoc)

Platelet count prior to transfusion
Definition: Platelet count before in-ICU platelet transfusions for each indication. Assumptions made during computation are explained in ESM 1. Unit: cells $x10^9$/L

The number of patients receiving at least one RBC transfusion during ICU stay
Definition: the number of patients that received at least one RBC administered in the ICU or during surgery while admitted to the ICU.

The number of RBC transfusions per patient during ICU stay
Definition: the number of RBC transfusions administered in the ICU and during surgery while admitted to the ICU.

Abbreviations: intensive care unit (ICU), red blood cell (RBC), interquartile range (IQR).

ESM 13. Missing data

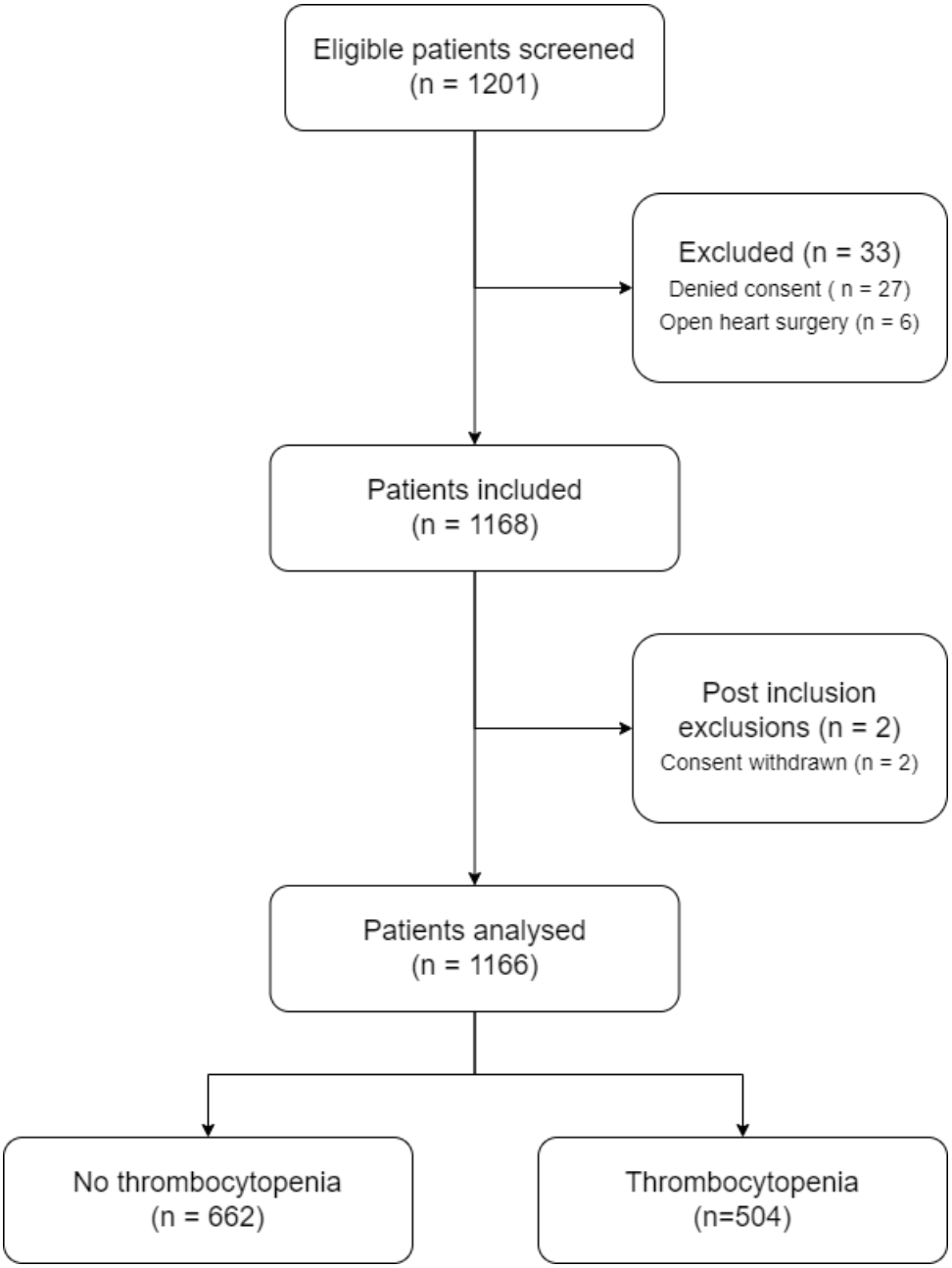
Missing platelet counts
In total, 195/1166 (16.7%) patients had no recorded platelet count at ICU admission and 15/1166 (1.3%) patients had no recorded platelet count during ICU admission. Of these, 10 patients had no recorded platelet count at ICU admission AND during ICU admission.

Handling
We logically imputed patients without a recorded platelet count at ICU admission AND during ICU admission as not having thrombocytopenia (n = 10). For the patients with no recorded platelet count at ICU admission but available platelet counts during ICU admission, the first available platelet count in the ICU was used as baseline platelet count (n = 185). The ICU-day with the first available platelet count was on (median (IQR)) day 1 (1 to 1) for these patients. For patients with no recorded platelet count during ICU admission but an available platelet count at ICU admission, we assumed that at least one platelet count during ICU was equal to the baseline platelet count (n = 5).

Patients transferred to non-study ICUs
In total, 56 / 1166 (4.8%) patients were transferred directly from a study ICU to a non-study ICU during the 90-day follow-up period. For 28 of these patients, we were able to collect full data on daily registered variables. For the remaining 28 patients, data on daily registered variables were not available during days spent in the non-study ICU.

Handling
We assumed that no events had occurred during the days spent in the non-study ICU (n = 28).

ESM 14. Study flow diagram



Only patients that fulfilled all inclusion criteria were screened for inclusion in the eCRF. Patients who were already admitted to the ICU at the start of the inception period were not screened. Two patients withdrew consent after inclusion and were deleted from the database before analysis.

ESM 15. Site characteristics

	ICUs (n = 52)[a]
Type of hospital	
- University - Non-university	49 (94.2%) 3 (5.8%)
Type of ICU	
- Medical - Surgical - Mixed	11 (21.2%) 1 (1.9%) 40 (76.9%)
Number of beds open for admission in the ICU	
- <10 - 10-19 - 20-29 - ≥30	16 (30.8%) 19 (36.5%) 14 (26.9%) 3 (5.8%)
Hospital protocol for platelet transfusions [b]	26 (50.0%)
ICU protocol for platelet transfusions [c]	8 (15.4%)

[a] There were no missing data.

[b] Presence of a general guideline/protocol for platelet transfusions in the hospital.

[c] Presence of a specific guideline/protocol for platelet transfusions in the ICU.

Abbreviations: intensive care unit (ICU).

ESM 16. Full baseline characteristics

	All (n = 1166)	Thrombocytopenia			
		None (n = 662)	Any [a] (n = 504)	Baseline [b] (n = 273)	ICU [c] (n = 231)
Age (years)	63.0 (49.0 - 73.0)	64.0 (47.0 - 74.0)	63.0 (51.0 - 72.0)	61.0 (50.0 - 70.0)	65.0 (53.0 - 74.0)
Female gender	461 (39.5%)	291 (44.0%)	170 (33.7%)	90 (33.0%)	80 (34.6%)
Comorbidities					
Pulmonary disease	217 (18.6%)	153 (23.1%)	64 (12.7%)	34 (12.5%)	30 (13.0%)
IHD or HF	208 (17.8%)	126 (19.0%)	82 (16.3%)	44 (16.1%)	38 (16.5%)
Chronic renal failure	100 (8.6%)	46 (6.9%)	54 (10.7%)	29 (10.6%)	25 (10.8%)
Chronic liver failure	62 (5.3%)	12 (1.8%)	50 (9.9%)	38 (13.9%)	12 (5.2%)
Solid tumour cancer	162 (13.9%)	89 (13.4%)	73 (14.5%)	45 (16.5%)	28 (12.1%)
Metastatic cancer	76 (6.5%)	39 (5.9%)	37 (7.3%)	27 (9.9%)	10 (4.3%)
Haematological malignancy	92 (7.9%)	17 (2.6%)	75 (14.9%)	66 (24.2%)	9 (3.9%)
Haematological emergency	6 (0.5%)	0 (0.0%)	6 (1.2%)	5 (1.8%)	1 (0.4%)
Chronic spleen enlargement	27 (2.3%)	2 (0.3%)	25 (5.0%)	21 (7.7%)	4 (1.7%)
Non-AIDS-, non-cancer-related immune deficiency [d]	61 (5.2%)	19 (2.9%)	42 (8.3%)	23 (8.4%)	19 (8.2%)
Coagulation disorder	7 (0.6%)	4 (0.6%)	3 (0.6%)	1 (0.4%)	2 (0.9%)
Previous thrombo-embolism	150 (12.9%)	89 (13.4%)	61 (12.1%)	35 (12.8%)	26 (11.3%)
Admitted to					
University Hospital	1089 (92.8%)	619 (93.5%)	463 (91.9%)	244 (89.4%)	219 (94.8%)
Admitted from					
- ED	571 (49.0%)	360 (54.4%)	211 (41.9%)	93 (34.1%)	118 (51.1%)
- Ward	340 (29.2%)	170 (25.7%)	170 (33.7%)	120 (44.0%)	50 (21.6%)
- OR	172 (14.8%)	95 (14.4%)	77 (15.3%)	32 (11.7%)	45 (19.5%)
- ICU	83 (7.1%)	37 (5.6%)	46 (9.1%)	28 (10.3%)	18 (7.8%)
Surgery					
Any surgery	296 (25.4%)	159 (24.0%)	137 (27.2%)	60 (22.0%)	77 (33.3%)
Elective surgery	102 (8.7%)	57 (8.6%)	45 (8.9%)	21 (7.7%)	24 (10.4%)
Acute surgery	219 (18.8%)	115 (17.4%)	104 (20.6%)	47 (17.2%)	57 (24.7%)
Illness severity					
Predicted 90-day mortality [e] (%)	22.8 (14.7 - 40.1)	20.5 (13.1 - 33.8)	30.8 (16.5 - 43.4)	30.8 (16.5 - 46.7)	28.0 (17.4 - 43.4)
Reason for ICU admission					
- Neurological	175 (15.0%)	108 (16.3%)	67 (13.3%)	33 (12.1%)	34 (14.7%)
- Respiratory	406 (34.8%)	277 (41.8%)	129 (25.6%)	76 (27.8%)	53 (22.9%)
- Circulatory	278 (23.8%)	125 (18.9%)	153 (30.4%)	78 (28.6%)	75 (32.5%)
- Renal	35 (3.0%)	13 (2.0%)	22 (4.4%)	13 (4.8%)	9 (3.9%)
- Liver	13 (1.1%)	1 (0.2%)	12 (2.4%)	8 (2.9%)	4 (1.7%)
- Metabolic	55 (4.7%)	32 (4.8%)	23 (4.6%)	13 (4.8%)	10 (4.3%)
- Multiple trauma	29 (2.5%)	12 (1.8%)	17 (3.4%)	4 (1.5%)	13 (5.6%)
- TBI	13 (1.1%)	8 (1.2%)	5 (1.0%)	3 (1.1%)	2 (0.9%)
- Burn	3 (0.3%)	2 (0.3%)	1 (0.2%)	1 (0.4%)	0 (0.0%)
- Haemorrhage	48 (4.1%)	12 (1.8%)	36 (7.1%)	19 (7.0%)	17 (7.4%)
- Other	111 (9.5%)	72 (10.9%)	39 (7.7%)	25 (9.2%)	14 (6.1%)
Acute conditions					
Sepsis	161 (13.8%)	88 (13.3%)	73 (14.5%)	52 (19.0%)	21 (9.1%)
Septic shock	174 (14.9%)	58 (8.8%)	116 (23.0%)	62 (22.7%)	54 (23.4%)
Acute liver failure	42 (3.6%)	8 (1.2%)	34 (6.7%)	18 (6.6%)	16 (6.9%)
COVID-19	140 (12.0%)	82 (12.4%)	58 (11.5%)	40 (14.7%)	18 (7.8%)
Treatments					
HCST [f]	28 (2.4%)	0 (0.0%)	28 (5.6%)	27 (9.9%)	1 (0.4%)
Chemotherapy [g]	86 (7.4%)	27 (4.1%)	59 (11.7%)	51 (18.7%)	8 (3.5%)
Drugs that may cause thrombocytopenia [h]	227 (19.5%)	114 (17.2%)	113 (22.4%)	74 (27.1%)	39 (16.9%)
Anticoagulating treatment [i]	399 (34.2%)	232 (35.0%)	167 (33.1%)	95 (34.8%)	72 (31.2%)
Platelet inhibitors [j]	198 (17.0%)	132 (19.9%)	66 (13.1%)	31 (11.4%)	35 (15.2%)
Biochemistry					
Habitual platelet count [k]	250.0 (200.0 - 300.0)	275.0 (223.0 - 338.8)	203.0 (160.0 - 275.2)	184.0 (145.0 - 250.0)	246.0 (199.5 - 296.5)

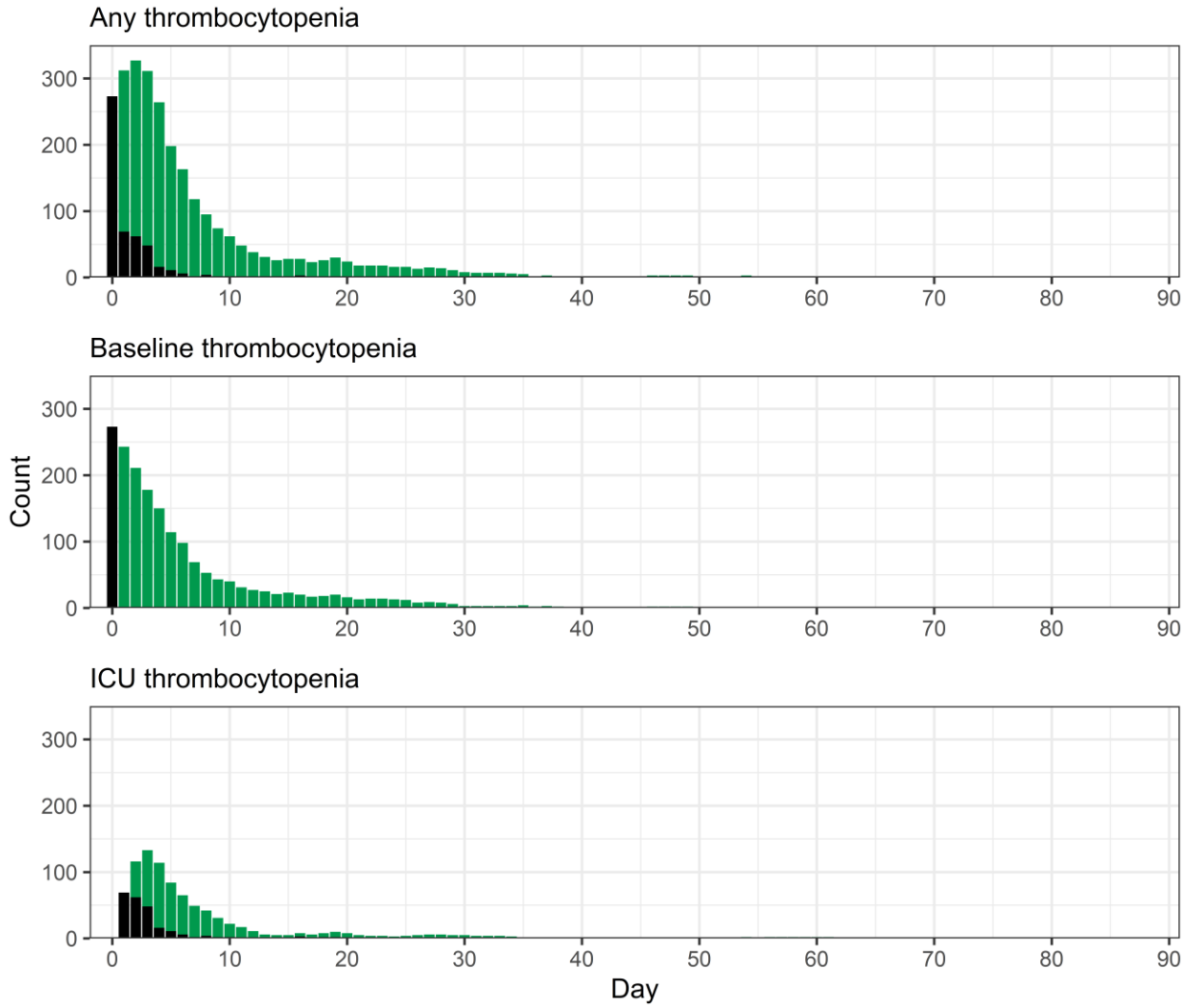
Platelet count [l]	222.0 (150.5 - 300.0)	278.0 (225.0 - 341.2)	146.0 (93.0 - 198.0)	97.0 (50.0 - 125.0)	204.0 (175.2 - 258.8)
WBC [m]	10.7 (7.3 - 15.4)	11.4 (8.5 - 15.8)	9.6 (5.6 - 14.8)	7.5 (4.2 - 11.9)	11.9 (8.1 - 16.8)
INR > 1.5 [n]	119 (14.6%)	36 (8.5%)	83 (21.3%)	51 (24.4%)	32 (17.7%)
Bleeding and transfusions 24 hours prior to ICU admission					
Bleeding	162 (13.9%)	66 (10.0%)	96 (19.0%)	50 (18.3%)	46 (19.9%)
Platelet transfusion	59 (5.1%)	9 (1.4%)	50 (9.9%)	35 (12.8%)	15 (6.5%)

Numeric variables are presented as medians (IQR) and categorical variables as numbers and percentages. Definitions of baseline variables are available in ESM 7 and 8.

[a] Patients with a platelet count <150x10^9/L at ICU admission and/or during ICU stay.
[b] Patients with a platelet count <150x10^9/L at ICU admission.
[c] Patients with a platelet count <150x10^9/L during ICU stay without thrombocytopenia at ICU admission.
[d] Non-AIDS-, non-cancer-related immune deficiencies (including solid organ transplant) or conditions requiring long-term (> 30 days) or high-dose (> 1 mg/kg/day) steroids, or any immunosuppressive drug for more than 30 days.
[e] The predicted 90-day mortality was based on the Simplified Mortality Score for the Intensive Care Unit. Scores range from 0-42 with corresponding predicted 90-day mortality of 3.3 to 91.0% [1, 2]. Details are provided in ESM 7.
[f] HSCT (treatment within one year prior to ICU admission.
[g] Chemotherapy treatment within six weeks prior to ICU admission.
[h] Including treatment with piperacillin, rituximab, abciximab, carbamazepine, valproic acid, and interferon-alfa within one week prior to ICU admission.
[i] Including treatment with anticoagulating drugs in any dose within 48 hours prior to ICU admission.
[j] Treatment with platelet inhibitors within 48 hours prior to ICU admission.
[k] Habitual platelet counts were estimated in 433 (37.1%) patients.
[l] Baseline platelet counts were unavailable in 195 (16.7%) patients.
[m] Baseline WBC was unavailable in 160 (13.7%) patients.
[n] Baseline INR was unavailable in 351 (30.1%) patients.

Abbreviations: emergency department (ED), operating room or recovery room (OR), intensive care unit (ICU), traumatic brain injury; (TBI), ischaemic heart disease (IHD), heart failure (HF), haematopoietic stem cell transplantation (HSCT), international normalized ratio (INR), white blood cell count (WBC), acquired immune deficiency syndrome (AIDS).

ESM 17. Number of patients with thrombocytopenia according to days since inclusion.



Number of patients with thrombocytopenia (platelet count <150x10^9) according to days since inclusion (ICU admission) stratified on the three categories of thrombocytopenia: “Any thrombocytopenia”, “Baseline thrombocytopenia” and “ICU thrombocytopenia”. Patients who had their first platelet count < 150x10^9/L on this day are represented by the black part of each bar while patients who had a platelet count <150x10^9/L on this day but had a platelet count <150x10^9/L previously are represented by the green part of each bar. Day 0 represent the baseline.

Abbreviations: intensive care unit (ICU).

ESM 18. Secondary outcome: severity of thrombocytopenia with 95% CIs

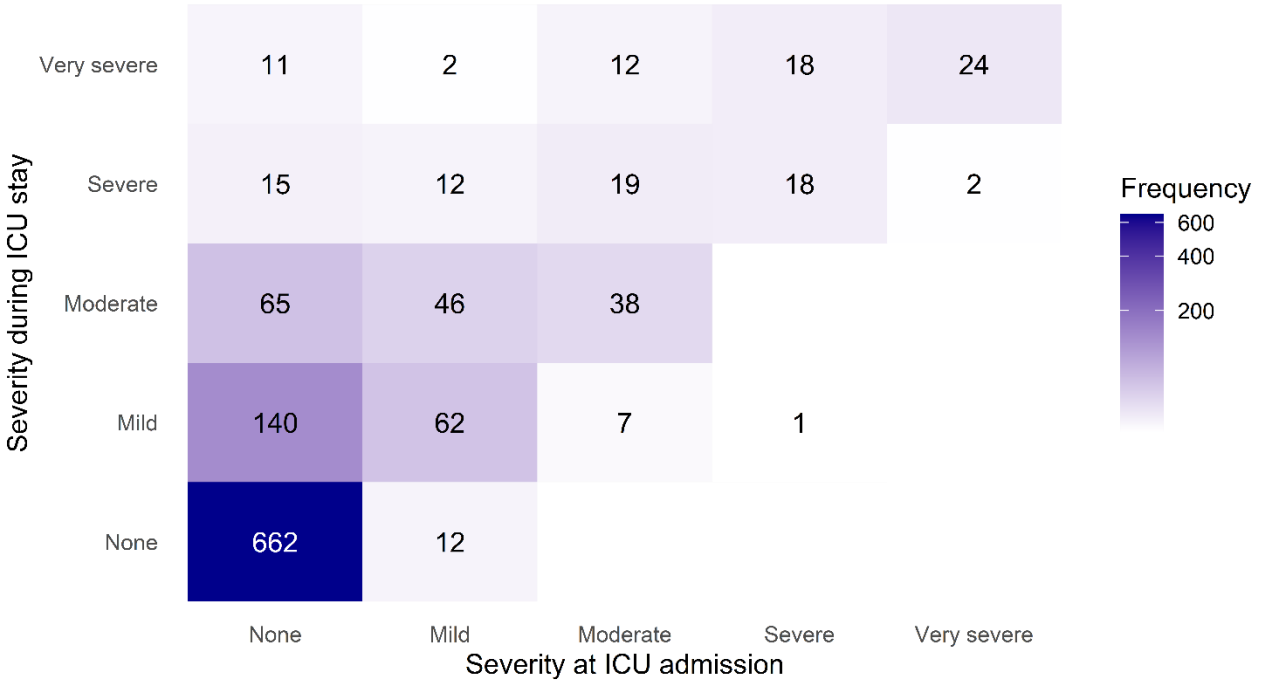
	Thrombocytopenia		
Severity	**Any (n = 504)** [a] n (%; 95% CI)	**Baseline (n = 273)** [b] n (%; 95% CI)	**ICU (n = 231)** [c] n (%; 95% CI)
Mild	214 (42.5; 38.1 - 46.9%)	134 (49.1; 43.0 - 55.2%)	140 (60.6; 54.0 - 67.0%)
Moderate	156 (31.0; 26.9 - 35.2%)	76 (27.8; 22.6 - 33.6%)	65 (28.1; 22.4 - 34.4%)
Severe	65 (12.9; 10.1 - 16.1%)	37 (13.6; 9.7 - 18.2%)	15 (6.5; 3.7 - 10.5 %)
Very severe	69 (13.7; 10.8 - 17.0%)	26 (9.5: 6.3 - 13.6%)	11 (4.8; 2.4 - 8.4%)

Results are presented as numbers, percentages and 95% CIs. The severity of thrombocytopenia was classified as mild (100–149x10^9/L), moderate (50–99x10^9/L), severe (20–49x10^9/L, and very severe (<20x10^9/L) based on the platelet count at ICU admission, and the nadir platelet count during ICU stay and overall, for baseline-, ICU-, and any thrombocytopenia, respectively.

[a] Patients with a platelet count <150x10^9/L at ICU admission and/or during the ICU stay.
[b] Patients with a platelet count <150x10^9/L at ICU admission.
[c] Patients with a platelet count <150x10^9/L during ICU stay without thrombocytopenia at ICU admission.

Abbreviations: intensive care unit (ICU), confidence interval (CI).

ESM 19. Severity of thrombocytopenia at ICU admission and during ICU stay.



All combinations of thrombocytopenia at ICU admission and during ICU stay. Numbers within each square correspond to the number of patients with that combination. Squares in the diagonal (from bottom left to top right) correspond to patients that remained in the same category throughout the ICU stay as they were on baseline. Squares above the diagonal correspond to patients that were classified in a “worse” category during ICU stay than they were on baseline (e.g., 140 patients that did not have thrombocytopenia at ICU admission developed mild ICU thrombocytopenia) and vice versa (e.g., 12 patients with mild thrombocytopenia at ICU admission did not have thrombocytopenia during ICU stay).

Abbreviations: intensive care unit (ICU).

ESM 20. Secondary clinical outcomes with 95% CIs

	All (n = 1166)	Thrombocytopenia								Missing
		None (n = 662)	Any [a] (n = 504)	Mild (n = 214)	Moderate (n = 156)	Severe (n = 65)	Very severe (n = 69)	Baseline [b] (n = 273)	ICU [c] (n = 231)	
Clinical outcomes										
90-day mortality	301 (25.9%) [23.4 - 28.5]	127 (19.3%) [16.3 - 22.5]	174 (34.6%) [30.4 - 38.9]	56 (26.3%) [20.5 - 32.7]	49 (31.4%) [24.2 - 39.3]	33 (50.8%) [38.1 - 63.4]	36 (52.2%) [39.8 - 64.4]	102 (37.4%) [31.6 - 43.4]	72 (31.3%) [25.4 - 37.7]	4 (0.3%)
Days alive without life-support [d]	87.0 [86.0 - 88.0]	88.0 [88.0 - 89.0]	82.0 [79.0 - 84.0]	86.0 [85.0 - 87.0]	83.0 [77.5 - 84.0]	0.0 [0.0 - 79.0]	0.0 [0.0 - 76.0]	81.0 [75.0 - 85.0]	83.0 [79.5 - 85.0]	4 (0.3%)
Days alive and out of hospital [e]	63.0 [59.0 - 66.0]	71.0 [68.0 - 74.0]	44.0 [31.0 - 51.0]	63.0 [53.0 - 70.0]	47.0 [30.0 - 58.5]	0.0 [0.0 - 44.0]	0.0 [0.0 - 5.0]	30.0 [18.0 - 50.0]	50.5 [39.0 - 60.5]	4 (0.3%)
Any WHO bleeding in the ICU [f]	187 (16.0%) [14.0 - 18.3]	48 (7.3%) [5.4 - 9.5]	139 (27.6%) [23.7 - 31.7]	39 (18.2%) [13.3 - 24.1]	44 (28.2%) [21.3 - 36.0]	24 (36.9%) [25.3 - 49.8]	32 (46.4%) [34.3 - 58.8]	75 (27.5%) [22.3 - 33.2]	64 (27.7%) [22.0 - 34.0]	0 (0.0%)
Worst-graded WHO bleeding in the ICU [g]										
- grade 1	15 (1.3%) [0.7 - 2.1]	5 (0.8%) [0.2 - 1.8]	10 (2.0%) [1.0 - 3.6]	2 (0.9%) [0.1 - 3.3]	2 (1.3%) [0.2 - 4.6]	3 (4.6%) [1.0 - 12.9]	3 (4.3%) [0.9 - 12.2]	3 (1.1%) [0.2 - 3.2]	7 (3.0%) [1.2 - 6.1]	0 (0.0%)
- grade 2	83 (7.1%) [5.7 - 8.7]	34 (5.1%) [3.6 - 7.1]	49 (9.7%) [7.3 - 12.6]	15 (7.0%) [4.0 - 11.3]	17 (10.9%) [6.5 - 16.9]	6 (9.2%) [3.5 - 19.0]	11 (15.9%) [8.2 - 26.7]	29 (10.6%) [7.2 - 14.9]	20 (8.7%) [5.4 - 13.1]	0 (0.0%)
- grade 3	42 (3.6%) [2.6 - 4.8]	5 (0.8%) [0.2 - 1.8]	37 (7.3%) [5.2 - 10.0]	11 (5.1%) [2.6 - 9.0]	11 (7.1%) [3.6 - 12.3]	6 (9.2%) [3.5 - 19.0]	9 (13.0%) [6.1 - 23.3]	20 (7.3%) [4.5 - 11.1]	17 (7.4%) [4.3 - 11.5]	0 (0.0%)
- grade 4	47 (4.0%) [3.0 - 5.3]	4 (0.6%) [0.2 - 1.5]	43 (8.5%) [6.2 - 11.3]	11 (5.1%) [2.6 - 9.0]	14 (9.0%) [5.0 - 14.6]	9 (13.8%) [6.5 - 24.7]	9 (13.0%) [6.1 - 23.3]	23 (8.4%) [5.4 - 12.4]	20 (8.7%) [5.4 - 13.1]	0 (0.0%)
New thrombosis in the ICU	68 (5.8%) [4.6 - 7.3]	30 (4.5%) [3.1 - 6.4]	38 (7.5%) [5.4 - 10.2]	15 (7.0%) [4.0 - 11.3]	16 (10.3%) [6.0 - 16.1]	4 (6.2%) [1.7 - 15.0]	3 (4.3%) [0.9 - 12.2]	19 (7.0%) [4.2 - 10.7]	19 (8.2%) [5.0 - 12.5]	0 (0.0%)
Platelet transfusions										
Transfused with platelets [h]	120 (10.3%) [8.6 - 12.2]	6 (0.9%) [0.3 - 2.0]	114 (22.6%) [19.0 - 26.5]	8 (3.7%) [1.6 - 7.2]	19 (12.2%) [7.5 - 18.4]	29 (44.6%) [32.3 - 57.5]	58 (84.1%) [73.3 - 91.8]	80 (29.3%) [24.0 - 35.1]	34 (14.7%) [10.4 - 20.0]	0 (0.0%)
No. of platelet transfusions per patient [i]	0.0 [0.0 - 0.0]	0.0 [0.0 - 0.0]	0.0 [0.0 - 0.0]	0.0 [0.0 - 0.0]	0.0 [0.0 - 0.0]	0.0 [0.0 - 1.0]	4.0 [3.0 - 5.0]	0.0 [0.0 - 0.0]	0.0 [0.0 - 0.0]	0 (0.0%)
Total volume (mL) of platelets per patient [j]	0.0 [0.0 - 0.0]	0.0 [0.0 - 0.0]	0.0 [0.0 - 0.0]	0.0 [0.0 - 0.0]	0.0 [0.0 - 0.0]	0.0 [0.0 - 227.0]	900.0 [701.0 - 1213.0]	0.0 [0.0 - 0.0]	0.0 [0.0 - 0.0]	2 (0.2%)
Indications for in-ICU platelet transfusions [k]										
- Prophylaxis	74 (6.3%) [5.0 - 7.9]	1 (0.2%) [0.0 - 0.8]	73 (14.5%) [11.5 - 17.9]	2 (0.9%) [0.1 - 3.3]	4 (2.6%) [0.7 - 6.4]	16 (24.6%) [14.8 - 36.9]	51 (73.9%) [61.9 - 83.7]	61 (22.3%) [17.5 - 27.8]	12 (5.2%) [2.7 - 8.9]	0 (0.0%)
- Pre-procedural	30 (2.6%) [1.7 - 3.7]	1 (0.2%) [0.0 - 0.8]	29 (5.8%) [3.9 - 8.2]	1 (0.5%) [0.0 - 2.6]	2 (1.3%) [0.2 - 4.6]	10 (15.4%) [7.6 - 26.5]	16 (23.2%) [13.9 - 34.9]	21 (7.7%) [4.8 - 11.5]	8 (3.5%) [1.5 - 6.7]	0 (0.0%)
- Therapeutic	40 (3.4%) [2.5 - 4.6]	1 (0.2%) [0.0 - 0.8]	39 (7.7%) [5.6 - 10.4]	2 (0.9%) [0.1 - 3.3]	9 (5.8%) [2.7 - 10.7]	12 (18.5%) [9.9 - 30.0]	16 (23.2%) [13.9 - 34.9]	22 (8.1%) [5.1 - 11.9]	17 (7.4%) [4.3 - 11.5]	0 (0.0%)
RBC transfusions										
Transfused with RBCs	307 (26.3%) [23.8 - 29.0]	90 (13.6%) [11.1 - 16.4]	217 (43.1%) [38.7 - 47.5]	61 (28.5%) [22.6 - 35.1]	69 (44.2%) [36.3 - 52.4]	41 (63.1%) [50.2 - 74.7]	46 (66.7%) [54.3 - 77.6]	116 (42.5%) [36.6 - 48.6]	101 (43.7%) [37.2 - 50.4]	0 (0.0%)
No. of RBC transfusions per patient	0.0 [0.0 - 0.0]	0.0 [0.0 - 0.0]	0.0 [0.0 - 0.0]	0.0 [0.0 - 0.0]	0.0 [0.0 - 1.0]	1.0 [1.0 - 2.0]	2.0 [1.0 - 4.0]	0.0 [0.0 - 0.0]	0.0 [0.0 - 1.0]	0 (0.0%)

Continuous variables are presented as medians with 95% CIs and categorical variables as numbers and percentages with 95% CIs. The severity of thrombocytopenia was based on the overall nadir platelet count; mild (100–149x10^9/L), moderate (50–99x10^9/L), severe (20–49x10^9/L, and very severe (<20x10^9/L).

[a] Patients with a recorded platelet count <150x10^9/L at ICU admission and/or during the ICU stay and within the specified severity subclasses according to the overall nadir platelet count.
[b] Patients with a platelet count <150x10^9/L at ICU admission.
[c] Patients with a platelet count <150x10^9/L during ICU stay without thrombocytopenia at ICU admission.
[d] Dead patients were assigned zero days alive without life-support.
[e] Dead patients were assigned zero days alive and out of hospital.
[f] Number of patients with at least one WHO bleeding in the ICU. We did not register bleedings occurring only during surgery while admitted to the ICU. Overall, 29 patients who did bleed in the ICU were transfused with 2 or more packed red blood cells during surgery: 11 patients without thrombocytopenia and 18 patients with any thrombocytopenia (6 patients with mild-, 8 patients with moderate-, 3 patients with severe-, 1 patient with very severe thrombocytopenia, respectively). Of those 8 patients with baseline thrombocytopenia and 10 with ICU thrombocytopenia, respectively.
[g] Number of patients with at least one WHO bleeding in the ICU graded into 1 to 4 according to the worst graded bleeding episode.
[h] Number of patients receiving at least one platelet transfusion.
[i] Total number of transfusions per patient.
[j] Total volume of platelet transfusions per patient.
[k] Number of patients that received at least one platelet transfusion administered in the ICU for each of the indications. Transfusions used during surgery are excluded as we did not collect data on indications for platelet transfusions used “outside” the ICU. In total 29 patients received a total of 57 platelet transfusions during surgery; 3 patients without thrombocytopenia received 4 transfusions, and 26 patients with thrombocytopenia received 53 transfusions (5 patients with mild thrombocytopenia received 14 transfusions, 7 patients with moderate thrombocytopenia received 12 transfusions, 6 patients with severe thrombocytopenia received 14 transfusions, and 8 patients with very severe thrombocytopenia received 13 transfusions). Of those, 11 patients with baseline thrombocytopenia received 17 transfusions and 15 patients with ICU thrombocytopenia received 36 transfusions.

Abbreviations: intensive care unit (ICU), red blood cell (RBC), World Health Organization (WHO), confidence interval (CI).

ESM 21. Use of life-support

	All (n = 1166)	Thrombocytopenia							
		None (n = 662)	Any [a] (n = 504)	Mild (n = 214)	Moderate (n = 156)	Severe (n = 65)	Very severe (n = 69)	Baseline [b] (n = 273)	ICU [c] (n = 231)
Vasopressors [d]	671 (57.5%) [54.7 - 60.4]	303 (45.8%) [41.9 - 49.7]	368 (73.0%) [68.9 - 76.8]	146 (68.2%) [61.5 - 74.4]	116 (74.4%) [66.8 - 81.0]	51 (78.5%) [66.5 - 87.7]	55 (79.7%) [68.3 - 88.4]	182 (66.7%) [60.7 - 72.2]	186 (80.5%) [74.8 - 85.4]
Invasive mechanical ventilation [e]	614 (52.7%) [49.7 - 55.6]	295 (44.6%) [40.7 - 48.4]	319 (63.3%) [58.9 - 67.5]	140 (65.4%) [58.6 - 71.8]	99 (63.5%) [55.4 - 71.0]	42 (64.6%) [51.8 - 76.1]	38 (55.1%) [42.6 - 67.1]	149 (54.6%) [48.5 - 60.6]	170 (73.6%) [67.4 - 79.2]
Renal replacement therapy [f]	161 (13.8%) [11.9 - 15.9]	35 (5.3%) [3.7 - 7.3]	126 (25.0%) [21.3 - 29.0]	33 (15.4%) [10.9 - 21.0]	46 (29.5%) [22.5 - 37.3]	23 (35.4%) [23.9 - 48.2]	24 (34.8%) [23.7 - 47.2]	60 (22.0%) [17.2 - 27.4]	66 (28.6%) [22.8 - 34.9]
ECMO [g]	18 (1.5%) [0.9 - 2.4]	4 (0.6%) [0.2 - 1.5]	14 (2.8%) [1.5 - 4.6]	4 (1.9%) [0.5 - 4.7]	6 (3.8%) [1.4 - 8.2]	3 (4.6%) [1.0 - 12.9]	1 (1.4%) [0.0 - 7.8]	4 (1.5%) [0.4 - 3.7]	10 (4.3%) [2.1 - 7.8]

Categorical variables are presented with numbers and percentages with 95% CIs. The severity of thrombocytopenia was based on the overall nadir platelet count; mild (100–149x10^9/L), moderate (50–99x10^9/L), severe (20–49x10^9/L, and very severe (<20x10^9/L).

[a] Patients with a platelet count <150x10^9/L at ICU admission and/or during the ICU stay and within the specified severity subclasses according to the overall nadir platelet count.

[b] Patients with a platelet count <150x10^9/L at ICU admission.

[c] Patients with a platelet count <150x10^9/L during ICU stay without thrombocytopenia at ICU admission.

[d] Any continuous treatment with norepinephrine, epinephrine, phenylephrine, vasopressin analogues, dopamine, dobutamine, milrinone or levosimendan at any point in time during ICU stay.

[e] Use of positive pressure ventilation using a ventilator via a cuffed tube (oral, nasal or tracheostomy) at any point in time during ICU stay.

[f] Treatment with any form of renal replacement therapy (e.g., dialysis, hemofiltration or hemodiafiltration) at any rate at any point in time during ICU stay.

[g] Treatment with any form of extracorporeal membrane oxygenation at any point in time during ICU stay

Abbreviations: intensive care unit (ICU), extra corporal membrane oxygenation (ECMO), confidence interval (CI).

ESM 22. Transfusions during ICU stay

	All	Thrombocytopenia							
		No	Any [a]	Mild	Moderate	Severe	Very severe	Baseline [b]	ICU [c]
	(n=1166)	(n=662)	(n=504)	(n=214)	(n=156)	(n=65)	(n=69)	(n=273)	(n=231)
Platelet transfusions									
In-ICU platelet transfusions									
Prophylaxis	365 (58.4%)	1 (14.3%)	364 (58.9%)	5 (20.0%)	9 (23.7%)	49 (34.0%)	301 (73.2%)	326 (70.4%)	38 (24.5%)
Therapeutic	157 (25.1%)	1 (14.3%)	156 (25.2%)	5 (20.0%)	15 (39.5%)	66 (45.8%)	70 (17.0%)	85 (18.4%)	71 (45.8%)
Pre-procedural	46 (7.4%)	1 (14.3%)	45 (7.3%)	1 (4.0%)	2 (5.3%)	15 (10.4%)	27 (6.6%)	35 (7.6%)	10 (6.5%)
Platelet transfusions during surgery									
Administered during surgery	57 (9.1%)	4 (57.1%)	53 (8.6%)	14 (56.0%)	12 (31.6%)	14 (9.7%)	13 (3.2%)	17 (3.7%)	36 (23.2%)
RBC transfusions									
In-ICU RBC transfusions									
Administered in the ICU	1216 (77.9%)	195 (85.9%)	1021 (76.5%)	188 (70.1%)	304 (69.6%)	218 (75.4%)	311 (91.5%)	545 (81.1%)	476 (71.9%)
RBC transfusions during surgery									
Administered during surgery	345 (22.1%)	32 (14.1%)	313 (23.5%)	80 (29.9%)	133 (30.4%)	71 (24.6%)	29 (8.5%)	127 (18.9%)	186 (28.1%)

Number of platelet- and RBC transfusions (%) used in the ICU (in-ICU) and during surgery while admitted to the ICU. For in-ICU platelet transfusions, data for platelet transfusions are presented for each indication. We did not collect data on indications for platelet transfusions administered during surgery. Lowercase “n” corresponds to the number of patients in each group.

[a] Patients with a platelet count <150x10^9/L at ICU admission and/or during the ICU stay and within the specified severity subclasses according to the overall nadir platelet count.

[b] Patients with a platelet count <150x10^9/L at ICU admission.

[c] Patients with a platelet count <150x10^9/L during ICU stay without thrombocytopenia at ICU admission.

Abbreviations: intensive care unit (ICU), red blood cells (RBC).

ESM 23. Platelet count before in-ICU pre-procedural platelet transfusions.

Procedure	No. of transfusions	Platelet count prior to transfusion [a]
CVC / dialysis catheter	21	27 (20–49) [5–126]
Lumbar puncture [b]	3	10; 22; 45
Epidural	1	57
Biopsy [b]	1	10
CNS surgery [c]	2	88; 266
Other surgery	5	31 (29–32) [13–45]
PDT	7	65 (38–66) [2–122]
Pigtail catheter	5	20 (17–31) [15–31]
Chest tube	2	42; 44

Platelet counts ($x10^9$/L) prior to pre-procedural platelet transfusions administered in the ICU for each procedure. Presentation of this process variable was added *post hoc*, and assumptions made during computation are explained in ESM 1. Transfusions administered during surgery are excluded as we did not collect data on indications and platelet counts prior to transfusions for these transfusions.

[a] Summarised using median (interquartile range) [full range], except where <5 transfusions were given, in which case all values are listed in ascending order separated by semicolons.
[b] One patient received a single pre-procedural platelet transfusion before lumbar puncture and biopsy. The platelet count prior to this transfusion was for both procedures.
[c] All cases of CNS surgery were placement or removal of extra-ventricular drain- or intracranial pressure devices.

Abbreviations: central venous catheter (CVC), central nervous system (CNS), percutaneous dilatational tracheostomy (PDT).

ESM 24. Model fits for the primary models

Method

Model fits were assessed by Nagelkerke's R^2 [21] and visually by calibration plots [22]. The calibration plots show the observed outcome (dependent variable) vs. the predicted risk of the outcome (independent variable) in 10 predicted risk deciles and a *loess smoother* with 95% confidence bands. Calibration plots were not assessed for the binary variables in the unadjusted analyses.

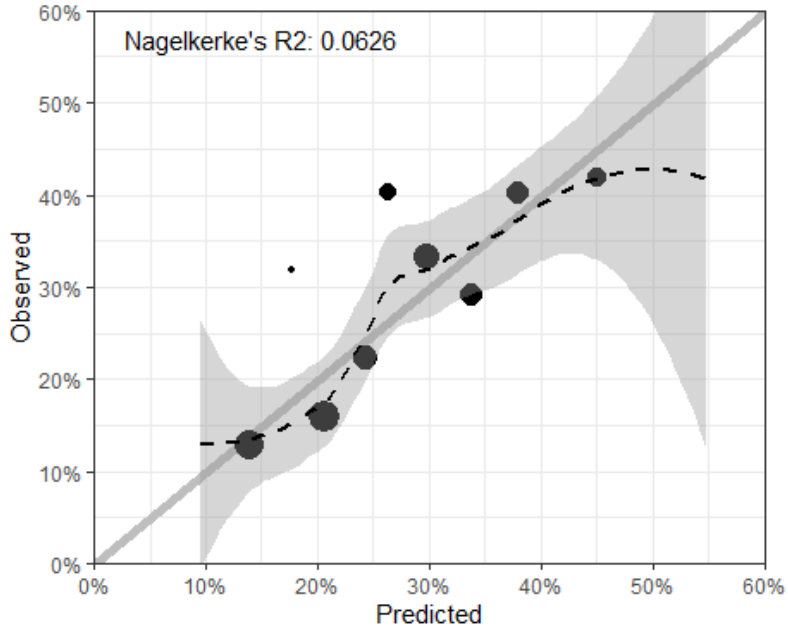
Unadjusted analyses: risk factors for ICU thrombocytopenia < 150x10^9/L

Independent variable	Dependent variable	Nagelkerke's R^2
Male sex	ICU thrombocytopenia < 150x10^9/L	0.0102
SMS-ICU [a]		0.0626
Bleeding [b]		0.0232
Haematological malignancy		0.0017
Non-AIDS-, non-cancer-related immune deficiency [c]		0.0173
Liver failure		0.0363
Septic shock		0.0484

Nagelkerkes's R^2 for the unadjusted analyses of risk factors for ICU thrombocytopenia < 150x10^9/L.

[a] SMS-ICU; an illness severity score ranging from 0-42 points with higher scores indicating higher predicted 90-day mortality [1, 2].
[b] Any WHO bleeding at baseline.
[c] Non-AIDS-, non-cancer-related immune deficiencies including solid organ transplant or conditions requiring long-term (> 30 days) or high-dose (> 1 mg/kg/day) steroids, or any immunosuppressive drug for more than 30 days.

Abbreviations: intensive care unit (ICU), Simplified Mortality Score for the Intensive Care Unit (SMS-ICU), World Health Organization (WHO), acquired immune deficiency syndrome (AIDS).



Calibration plot for the model including only SMS-ICU as the independent variable. The grey identity line represents perfect fit and the dashed line with 95% confidence bands represents a *loess smoother*. Black dots represents the predicted risk deciles sized according to the number of patients in each group; only 9 deciles were formed as patients with the same predicted risk are included in the same deciles. Uncertainty exist in both tails as these are based on few observations. Note that the scaling varies between plots.

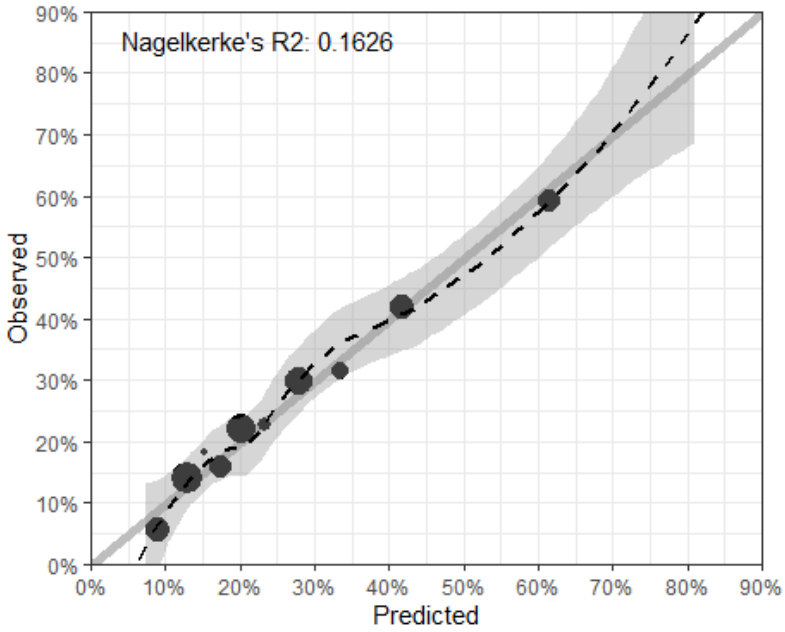
Adjusted analysis: risk factors for ICU thrombocytopenia < 150x10^9/L

Independent variables	Dependent variable	Nagelkerke's R^2
Male sex SMS-ICU [a] Bleeding [b] Haematological malignancy Non-AIDS-, non-cancer-related immune deficiency [c] Liver failure Septic shock	ICU thrombocytopenia < 150x10^9/L	0.1626

Nagelkerkes's R^2 for the adjusted analysis of risk factors for ICU thrombocytopenia < 150x10^9/L.

[a] SMS-ICU; an illness severity score ranging from 0-42 points with higher scores indicating higher predicted 90-day mortality [1, 2].
[b] Any WHO bleeding at baseline.
[c] Non-AIDS-, non-cancer-related immune deficiencies including solid organ transplant or conditions requiring long-term (> 30 days) or high-dose (> 1 mg/kg/day) steroids, or any immunosuppressive drug for more than 30 days.

Abbreviations: intensive care unit (ICU), Simplified Mortality Score for the Intensive Care Unit (SMS-ICU), World Health Organization (WHO), acquired immune deficiency syndrome (AIDS).



Calibration plot for the full model including all risk factors as the independent variables. The grey identity line represents perfect fit and the dashed line with 95% confidence bands represents a *loess smoother*. Black dots represents the predicted risk deciles sized according to the number of patients in each group. Uncertainty exist in both tails as these are based on few observations. Note that the scaling varies between plots.

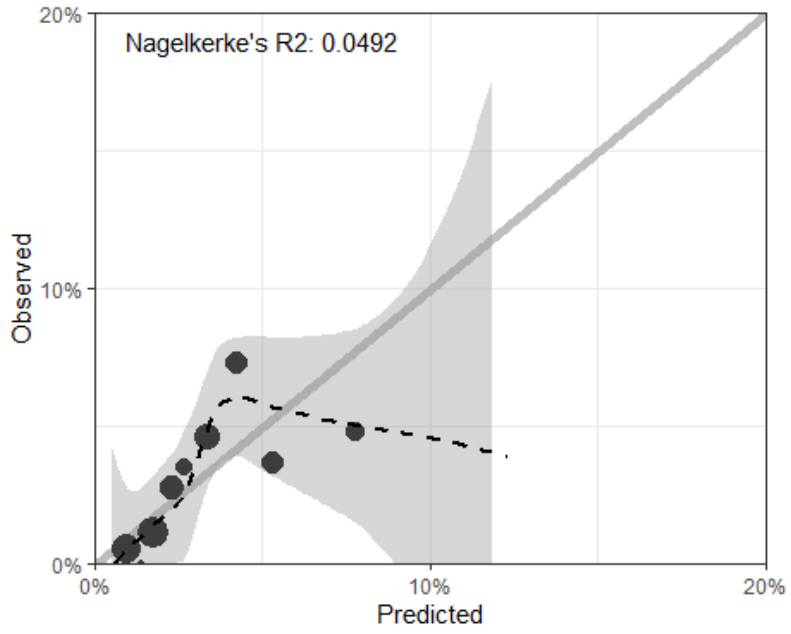
Unadjusted analyses: risk factors for ICU thrombocytopenia < 50x10^9/L

Independent variable	Dependent variable	Nagelkerke's R^2
Male sex	ICU thrombocytopenia < 50x10^9/L	0.0011
SMS-ICU [a]		0.0492
Bleeding [b]		0.0001
Haematological malignancy		0.0074
Non-AIDS-, non-cancer-related immune deficiency [c]		0.0404
Liver failure		0.0099
Septic shock		0.1273

Nagelkerkes's R^2 for the unadjusted analyses of risk factors for ICU thrombocytopenia < 50x10^9/L.

[a] SMS-ICU; an illness severity score ranging from 0-42 points with higher scores indicating higher predicted 90-day mortality [1, 2].
[b] Any WHO bleeding at baseline.
[c] Non-AIDS-, non-cancer-related immune deficiencies including solid organ transplant or conditions requiring long-term (> 30 days) or high-dose (> 1 mg/kg/day) steroids, or any immunosuppressive drug for more than 30 days.

Abbreviations: intensive care unit (ICU), Simplified Mortality Score for the Intensive Care Unit (SMS-ICU), World Health Organization (WHO), acquired immune deficiency syndrome (AIDS).



Calibration plot for the model including only SMS-ICU as the independent variable. The grey identity line represents perfect fit and the dashed line with 95% confidence bands represents a *loess smoother*. Black dots represents the predicted risk deciles sized according to the number of patients in each group; only 9 deciles were formed as patients with the same predicted risk are included in the same deciles). Meaningful interpretation of calibration plot (and the model) is hampered by the low number of events (n =26). Note that the scaling varies between plots.

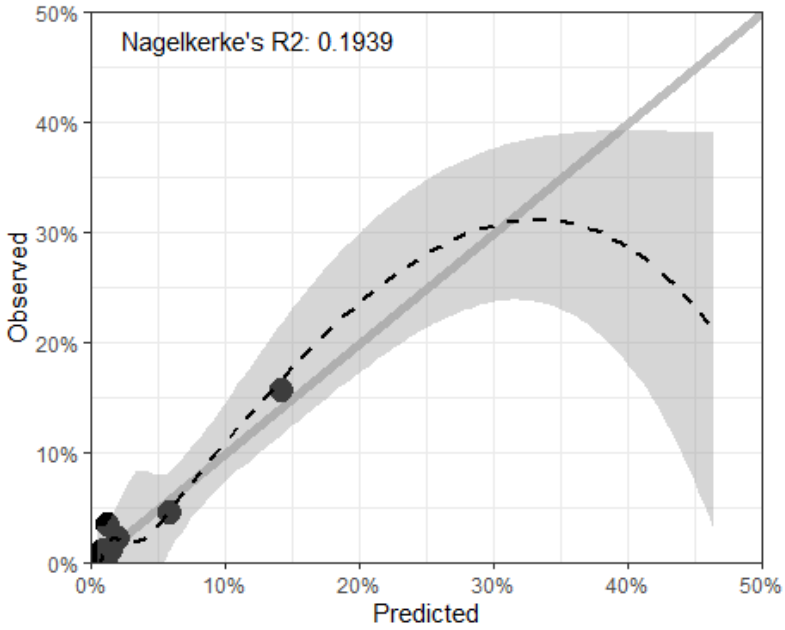
Adjusted analysis: risk factors for ICU thrombocytopenia < $50x10^9$/L

Independent variables	Dependent variable	Nagelkerke's R^2
Male sex SMS-ICU[a] Bleeding [b] Haematological malignancy Non-AIDS-, non-cancer-related immune deficiency [c] Liver failure Septic shock	ICU thrombocytopenia < $50x10^9$/L	0.1939

Nagelkerkes's R^2 for the adjusted analysis of risk factors for ICU thrombocytopenia < $50x10^9$/L..

[a] SMS-ICU; an illness severity score ranging from 0-42 points with higher scores indicating higher predicted 90-day mortality [1, 2].
[b] Any WHO bleeding at baseline.
[c] Non-AIDS-, non-cancer-related immune deficiencies including solid organ transplant or conditions requiring long-term (> 30 days) or high-dose (> 1 mg/kg/day) steroids, or any immunosuppressive drug for more than 30 days.

Abbreviations: intensive care unit (ICU), Simplified Mortality Score for the Intensive Care Unit (SMS-ICU), World Health Organization (WHO), acquired immune deficiency syndrome (AIDS).



Calibration plot for the full model including all risk factors as independent variables. The grey identity line represents perfect fit and the dashed line with 95% confidence bands represents a *loess smoother*. Black dots represents the predicted risk deciles sized according to the number of patients in each group. Meaningful interpretation of calibration plot (and the model) is hampered by the low number of events (n =26). Note that the scaling varies between plots.

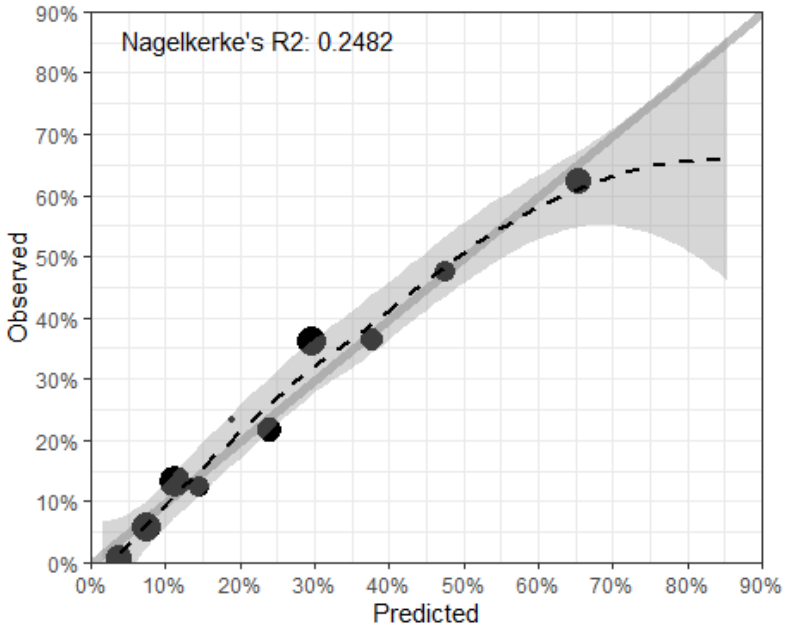
Adjusted analysis: association between baseline thrombocytopenia <150x10^9/L and 90-day mortality

Independent variables	Dependent variable	Nagelkerke's R^2
Baseline thrombocytopenia < 150x10^9/L Male SMS-ICU [a] Haematological malignancy Country [b] Septic shock	90-day mortality	0.2482

Nagelkerkes's R^2 for the adjusted analysis of the association between baseline thrombocytopenia < 150x10^9/L and 90-day mortality.

[a] SMS-ICU; an illness severity score ranging from 0-42 points with higher scores indicating higher predicted 90-day mortality [1, 2].

Abbreviations: Simplified Mortality Score for the Intensive Care Unit (SMS-ICU).



Calibration plot for the full model assessing the impact of baseline thrombocytopenia <150x10^9/L on 90-day mortality. The grey identity line represents perfect fit and the dashed line with 95% confidence bands represents a *loess smoother*. Black dots represents the predicted risk deciles sized according to the number of patients in each group. Uncertainty exist in both tails as these are based on few observations. Note that the scaling varies between plots.

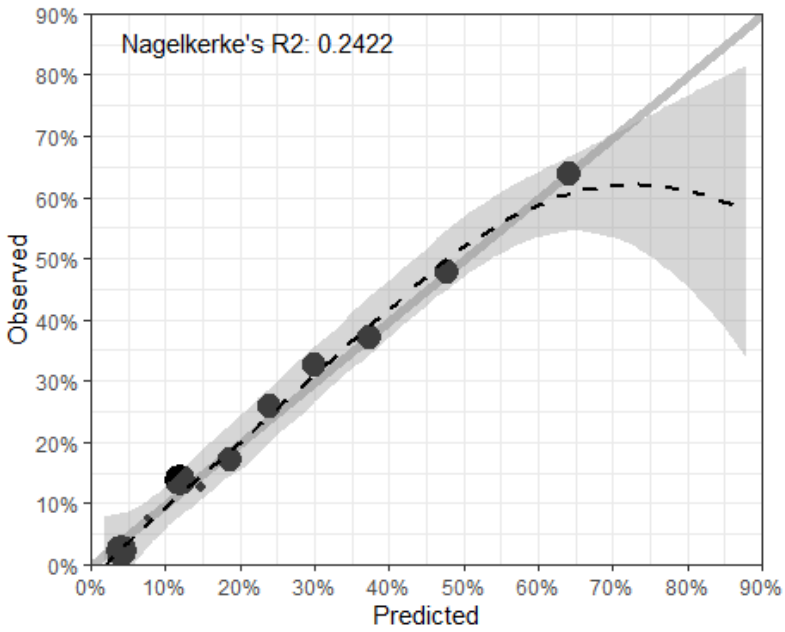
Adjusted analysis: association between baseline thrombocytopenia <50x10^9/L and 90-day mortality

Independent variables	Dependent variable	Nagelkerke's R^2
Baseline thrombocytopenia < 50x10^9/L Male SMS-ICU Haematological malignancy Country Septic shock	90-day mortality	0.2422

Nagelkerkes's R^2 for the adjusted analysis of the association between baseline thrombocytopenia < 50x10^9/L and 90-day mortality.

[a] SMS-ICU; an illness severity score ranging from 0-42 points with higher scores indicating higher predicted 90-day mortality [1, 2].
[b] Country of inclusion.

Abbreviations: Simplified Mortality Score for the Intensive Care Unit (SMS-ICU).



Calibration plot for the full model assessing the impact of baseline thrombocytopenia <50x10^9/L on 90-day mortality. The grey identity line represents perfect fit and the dashed line with 95% confidence bands represents a *loess smoother*. Black dots represents the predicted risk deciles sized according to the number of patients in each group. Uncertainty exist in both tails as these are based on few observations. Note that the scaling varies between plots.

ESM 25. Sensitivity analyses of risk factor analyses

During the peer-review process, we performed three post hoc sensitivity analyses to challenge the results of the primary logistic regression models.

Sensitivity analysis 1

Method

To assess impact of missing platelet counts on baseline and during ICU stay and the assumptions made, we performed the analysis of risk factors for ICU thrombocytopenia <150x10^9/L in complete cases only (i.e., patients with available platelet counts on baseline AND during ICU stay who did not have thrombocytopenia (<150x10^9/L) at baseline). Due to few events (n = 26) of severe ICU thrombocytopenia, we did not perform a similar analysis for risk factors for severe ICU thrombocytopenia as it would not have any meaningful interpretation.

Results

	ICU thrombocytopenia <150x10^9/L [a] OR (95% CI)	
	Unadjusted	**Adjusted [b]**
Male sex	1.42 (1.02 to 1.98)	1.42 (0.996 to 2.03)
SMS-ICU [c]	1.07 (1.04 to 1.10)	1.06 (1.03 to 1.09)
Bleeding [d]	2.11 (1.38 to 3.23)	2.14 (1.36 to 3.37)
Haematological malignancy	1.24 (0.52 to 2.93)	0.99 (0.39 to 2.49)
Non-AIDS-, non-cancer-related immune deficiency [e]	3.18 (1.50 to 6.74)	4.29 (1.95 to 9.45)
Liver failure	4.62 (2.34 to 9.12)	4.38 (2.14 to 8.93)
Septic shock	2.78 (1.81 to 4.27)	2.29 (1.43 to 3.66)

Baseline risk factors for ICU thrombocytopenia in 725 patients with available platelet counts at baseline and during ICU stay who did not have thrombocytopenia at baseline.

[a] Patients with at least one recorded platelet count <150x10^9/L during ICU stay without pre-existing thrombocytopenia at ICU admission.

[b] Adjusted for the following baseline variables: male sex, SMS-ICU, bleeding, haematological malignancy, non-AIDS-, non-cancer-related immune deficiency, liver failure (acute or chronic) and septic shock.

[c] OR for a one-point increase in SMS-ICU; an illness severity score ranging from 0-42 points with higher scores indicating higher predicted 90-day mortality [1, 2].

[d] Any WHO bleeding at baseline.

[e] Non-AIDS-, non-cancer-related immune deficiencies including solid organ transplant or conditions requiring long-term (> 30 days) or high-dose (> 1 mg/kg/day) steroids, or any immunosuppressive drug for more than 30 days.

Abbreviations: intensive care unit (ICU), odds ratio (OR), confidence interval (CI), Simplified Mortality Score for the Intensive care Unit (SMS-ICU), World Health Organization (WHO), acquired immune deficiency syndrome (AIDS).

Interpretation

Complete case analysis were largely consistent with the primary analysis; 95% CIs were slightly wider due to the decreased sample size.

Sensitivity analysis 2

Method

To control for age as an individual variable in the assessment of risk factors for ICU thrombocytopenia <150x10^9/L we included age as a continuous variable in model. Due to few events (n = 26) of severe ICU thrombocytopenia (<50x10^9/L), we did not perform a similar analysis for risk factors for ICU thrombocytopenia <50x10^9/L as it would not have any meaningful interpretation.

Results

	ICU thrombocytopenia <150x10^9/L [a] OR (95% CI)	
	Unadjusted	**Adjusted [b]**
Male sex	1.48 (1.08 to 2.02)	1.46 (1.05 to 2.05)
SMS-ICU [c]	1.07 (1.05 to 1.10)	1.09 (1.06 to 1.13)
Bleeding [d]	2.25 (1.49 to 3.39)	2.19 (1.41 to 3.40)
Haematological malignancy	1.54 (0.68 to 3.50)	1.08 (0.44 to 2.64)
Non-AIDS-, non-cancer-related immune deficiency [e]	3.03 (1.58 to 5.84)	4.41 (2.19 to 8.90)
Liver failure	4.60 (2.44 to 8.70)	3.86 (1.96 to 7.62)
Septic shock	3.18 (2.12 to 4.77)	2.44 (1.56 to 3.82)
Age [f]	1.03 (0.99 to 1.08)	0.92 (0.86 to 0.98)

Baseline risk factors for ICU thrombocytopenia in 893 patients without baseline thrombocytopenia using a model with age added as a continuous variable.

[a] Patients with at least one recorded platelet count <150x10^9/L during ICU stay without pre-existing thrombocytopenia at ICU admission.

[b] Adjusted for the following baseline variables: male sex, SMS-ICU, bleeding, haematological malignancy, non-AIDS-, non-cancer-related immune deficiency, liver failure (acute or chronic) and septic shock.

[c] OR for a one-point increase in SMS-ICU; an illness severity score ranging from 0-42 points with higher scores indicating higher predicted 90-day mortality[1, 2].

[d] Any WHO bleeding at baseline.

[e] Non-AIDS-, non-cancer-related immune deficiencies including solid organ transplant or conditions requiring long-term (> 30 days) or high-dose (> 1 mg/kg/day) steroids, or any immunosuppressive drug for more than 30 days.

[f] OR for a five-year increase

Abbreviations: intensive care unit (ICU), odds ratio (OR), confidence interval (CI) Simplified Mortality Score for the Intensive care Unit (SMS-ICU), World Health Organization (WHO), acquired immune deficiency syndrome (AIDS).

Interpretation

Adding age as an individual variable in the model did not change results and estimates for the ORs and 95% CIs for the selected risk factors were comparable to the primary analysis.

Sensitivity analysis 3

Method

To account for competing risks in the analysis of risk factors for ICU thrombocytopenia <150x10^9/L, we carried out the analysis using a Cox proportional hazards model censoring patients at death, last ICU discharge (assuming that no events occurred on days between ICU admissions) and loss to follow-up, whichever came first. We observed no statistically significant evidence of non-linearity of the 'SMS-ICU' variable. We observed statistically significant evidence against the proportional hazards assumption for the variables 'bleeding' and 'haematological malignancy' and thus, we used a time-transformation with a cut-off at days 1–2 vs. days 3–90 for these variables. Results without the time-transformation are also reported; in these, estimates can be interpreted as the average effects over the full period. Due to few events of severe ICU thrombocytopenia (n = 26), we did not perform a similar analysis for risk factors for ICU thrombocytopenia <50x10^9/L as it would not have any meaningful interpretation.

Results

Cox proportional hazards regression model with time-transformation

	ICU thrombocytopenia <150x10^9/L [a] HR (95% CI)	
	Unadjusted	**Adjusted [b]**
Male sex	1.35 (1.03 to 1.77)	1.29 (0.98 to 1.69)
SMS-ICU [c]	1.05 (1.03 to 1.07)	1.04 (1.02 to 1.06)
Bleeding [d]	2.70 (1.82 to 4.01)	2.62 (1.76 to 3.90)
Haematological malignancy	1.29 (0.72 to 2.31)	0.25 (0.06 to 1.06)
Non-AIDS-, non-cancer-related immune deficiency [e]	2.18 (1.36 to 3.49)	2.16 (1.37 to 3.43)
Liver failure	3.48 (2.30 to 5.28)	2.88 (1.89 to 4.39)
Septic shock	2.20 (1.62 to 2.98)	1.78 (1.29 to 2.47)

Baseline risk factors for ICU thrombocytopenia in 893 patients without baseline thrombocytopenia assessed using a proportional hazards model using a time-transformation with a cut-off at days 1-2 vs. days 3-90 for the variables 'bleeding' and 'haematological malignancy'. The primary estimates for 'bleeding' and 'haematological malignancy' in the table are for the early period. The HR for 'bleeding' and 'haematological malignancy' in the later period was 1.29 (0.72 to 2.31) and 2.42 (1.12 to 5.21) in the unadjusted analyses and 1.19 (0.66 to 2.14) and 1.77 (0.79 to 3.96) in the adjusted analysis, respectively.

[a] Patients a platelet count <150x10^9/L during ICU stay without thrombocytopenia at ICU admission.

[b] Adjusted for the following baseline variables: male sex, SMS-ICU, bleeding, haematological malignancy, non-AIDS.-, non-cancer-related immune deficiency, liver failure (acute or chronic) and septic shock.

[c] HR for a one-point increase in SMS-ICU; an illness severity score ranging from 0-42 points with higher scores indicating higher predicted 90-day mortality [1, 2].

[d] Any WHO bleeding at baseline.

[e] Non-AIDS-, non-cancer-related immune deficiencies including solid organ transplant or conditions requiring long-term (> 30 days) or high-dose (> 1 mg/kg/day) steroids, or any immunosuppressive drug for more than 30 days.

Abbreviations: intensive care unit (ICU), hazard ratio (HR), confidence interval (CI), Simplified Mortality Score for the Intensive Care Unit (SMS-ICU), World Health Organization (WHO), acquired immune deficiency syndrome (AIDS).

Cox proportional hazards regression model without time-transformation

	ICU thrombocytopenia <150x10^9/L [a] HR (95% CI)	
	Unadjusted	**Adjusted [b]**
Male sex	1.35 (1.03 to 1.77)	1.31 (1.001 to 1.73)
SMS-ICU [c]	1.05 (1.03 to 1.07)	1.04 (1.02 to 1.06)
Bleeding [d]	2.06 (1.49 to 2.84)	2.01 (1.45 to 2.78)
Haematological malignancy	1.27 (0.65 to 2.48)	1.10 (0.56 to 2.19)
Non-AIDS-, non-cancer-related immune deficiency [e]	2.18 (1.36 to 3.49)	2.68 (1.66 to 4.31)
Liver failure	3.48 (2.30 to 5.28)	2.93 (1.92 to 4.48)
Septic shock	2.20 (1.62 to 2.98)	1.74 (1.26 to 2.42)

Baseline risk factors for ICU thrombocytopenia in 893 patients without baseline thrombocytopenia assessed using a proportional hazards model without using time-transformation; these estimates can be interpreted as the average effects over the full period.

[a] Patients a platelet count <150x10^9/L during ICU stay without thrombocytopenia at ICU admission.

[b] Adjusted for the following baseline variables: male sex, SMS-ICU, bleeding, haematological malignancy, non-AIDS-, non-cancer-related immune deficiency, liver failure (acute or chronic) and septic shock.

[c] HR for a one-point increase in SMS-ICU; an illness severity score ranging from 0-42 points with higher scores indicating higher predicted 90-day mortality.

[d] Any WHO bleeding at baseline.

[e] Non-AIDS-, non-cancer-related immune deficiencies including solid organ transplant or conditions requiring long-term (> 30 days) or high-dose (> 1 mg/kg/day) steroids, or any immunosuppressive drug for more than 30 days.

Abbreviations: intensive care unit (ICU), hazard ratio (HR), confidence interval (CI), Simplified Mortality Score for the Intensive Care Unit (SMS-ICU), World Health Organization (WHO), acquired immune deficiency syndrome (AIDS).

.

Interpretation

Results from both models were largely consistent with the primary analyses. Using time-transformation specified above, there was some uncertainty about the association between male sex and ICU thrombocytopenia in the adjusted analyses and bleeding was only associated with ICU thrombocytopenia in the earlier period but not in the later period.

ESM 26. Full results of the analysis of the association between baseline thrombocytopenia and 90-day mortality

	Adjusted OR (95% CI) for 90-day mortality assessing baseline thrombocytopenia < 150x10^9/L	**Adjusted OR (95% CI) for 90-day mortality assessing baseline thrombocytopenia < 50x10^9/L**
Baseline thrombocytopenia	**1.70 (1.19 to 2.42)**	**1.79 (0.89 to 3.61)**
Male sex	0.82 (0.61 to 1.10)	0.85 (0.63 to 1.14)
SMS-ICU [a]	1.16 (1.13 to 1.19)	1.16 (1.13 to 1.19)
Haematological malignancy	1.07 (0.63 to 1.81)	1.06 (0.60 to 1.90)
Country – Finland	0.31 (0.09 to 1.12)	0.33 (0.09 to 1.18)
Country – France	0.82 (0.54 to 1.24)	0.84 (0.56 to 1.27)
Country – Germany	1.35 (0.56 to 3.26)	1.41 (0.58 to 3.42)
Country – Norway	1.45 (0.86 to 2.45)	1.41 (0.83 to 2.39)
Country – Portugal	0.99 (0.50 to 1.94)	1.01 (0.52 to 1.97)
Country – Spain	0.50 (0.25 to 0.97)	0.50 (0.25 to 0.98)
Country – Sweden	1.14 (0.51 to 2.56)	1.08 (0.48 to 2.42)
Country – UK	0.80 (0.47 to 1.37)	0.85 (0.50 to 1.44)
Country – USA	1.01 (0.56 to 1.84)	1.15 (0.64 to 2.06)
Septic shock	1.04 (0.71 to 1.53)	1.07 (0.73 to 1.57)

Adjusted ORs with 95% CIs for 90-day mortality for all variables included in the logistic regression model. Denmark was the reference country. Four patients (0.3%) with missing outcome data for 90-day mortality were excluded from the analyses.

[a] SMS-ICU; an illness severity score ranging from 0-42 points with higher scores indicating higher predicted 90-day mortality [1, 2].

Abbreviations: odds ratio (OR), Simplified Mortality Score for the Intensive Care Unit (SMS-ICU), intensive care unit (ICU), United Kingdom (UK), United States of America (USA).

ESM 27. Sensitivity analyses of the association between baseline thrombocytopenia and 90-day mortality

During the peer-review process, we performed two post hoc sensitivity analyses to challenge the results of the primary logistic regression analyses.

Sensitivity analysis 1

Method

To assess impact of missing platelet counts on baseline and the assumptions made (ESM 13) we performed the analysis of the associations between baseline thrombocytopenia (<150x10^9/L and <50x10^9/L) and 90-day mortality in complete cases only (i.e., patients with available platelet count at baseline).

Results

	Adjusted OR (95% CI) for 90-day mortality assessing baseline thrombocytopenia as < 150x10^9/L	**Adjusted OR (95% CI) for 90-day mortality assessing severe baseline thrombocytopenia as < 50x10^9/L**
Baseline thrombocytopenia	**1.75 (1.20 to 2.56)**	**1.57 (0.75 to 3.27)**
Male sex	0.85 (0.61 to 1.17)	0.88 (0.64 to 1.22)
SMS-ICU [a]	1.15 (1.12 to 1.19)	1.16 (1.12 to 1.19)
Haematological malignancy	0.98 (0.56 to 1.72)	1.04 (0.56 to 1.92)
Country – Finland	0.33 (0.09 to 1.19)	0.35 (0.10 to 1.28)
Country – France	0.86 (0.54 to 1.37)	0.90 (0.57 to 1.42)
Country – Germany	1.47 (0.60 to 3.59)	1.60 (0.65 to 3.94)
Country – Norway	1.54 (0.89 to 2.69)	1.50 (0.86 to 2.62)
Country – Portugal	0.83 (0.41 to 1.70)	0.85 (0.42 to 1.74)
Country – Spain	0.45 (0.22 to 0.90)	0.45 (0.23 to 0.91)
Country – Sweden	0.60 (0.19 to 1.89)	0.58 (0.18 to 1.84)
Country – UK	0.80 (0.47 to 1.38)	0.85 (0.50 to 1.46)
Country – USA	1.12 (0.59 to 2.12)	1.27 (0.68 to 2.36)
Septic shock	1.05 (0.70 to 1.57)	1.08 (0.72 to 1.62)

Adjusted ORs with 95% CIs for 90-day mortality for all variables included in the logistic regression model in 971 patients with available platelet counts on baseline. An additional two patients were excluded because of missing 90-day mortality. Denmark was the reference country.

[a] SMS-ICU; an illness severity score ranging from 0-42 points with higher scores indicating higher predicted 90-day mortality [1, 2].

Abbreviations: hazard ratio (HR), Simplified Mortality Score for the Intensive Care Unit (SMS-ICU), intensive care unit (ICU), United Kingdom (UK), United States of America (USA).

Interpretation

Results were consistent with the primary analysis.

Sensitivity analysis 2

Method

To account for the time to death in the analysis of the associations between baseline thrombocytopenia <150x10^9/L and <50x10^9/L and 90-day mortality, we carried out the analysis using a Cox proportional hazards model censoring patients with loss to follow-up at last day (with data) in the ICU within the 90-day follow-up period. We observed statistically significant evidence for non-linearity of the SMS-ICU. Thus, we introduced an additional term with a transformation of SMS-ICU (SMS-ICU x log(SMS-ICU + 1) in the model. We observed no statistically significant evidence against the proportional hazards assumption.

Results

	Adjusted HR (95% CI) for 90-day mortality assessing baseline thrombocytopenia as < 150x10^9/L	**Adjusted HR (95% CI) for 90-day mortality assessing severe baseline thrombocytopenia as 50x10^9/L**
Baseline thrombocytopenia	**1.38 (1.05 to 1.80)**	**1.40 (0.85 to 2.29)**
Male sex	0.85 (0.67 to 1.08)	0.87 (0.69 to 1.10)
SMS-ICU [a]	1.94 (1.32 to 2.84)	1.91 (1.30 to 2.80)
SMS-ICU x log(SMS-ICU + 1)	0.87 (0.79 to 0.96)	0.87 (0.79 to 0.96)
Haematological malignancy	1.01 (0.69 to 1.47)	1.01 (0.66 to 1.53)
Country – Finland	0.38 (0.12 to 1.19)	0.39 (0.12 to 1.23)
Country – France	0.91 (0.65 to 1.26)	0.91 (0.65 to 1.26)
Country – Germany	1.62 (0.88 to 2.97)	1.71 (0.93 to 3.15)
Country – Norway	1.38 (0.93 to 2.05)	1.35 (0.90 to 2.00)
Country – Portugal	1.01 (0.61 to 1.67)	1.01 (0.61 to 1.68)
Country – Spain	0.57 (0.33 to 1.00)	0.57 (0.33 to 0.99)
Country – Sweden	1.16 (0.60 to 2.25)	1.12 (0.58 to 2.17)
Country – UK	0.89 (0.57 to 1.37)	0.91 (0.59 to 1.40)
Country – USA	1.05 (0.68 to 1.63)	1.13 (0.73 to 1.74)
Septic shock	1.07 (0.81 to 1.42)	1.08 (0.81 to 1.43)

Adjusted HRs with 95% CIs for 90-day mortality for all variables included in the proportional hazards model. Denmark was the reference country.

[a] SMS-ICU; an illness severity score ranging from 0-42 points with higher scores indicating higher predicted 90-day mortality [1, 2].

Abbreviations: hazard ratio (HR), Simplified Mortality Score for the Intensive Care Unit (SMS-ICU), intensive care unit (ICU), United Kingdom (UK), United States of America (USA).

Interpretation

Results were largely consistent with the primary analysis.

ESM 28. Baseline variables stratified by outcome

The tables below show baseline variables included in the logistic regression models stratified by outcome (i.e, ICU thrombocytopenia <150x10^9/L, ICU thrombocytopenia <50x10^9/L and 90-day mortality, respectively). Categorical variables are presented as numbers and percentages while continuous variables are presented with medians and interquartile ranges.

	ICU thrombocytopenia <150x10^9/L	
Baseline variable	**No (n = 662)**	**Yes (n = 231)**
Male sex	371 (56.0%)	151 (65.4%)
SMS-ICU [a]	15.0 (11.0 - 20.0)	18.0 (13.5 - 23.0)
Bleeding [b]	66 (10.0%)	46 (19.9%)
Haematological malignancy	17 (2.6%)	9 (3.9%)
Non-AIDS-, non-cancer-related immune deficiency [c]	19 (2.9%)	19 (8.2%)
Liver failure	17 (2.6%)	25 (10.8%)
Septic Shock	58 (8.8%)	54 (23.4%)

Patients with baseline thrombocytopenia are excluded (n = 273).

[a] SMS-ICU; an illness severity score ranging from 0-42 points with higher scores indicating higher predicted 90-day mortality [1, 2].
[b] Any WHO bleeding at baseline.
[c] Non-AIDS-, non-cancer-related immune deficiencies including solid organ transplant or conditions requiring long-term (> 30 days) or high-dose (> 1 mg/kg/day) steroids, or any immunosuppressive drug for more than 30 days.

Abbreviations: intensive care unit (ICU), Simplified Mortality Score for the Intensive Care Unit (SMS-ICU), World Health Organization (WHO), acquired immune deficiency syndrome (AIDS).

	ICU thrombocytopenia <50x10^9/L	
Baseline variable	**No (n = 867)**	**Yes (n = 26)**
Male sex	508 (58.6%)	14 (53.8%)
SMS-ICU	16.0 (12.0 - 20.0)	20.0 (17.0 - 22.0)
Bleeding	109 (12.6%)	3 (11.5%)
Haematological malignancy	24 (2.8%)	2 (7.7%)
Non-AIDS-, non-cancer-related immune deficiency	33 (3.8%)	5 (19.2%)
Liver failure	39 (4.5%)	3 (11.5%)
Septic Shock	98 (11.3%)	14 (53.8%)

Patients with baseline thrombocytopenia are excluded (n = 273).

[a] SMS-ICU; an illness severity score ranging from 0-42 points with higher scores indicating higher predicted 90-day mortality [1, 2].
[b] Any WHO bleeding at baseline.
[c] Non-AIDS-, non-cancer-related immune deficiencies including solid organ transplant or conditions requiring long-term (> 30 days) or high-dose (> 1 mg/kg/day) steroids, or any immunosuppressive drug for more than 30 days.

Abbreviations: intensive care unit (ICU), Simplified Mortality Score for the Intensive Care Unit (SMS-ICU), World Health Organization (WHO), acquired immune deficiency syndrome (AIDS).

	Dead at day 90	
Baseline variable	**No (n = 861)**	**Yes (n = 301)**
Male sex	521 (60.5%)	182 (60.5%)
SMS-ICU [a]	15.0 (11.0 - 20.0)	22.0 (17.0 - 25.0)
Haematological malignancy	49 (5.7%)	43 (14.3%)
Septic shock	105 (12.2%)	69 (22.9%)
Country [b]		
- Denmark	215 (25.0%)	80 (26.6%)
- Finland	22 (2.6%)	3 (1.0%)
- France	252 (29.3%)	67 (22.3%)
- Germany	16 (1.9%)	14 (4.7%)
- Norway	65 (7.5%)	36 (12.0%)
- Portugal	40 (4.6%)	19 (6.3%)
- Spain	61 (7.1%)	15 (5.0%)
- Sweden	30 (3.5%)	10 (3.3%)
- UK	109 (12.7%)	28 (9.3%)
- USA	51 (5.9%)	29 (9.6%)
Baseline thrombocytopenia < $150x10^9$/L	171 (19.9%)	102 (33.9%)
Baseline thrombocytopenia < $50x10^9$/L	36 (4.2%)	27 (9.0%)

Four patients (0.3%) with missing data on 90-day mortality were excluded.

[a] SMS-ICU; an illness severity score ranging from 0-42 points with higher scores indicating higher predicted 90-day mortality [1, 2].
[b] Country of inclusion.

Abbreviations: Simplified Mortality Score for the Intensive Care Unit (SMS-ICU), United Kingdom (UK), United States of America (USA).

References

1. Granholm A, Perner A, Krag M, et al (2018) Development and internal validation of the Simplified Mortality Score for the Intensive Care Unit (SMS-ICU). Acta Anaesthesiol Scand 62:336–346. https://doi.org/10.1111/aas.13048

2. Granholm A, Perner A, Krag M, et al (2019) External validation of the Simplified Mortality Score for the Intensive Care Unit (SMS-ICU). Acta Anaesthesiol Scand 63:1216–1224. https://doi.org/10.1111/aas.13422

3. Sjoberg BP, Menias CO, Lubner MG, et al (2018) Splenomegaly: A Combined Clinical and Radiologic Approach to the Differential Diagnosis. Gastroenterol Clin North Am 47:643–666. https://doi.org/10.1016/j.gtc.2018.04.009

4. Bernal W, Wendon J (2013) Acute liver failure. N Engl J Med 369:2525–34. https://doi.org/10.1016/j.bpg.2013.08.010

5. Wendon J, Cordoba J, Dhawan A, et al (2017) EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatol 66:1047–1081. https://doi.org/10.1016/j.jhep.2016.12.003

6. Singer M, Deutschman CS, Seymour CW, et al (2016) The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 315:801. https://doi.org/10.1001/jama.2016.0287

7. Anthon CT, Pène F, Perner A, et al (2022) Platelet transfusions and thrombocytopenia in intensive care units: Protocol for an international inception cohort study (PLOT-ICU). Acta Anaesthesiol Scand. https://doi.org/10.1111/AAS.14124

8. Stanworth SJ, Estcourt LJ, Powter G, et al (2013) A no-prophylaxis platelet-transfusion strategy for hematologic cancers. N Engl J Med 368:1771–1780. https://doi.org/10.1056/NEJMoa1212772

9. Wandt H, Schaefer-Eckart K, Wendelin K, et al (2012) Therapeutic platelet transfusion versus Routine prophylactic transfusion in patients with haematological malignancies: An open-label, multicentre, randomised study. Lancet 380:1309–1316. https://doi.org/10.1016/S0140-6736(12)60689-8

10. Heddle NM, Cook RJ, Tinmouth A, et al (2009) A randomized controlled trial comparing standard- and low dose strategies for transfusion of platelets (SToP) to patients with thrombocytopenia. Blood 113:1564–1573. https://doi.org/10.1182/blood-2008-09-

178236.The

11. Slichter SJ, Kaufman RM, Assmann SF, et al (2010) Dose of prophylactic platelet transfusions and prevention of hemorrhage. N Engl J Med 362:600–613. https://doi.org/10.1056/NEJMoa0904084

12. Anand SS, Bosch J, Eikelboom JW, et al (2018) Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial. Lancet 391:219–229. https://doi.org/10.1016/S0140-6736(17)32409-1

13. Vogel B, Claessen BE, Arnold S V, et al (2019) ST- segment elevation myocardial infarction. Nat Rev Dis Prim 5:1–20. https://doi.org/10.1038/s41572-019-0090-3

14. Bala M, Kashuk J, Moore EE, et al (2017) Acute mesenteric ischemia: Guidelines of the World Society of Emergency Surgery. World J Emerg Surg 12:1–11. https://doi.org/10.1186/s13017-017-0150-5

15. Hetts S, Khangura R (2019) Imaging of Acute Stroke: Current State. Radiol Clin North Am 57:1083–1091. https://doi.org/10.1016/J.RCL.2019.07.009

16. Couban S, Goodyear M, Burnell M, et al (2005) Randomized placebo-controlled study of low-dose warfarin for the prevention of central venous catheter-associated thrombosis in patients with cancer. J Clin Oncol 23:4063–4069. https://doi.org/10.1200/JCO.2005.10.192

17. Intagliata NM, Caldwell SH, Tripodi A (2019) Diagnosis, Development, and Treatment of Portal Vein Thrombosis in Patients With and Without Cirrhosis. Gastroenterology 156:1582-1599.e1. https://doi.org/10.1053/j.gastro.2019.01.265

18. Russell CE, Wadhera RK, Piazza G (2015) Mesenteric Venous Thrombosis. Circulation 131:1599–1603. https://doi.org/10.1161/CIRCULATIONAHA.114.012871

19. Tran HA, Gibbs H, Merriman E, et al (2019) New guidelines from the Thrombosis and Haemostasis Society of Australia and New Zealand for the diagnosis and management of venous thromboembolism. Med J Aust 210:227–235. https://doi.org/10.5694/mja2.50004

20. Cook D, Meade M, Guyatt G, et al (2011) Dalteparin versus unfractionated heparin in critically ill patients. N Engl J Med 364:1305–1314. https://doi.org/10.1056/NEJMoa1014475

21. Nagelkerke NJD (1991) A Note on a General Definition of the Coefficient of Determination. Biometrika 78:691. https://doi.org/10.2307/2337038

22. Labarère J, Bertrand R, Fine MJ (2014) How to derive and validate clinical prediction models for use in intensive care medicine. Intensive Care Med 40:513–527. https://doi.org/10.1007/S00134-014-3227-6/TABLES/4