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Incidence, kinetics, and clinical impact of thrombocytopenia in venovenous ECMO: insights from the multicenter observational PROTECMO study

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Abstract

Background Thrombocytopenia is a recognized risk factor for bleeding during extracorporeal membrane oxygenation (ECMO). This study determines the incidence, risk factors, and clinical relevance of thrombocytopenia and platelet transfusions during venovenous (VV) ECMO.

Methods The multicenter, prospective observational PROTECMO study included 652 adult patients who received VV ECMO for respiratory failure. Thrombocytopenia was classified as mild (100–149·10^9/L), moderate (50–99·10^9/L), or severe (< 50·10^9/L). Bleeding events were evaluated using a modified Bleeding Academy Research Consortium score. Cox proportional hazards and logistic regression analyses were done to identify predictors, and quantify the association between platelet counts and bleeding risk.

Results A total of 182 patients (27.9%) had thrombocytopenia at baseline (mild in 14.7%, moderate in 8.7%, and severe in 4.4%). Thrombocytopenia during ECMO, at least once in 80.2% of patients, was mild in 21.3% of cases, moderate in 32.2%, and severe in 26.7%. A 10·10^9/L decrease in platelet count was associated with a 3.7% (95% CI: 2.4–5.0%) increase in risk of bleeding. There was no strong evidence of nonlinear relationship within the platelet count range between 25,000 and 300,000. This relation remained consistent across all ECMO weeks. Mild thrombocytopenia increased the risk of experiencing a bleeding event by 61% (hazard ratio (HR) 1.611, 95% CI 1.230–2.109, $p = 0.0005$), while moderate and severe thrombocytopenia increased the risk by roughly 90% (moderate: HR 1.944 (CI 1.484–2.545), $p < 0.0001$; severe: HR 1.876 (CI 1.275–2.7680), $p = 0.0014$). The risk for thrombocytopenia < 100·10^9/L during ECMO significantly increased with ICU days prior to ECMO start, postoperative admission, immunocompromised state, renal replacement therapy, septic shock, low hemoglobin, and circuit exchange.

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Conclusions Thrombocytopenia is highly prevalent in VV ECMO, and associated with a significant increase in the risk of bleeding, and a reduction in 6-month survival, particularly at platelet counts below $100{\cdot}10^9$/L. Further research is needed to better define the outcomes associated with specific thresholds for transfusion of platelets.

Keywords Thrombocytopenia, VV ECMO, Bleeding, Platelet kinetics, Intensive care, Anticoagulation, Predictors

Background information

A common complication during extracorporeal membrane oxygenation (ECMO) is bleeding, affecting up to 50% of patients [1, 2]. Bleeding during ECMO is associated with increased mortality, underscoring its clinical relevance [1, 3]. In addition to ventilatory characteristics, disease severity, and ECMO duration, thrombocytopenia (platelet count < $150{\cdot}10^9$/L) has been described as an important risk factor for bleeding [3–5].

Thrombocytopenia is a common finding during ECMO. However, its prevalence is highly variable [2, 6]. The causes include interactions with the ECMO circuit, sepsis, disseminated intravascular coagulation, immunological and drug-related causes, as well as patient pre-ECMO conditions (particularly malnutrition and cachexia). The underlying mechanisms can involve all aspects of the platelet function and life cycle, including production, distribution, and degradation [7–9].

Platelet count thresholds for predicting bleeding during ECMO have been studied only for intracranial hemorrhage (ICH), and a platelet count of $56{\cdot}10^9$/L has been suggested as a potentially useful cutoff [10]. This value is close to the commonly used definition of severe thrombocytopenia (platelet count < $50{\cdot}10^9$/L), which occurs in 6–27% of ECMO patients [6]. However, aside from previously reported cases of kidney and liver failure, risk factors for thrombocytopenia are largely unknown [11]. Moreover, it remains unclear whether relative decreases in platelet count or duration of thrombocytopenia can predict bleeding events during ECMO [12, 13].

We sought to characterize the incidence, time course, and risk factors for thrombocytopenia and the associated risk of bleeding during venovenous (VV) ECMO.

Methods

This is a sub-study from the multicenter, prospective, observational PROTECMO study, which was conducted in 41 ECMO centers from 19 countries [1, 14]. The study was approved by the local institutional review boards of all participating centers according to local regulations.

The study population, previously described [1, 14], included consecutive adult (≥ 18 years) patients requiring VV ECMO for respiratory failure over a one-year enrollment period.

Data were collected through an online case report form customized on a REDCap server (Vanderbilt University, Nashville, TN, USA). The quality control of data for completeness and plausibility was done weekly by an automated check for missing data and outliers, which was then reported to the local investigator for confirmation or correction. Hospital survival and discharge date was assessed from electronic health care records or by contacting the admitting institution. For the 6-month follow up, patients or, if they were still in hospital or any healthcare related facility, their caretakers were contacted.

The complete list of collected variables is available in the Supplement, and included data of baseline characteristics, daily collected variables, and outcome parameters. According to the baseline dataset, which included the items of the PRESERVE score and RESP score, patients were considered immunosuppressed if they carried a diagnosis of hematologic malignancies, solid tumor, solid organ transplantation, high-dose or long-term corticosteroids, immunosuppressive agents, or human immunodeficiency virus [15, 16]. Platelet counts were assessed once daily.

Bleeding was assessed on a daily basis, including assessment of the bleeding site and severity. Bleeding severity was classified using a modified Bleeding Academic Research Consortium (BARC) score, as follows: Type 1 (bleeding requiring heparin infusion rate reduction **or** packed red blood cell (PRBC) transfusion due to a drop in hemoglobin concentration related to bleeding); Type 2 (bleeding requiring heparin infusion rate reduction **and** PRBC transfusion due to a hemoglobin drop related to bleeding, or a nonsurgical procedure to stop bleeding); Type 3 (life-threatening bleeding requiring PRBC transfusion **and** surgical intervention to control bleeding or ECMO discontinuation); and Type 4 (any fatal bleeding) [1].

ECMO center volume was classified as low (one to 11 runs per year), medium (12 to 20 runs per year), and high volume (> 20 runs per year).

Outcome measures

The primary outcome was the incidence of thrombocytopenia during VV ECMO support (time from cannulation to ECMO removal or death), which was defined as a platelet count < $150{\cdot}10^9$/L. Thrombocytopenia was further classified according to the SOFA score for coagulation as mild ($100–149{\cdot}10^9$/L), moderate ($50–99{\cdot}10^9$/L), and severe (< $50{\cdot}10^9$/L), which has been used in a previous large observational study on thrombocytopenia in venoarterial ECMO [2].

Platelet nadir was defined as the lowest platelet count during ECMO treatment. Relative platelet drop was

calculated as (*baseline platelet count (10^9/L) – platelet nadir (10^9/L))/baseline platelet count (10^9/L).* Absolute platelet drop was calculated as *baseline platelet count (10^9/L) – platelet nadir (10^9/L).*

Statistical analysis

Quantitative variables are expressed as median and interquartile range, and qualitative variables as percentage and frequency distribution. Missing data were imputed using stochastic regression imputation for the quantitative variables. Qualitative variables were imputed using the last-observation-carried-forward method.

We carried out a time-dependent Cox proportional hazards regression to evaluate the association between platelet counts and the risk of bleeding events, adjusted for baseline thrombocytopenia severity. A Directed Acyclic Graph illustrating the relationships between clinical, procedural, and patient-related factors potentially influencing thrombocytopenia and bleeding is presented in sFigure 1. The model included ECMO initiation and ECMO removal or death as interval boundaries for time-dependent covariates, with baseline thrombocytopenia classified as none, mild, moderate, or severe. Observations were censored if no bleeding event occurred during the follow-up period. A similar model was used to assess the impact of thrombocytopenia during ECMO (stratified as none, mild, moderate, and severe) and its duration (consecutive days) on bleeding events. Results are expressed as hazard ratios and 95% confidence intervals.

We did a binary logistic regression analysis to evaluate the association between the first bleeding event and potential predictors, including baseline platelet count, baseline thrombocytopenia classification (none, mild, moderate, severe), relative and absolute platelet drop, and duration of thrombocytopenia. Results are expressed as odds ratios and 95% confidence intervals. For patients experiencing the outcome event, only values prior to the event were considered. For patients not experiencing

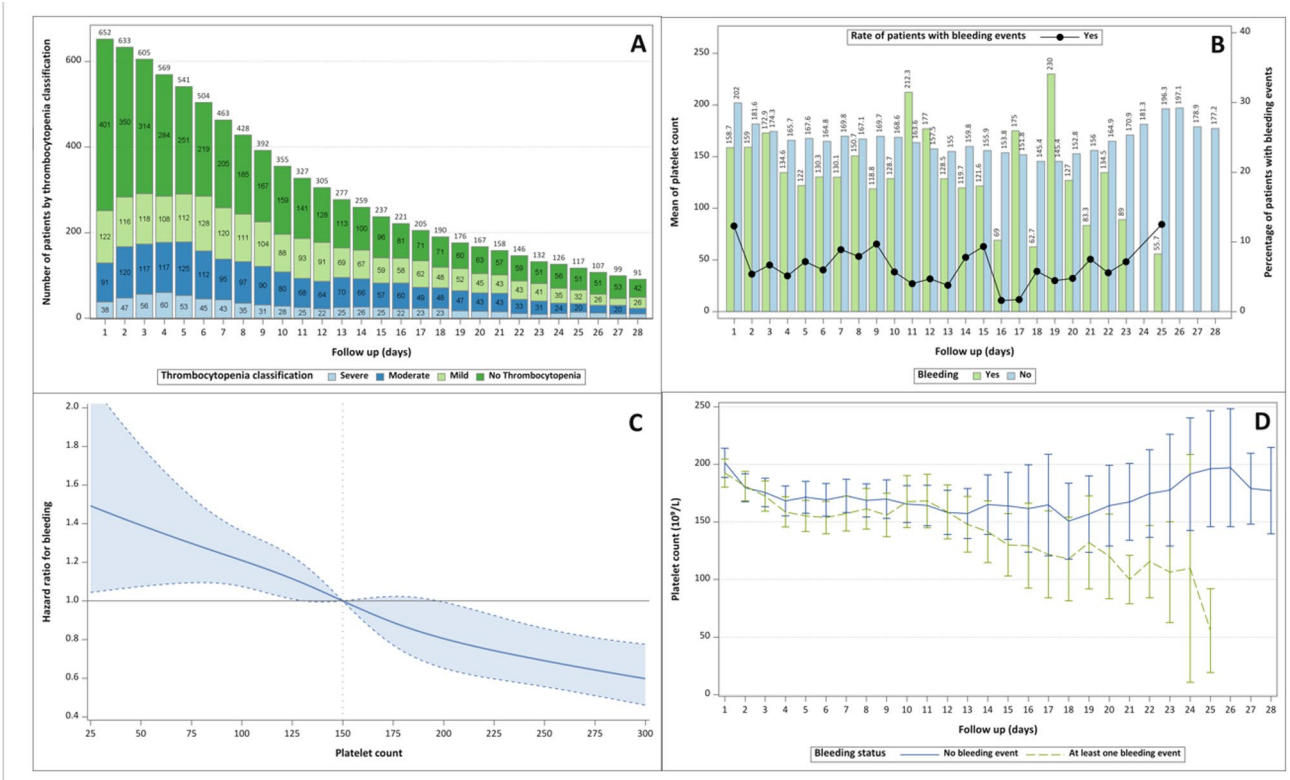

Fig. 1 **a**. Progression of Thrombocytopenia Classification Over Time. This stacked bar chart displays the progression of thrombocytopenia severity during 28 days of follow-up. The y-axis represents the number of patients stratified by thrombocytopenia severity; the x-axis indicates the follow-up period in days. **b**. Platelet Trends and Bleeding Incidence over 28 Days of Follow-Up. The bar chart represents the mean platelet count (y-axis on the left) over the follow-up period (x-axis in days), stratified by bleeding status. The black line with markers shows the rate of bleeding patients as a percentage (y-axis on the right) at each follow-up day. Numerical values displayed on the bars correspond to the mean platelet counts for the respective groups. **c**. Association between Platelet Count and Hazard Ratio for Bleeding. The relationship was assessed using restricted cubic splines in a Cox proportional-hazard model, with platelet count as a continuous variable. The solid line represents the estimated hazard ratio, and the shaded area indicates the 95% confidence interval. **d**. Platelet Count Trajectories by Bleeding Status over 28 Days. This line graph illustrates the trajectory of platelet count (y-axis) over a 28-day follow-up period (x-axis) in patients grouped by bleeding status. The blue line represents patients who did not experience any bleeding event during the follow-up period, while the green dashed line represents patients who experienced at least one bleeding event. Data points and error bars for each day represent mean platelet count with its 95% confidence interval

the outcome event, all values until ECMO removal were considered.

Generalized estimating equations (GEE) models were applied to assess the effect of covariates on thrombocytopenia, both as a continuous variable and using the $\geq 100{\cdot}10^9$/L cut-off. GEE models were applied to estimate the impact of variables on the outcome, accounting for correlated repeated measures over time within the same subjects. Models were adjusted for baseline platelet count and platelet transfusion volume within the last 24 h.

An exchangeable correlation structure was specified to account for within-subject correlations over time. A logit link function was used to model the binary outcome. Covariates included baseline factors (e.g., age, intensive care unit [ICU] length of stay) and daily variables (e.g., ECMO duration, fluid balance, and septic shock). Covariates were included in the model if their p-value was < 0.1. Population-averaged estimates (β), 95% confidence intervals, and p-values are reported, with robust standard errors to ensure valid inference despite potential misspecification of the working correlation structure.

To analyze recurrent events of platelet transfusion, we applied a Prentice-Williams-Peterson model with common and non-common effects. This model accounts for the time-to-event nature of the data, where recurrent events (platelet transfusions) were measured over multiple time intervals from start of ECMO until ECMO removal or death. The analysis included the following variables: age, postoperative state, type of pneumonia (bacterial pneumonia, coronavirus disease 2019 [COVID-19], other, and viral pneumonia), pregnancy, daily platelet counts, immunocompromised state, geographic variation, center volume, septic shock, fluid balance, bleeding, presence of heparin-induced thrombocytopenia (HIT), packed red blood cells (PRBCs), plasma, and fibrinogen transfusion, and tranexamic acid administration. The dataset was stratified into four strata to control for heterogeneity across repetition of platelet transfusion. Reporting of the study results follows the STROBE guidelines.

Overall, a p-value < 0.05 was considered statistically significant. Statistical analysis was carried out using SAS® 9.4 software (SAS Institute Inc., Cary, NC, U.S.A.).

Results

Between December 2018 and February 2021, 652 patients were included in the study, comprising a total of 8,482 timepoints. The majority of patients were male (71%, $n = 463$), with a median age of 52 years (IQR 40–60). About one-third of patients ($n = 218$) received VV ECMO for severe COVID-19-associated acute respiratory distress syndrome, followed by other viral pneumonia in 17.6% ($n = 115$) and bacterial pneumonia (15.8%, $n = 103$). Nearly one in five patients ($n = 128$) was immunocompromised (Table 1). The overall ICU survival in the study population was 60.7% ($n = 396$), with a median ICU length of stay of 26.3 days (15.5–43.7). Six-month survival was 56.9% ($n = 371$; Table 2).

Distribution of thrombocytopenia at baseline

A total of 182 patients (27.9%) had thrombocytopenia at baseline, defined as platelet count < $150{\cdot}10^9$/L. Mild thrombocytopenia was present in 14.7%, moderate thrombocytopenia in 8.7%, and severe thrombocytopenia in 4.4% of patients. Patients with severe baseline thrombocytopenia had the lowest ICU survival (34.5%; sTable 1). The bleeding rate was comparable across baseline thrombocytopenia classifications ($p = 0.954$; sTable 1).

Incidence of thrombocytopenia during ECMO and clinical endpoints

A total of 523 patients (80.2%) experienced thrombocytopenia on at least one day during ECMO support, including 21.3% with mild, 32.2% with moderate, and 26.7% with severe thrombocytopenia (Fig. 1a; Table 2).

ICU survival was similar between patients who never developed thrombocytopenia and patients with mild thrombocytopenia during ECMO (76% vs. 71%). Those who developed moderate or severe thrombocytopenia at any timepoint during ECMO had worse outcomes (ICU survival 61% and 41%, respectively; Table 2). Twenty-nine cases (4.4%) of HIT were identified. More than half of these patients (55%) developed severe thrombocytopenia during ECMO, but the majority had normal platelet counts at baseline (72%). Patients with HIT had a slightly higher incidence of bleeding complications than those without, though the difference was not statistically significant (69% vs. 52%, $p = 0.074$).

Association of platelet count and kinetics with bleeding

The median time from ECMO start to platelet nadir was 5 days (3-11.5, sFigure 2). Overall, 344 patients (52.8%) experienced a bleeding event during ECMO (Fig. 1b). Patients with no bleeding event had a median platelet nadir of $104{\cdot}10^9$/L (57.0-153.5·10^9/L) during ECMO. The platelet nadir of patients with at least one bleeding event was $70{\cdot}10^9$/L (38.5-107.5·10^9/L). Considering only the time until the first bleeding event, their median lowest platelet count was $112{\cdot}10^9$/L (62-181.5·10^9/L).

Mild thrombocytopenia during ECMO increased the risk of experiencing a bleeding event by 61% (hazard ratio (HR) 1.611, 95% CI 1.230–2.109, $p = 0.0005$), while moderate and severe thrombocytopenia increased the risk by roughly 90% (moderate: HR 1.944 (CI 1.484–2.545), $p < 0.0001$; severe: HR 1.876 (CI 1.275–2.7680), $p = 0.0014$; sTable 2).

Absolute platelet count had a strong association with the first bleeding event. In the time-dependent Cox

Table 1 Baseline characteristics by baseline thrombocytopenia severity

Baseline variables	All patients, *n* = 652	No thrombocytopenia, *n* = 470	Mild thrombocytopenia, *n* = 96	Moderate thrombocytopenia, *n* = 57	Severe thrombocytopenia, *n* = 29
Age (years)	52 (40–60)	52 (40–61)	50 (33.5–58)	51 (42–60)	52 (42–61)
Sex (Male), n (% column)	463 (71.0%)	348 (74.0%)	66 (68.8%)	31 (54.4%)	18 (62.1%)
Body mass index (kg/m^2)	28.4 (24.9–33.7)	29.0 (25.3–34.3)	28.1 (24.8–36.2)	27.7 (23.7–31.1)	25.8 (24.2–28.6)
Immunocompromised (Yes), n (% column)	128 (19.6%)	81 (17.2%)	12 (12.5%)	22 (38.6%)	13 (44.8%)
Center volume					
Low	153 (23.5%)	109 (23.2%)	21 (21.9%)	16 (28.1%)	7 (21.1%)
Medium	163 (25.0%)	122 (26.0%)	27 (28.1%)	9 (15.8%)	5 (17.2%)
High	336 (51.5%)	239 (50.9%)	48 (50.0%)	32 (56.1%)	17 (58.6%)
Pre-ECMO hospital stay (days), median (IQR)	5.4 (1.9–10.9)	6.3 (2.2–11.3)	3.1 (1.2–6.5)	3.8 (0.8–10.1)	5.2 (2.0–16.0)
Pre-ECMO ICU stay (days), median (IQR)	3.0 (1.0–7.0)	3.9 (1.0-7.5)	1.6 (0.9–3.7)	2.0 (0.5–5.2)	3.0 (1.4–7.1)
SAPS 2 score, median (IQR)	40 (30–55)	39 (29–53)	39 (32–55)	50 (39–64)	54 (45–68)
PaO2/FiO2 (mmHg), median (IQR)	72 (60–95)	73 (60–98)	71 (56–88)	63 (5–80)	70 (58–100)
Bilirubin (mg/dL), median (IQR)	0.8 (0.5–1.4)	0.7 (0.4–1.2)	0.8 (0.5–1.6)	1.2 (0.8–1.8)	1.4 (1.0-2.3)
Platelets (10^9/L), median (IQR)	207 (140–291)	255 (197–331)	122 (113–136)	82 (70–91)	32 (19–39)
Creatinine (mg/dL), median (IQR)	1.0 (0.7–1.8)	1.0 (0.7–1.6)	1.3 (0.8–2.4)	1.1 (0.7–2.5)	1.4 (0.7–2.1)
Cause of Acute Respiratory Failure					
COVID-19, n (% column)	218 (33.4%)	187 (39.8%)	21 (21.9%)	10 (17.5%)	0 (0.0%)
Viral pneumonia, n (% column)	115 (17.6%)	68 (14.5%)	29 (30.2%)	8 (14.0%)	10 (34.5%)
Bacterial pneumonia, n (% column)	103 (15.8%)	58 (12.3%)	22 (22.9%)	11 (19.3%)	12 (41.4%)
Non-respiratory and chronic respiratory diagnoses, n (% column)	50 (7.7%)	40 (8.5%)	4 (4.2%)	5 (8.8%)	1 (3.5%)
Graft failure after lung transplantation, n (% column)	31 (4.8%)	14 (3.0%)	5 (5.2%)	11 (19.3%)	1 (3.5%)
Aspiration pneumonia, n (% column)	27 (4.1%)	21 (4.5%)	4 (4.2%)	2 (3.5%)	0 (0.0%)
Trauma/burns, n (% column)	25 (3.8%)	15 (3.2%)	3 (3.1%)	5 (8.8%)	2 (6.9%)
Asthma, n (% column)	14 (2.2%)	13 (2.8%)	0 (0.0%)	1 (1.8%)	0 (0.0%)
Pancreatitis, n (% column)	8 (1.2%)	4 (0.9%)	3 (3.1%)	1 (1.8%)	0 (0.0%)
Other acute respiratory diagnosis, n (% column)	61 (9.4%)	50 (10.6%)	5 (5.2%)	3 (5.3%)	3 (10.3%)

ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; IQR: interquartile range; SAPS 2: Simplified Acute Physiology Score 2

Table 2 Clinical outcomes by thrombocytopenia classification during ECMO

Outcome variables	All patients, *n* = 652	No thrombocytopenia during ECMO, *n* = 129	Mild thrombocytopenia during ECMO, *n* = 139	Moderate thrombocytopenia during ECMO, *n* = 210	Severe thrombocytopenia during ECMO, *n* = 174
Volume of transfused platelets during ECMO (mL), median (IQR)	0 (0–454)	0 (0–0)	0 (0–0)	0 (0–330)	676 (0–1697)
Total ECMO days, median (IQR)	10.8 (5.9–19.9)	6.9 (3.8–11.9)	10.4 (5.0–17.8)	11.3 (6.2–21.7)	14.2 (7.8–24.1)
ICU length of stay, median (IQR)	26.3 (15.5–43.7)	22.6 (12.1–37.9)	24.0 (14.3–39.0)	26.9 (16.6–47.8)	29.9 (18.9–47.6)
Hospital length of stay, median (IQR)	38.1 (23.0–60.1)	34.1 (19.3–53.7)	36.6 (21.0–52.1)	39.3 (24.8–68.2)	40.4 (24.7–69.7)
Successful ECMO weaning	445 (68.3%)	106 (82.2%)	104 (74.8%)	143 (68.1%)	92 (52.9%)
ICU survival	396 (60.7%)	98 (76.0%)	98 (70.5%)	129 (61.4%)	71 (40.8%)
Hospital survival	387 (59.4%)	96 (74.4%)	97 (69.8%)	124 (59.1%)	70 (40.2%)
6-month survival	371 (56.9%)	94 (72.9%)	96 (69.1%)	115 (54.8%)	66 (37.9%)

ECMO: extracorporeal membrane oxygenation; ICU: intensive care unit; IQR: interquartile range

Table 3 Time-dependent Cox Proportional-Hazard model for the association of absolute platelet counts and bleeding events over time

	Overall HR (95% CI)	Week 1 HR (95% CI)	Week 2 HR (95% CI)	Week 3 HR (95% CI)	Week 4 HR (95% CI)
Platelet count, $10{\cdot}10^9$/L increase	0.96 (0.95–0.98)	0.97 (0.96–0.98)	0.97 (0.94–0.99)	0. 95 (0.89-1.00)	0.84 (0.73–0.95)

proportional-hazards model, a $10{\cdot}10^9$/L decrease in platelet count was associated with a 3.7% (2.4-5.0%) increase in the risk of bleeding (sTable 3). No significant interaction was observed with baseline thrombocytopenia severity. Excluding patients with HIT yielded similar results (HR per $10{\cdot}10^9$/L increase 0.96, 95% CI 0.95–0.98, p = < 0.001). Linearity in the reduction of the hazard rate was assessed using restricted cubic splines in the Cox model, with no strong evidence of nonlinear relationship within the platelet count range between 25,000 and 300,000 (Fig. 1c). Exploring the relation over time by splitting the follow-up into 4 weeks using Heaviside functions, this relation remained consistent across all weeks (Table 3).

The trajectory of platelet count of patients with and without bleeding events is shown in Fig. 1d.

There was no association between the relative or absolute platelet drop and bleeding events, with poor discriminatory accuracy (sTables 4 and 5). A slight reduction in bleeding risk was observed with longer consecutive days of thrombocytopenia (sTable 6).

Risk factors for thrombocytopenia

In a multiple GEE model, baseline variables such as age, postoperative admission, and immunocompromised status were significant predictors of thrombocytopenia occurrence. Among follow-up variables, septic shock, continuous renal replacement therapy (CRRT), hemoglobin, fibrinogen, bleeding, circuit exchange, and ECMO pump speed remained significant (sTable 7). Center volume had no effect on thrombocytopenia. Considering the clinically meaningful thrombocytopenia cut-off of $100{\cdot}10^9$/L, days in ICU prior to ECMO initiation, postoperative admission, immunocompromised state, CRRT, septic shock, hemoglobin, and circuit exchange were associated with an increased risk (sTable 8).

Platelet transfusions during ECMO

During ECMO, 210 patients (32.21%) received at least one platelet transfusion, and 91 patients were transfused before their first bleeding event. The majority of platelet transfusions were done in patients with severe thrombocytopenia; median platelet count before transfusion was $54{\cdot}10^9$/L ($34–85{\cdot}10^9$/L).

The Cox proportional-hazard regression analyses for platelet transfusions identified several significant associations for prespecified variables: daily platelet count had the strongest association with platelet transfusion recurrence. Transfusions of PRBCs and plasma, fibrinogen supplementation, tranexamic acid administration, and fluid balance had a variable impact on platelet transfusions, indicating effect variation across number of platelet transfusions. Septic shock and circuit exchange had a consistently strong effect across all analyzed transfusion episodes (sTables 9 and 10).

Across the thrombocytopenia classification (< 50, 50–99, and ≥ 100), transfusion of platelets was not significantly associated with a reduced risk of the first bleeding episode (< 50: HR 1.98, 0.97–4.02; 50–99: HR 0.46, 0.16–1.32; ≥100: HR 1.59, 0.46–5.53).

Discussion

In this large, prospective observational study, we present comprehensive data on the incidence, risk factors, and clinical consequences of thrombocytopenia in VV ECMO patients. We observed a notably high incidence of thrombocytopenia, and identified key risk factors for its development. Importantly, we found a strong association between absolute platelet count and bleeding complications. However, data need to be interpreted in the context of its observational design, where, although it appears rational, association does not essentially mean causality.

Prevalence of thrombocytopenia

Previous reports on the prevalence of thrombocytopenia during VV ECMO have varied considerably, partly due to differences in definitions. A systematic review and meta-analysis revealed a pooled prevalence of thrombocytopenia ($< 150{\cdot}10^9$/L) of 25.4%, with substantial heterogeneity across studies with limited sample sizes [6]. In contrast, we observed an 80% prevalence of thrombocytopenia of any degree. A recent observational cohort study in VA ECMO patients reported a similar but even higher thrombocytopenia prevalence of 95% [2]. One explanation of the higher incidence observed in veno-arterial (VA) ECMO is the overall lower platelet count described before ECMO initiation. Raasveld et al. report a baseline platelet count of $179{\cdot}10^9$/L ($119–253{\cdot}10^9$/L), which is considerably lower than our observed median platelet count of 207·109/L ($140–291{\cdot}10^9$/L). We interpret this difference in the context of the underlying pathologies, why ECMO is required for circulatory and respiratory support, respectively. Raasveld et al. reported on a significant amount of ECMO patients after cardiotomy, which is a common risk factor for thrombocytopenia. In our VV ECMO cohort, on the other hand, almost half of the included patients had ARDS related to viral infection, which is associated with a lower risk

of thrombocytopenia compared to bacterial infection. In our view, this supports the hypothesis, that coagulopathy in VA and VV ECMO may share similarities, including a high risk of thrombocytopenia, but should be considered as distinct entities, due to, for example, underlying conditions.

Smaller retrospective cohorts often report much lower thrombocytopenia rates, supporting the need for longitudinal, multi-centric comprehensive data - such as the PROTECMO study - to provide a robust representation of key real-world ECMO data [17–19]. Approximately one in four patients in our study developed severe thrombocytopenia, aligning with the largest study to date on the prevalence of thrombocytopenia during VV ECMO [11], but slightly lower than the 40% reported in the EOLIA trial [20]. This difference may be attributable to the higher proportion of COVID-19 patients and lower prevalence of patients with bacterial pneumonia in our cohort. None of the COVID-19 patients, who made up about a third of our total study population, had severe thrombocytopenia at baseline, which contributed to the lower prevalence of severe thrombocytopenia. Additionally, patients with cancer, solid organ transplant or drug-related immunosuppression, who are known to be at greater risk for severe thrombocytopenia [21], were less represented in our study cohort compared to the EOLIA population [20]. Severe thrombocytopenia has been associated with increased mortality in ECMO, which contributes to bleeding complications, but may also represent progressive (multi)organ failure [21, 22]. In our cohort, patients with severe thrombocytopenia during ECMO had a 6-month survival of 38%, compared to an overall 6-month survival of 57%. Though the bleeding rate was not meaningfully affected by baseline thrombocytopenia, patients with severe thrombocytopenia at baseline had a 6-month survival rate of only 28%. This may well reflect a higher severity of illness at baseline, and a higher prevalence of immunosuppression.

Platelet trajectories during ECMO

We observed a temporal relationship between decline in platelet count and ECMO initiation, consistent with previous studies [11]. This likely reflects a multifactorial mechanism related to extracorporeal circulation, including platelet adherence within the extracorporeal circuit, low-level consumptive coagulopathy, inflammatory mechanisms, and inflammatory processes such as neutrophil extracellular trap (NET) formation and non-immunological HIT type I [23, 24].

A decrease in platelet counts due to (subclinical) consumptive coagulopathy triggered by clot formation in the oxygenator remains a significant challenge in ECMO management [25]. In our cohort, there was an association between circuit exchange and thrombocytopenia, which likely reflects the clinical practice of circuit change due to incipient coagulopathy. Though membrane oxygenation may remain functional, (micro)thrombi can already induce coagulopathy and hemolysis, further increasing the risk of bleeding (and thrombocytopenia) [26, 27]. Retrospective data suggest that circuit exchanges may be an effective intervention for bleeding [28]. While our data structure did not permit a more detailed analysis, future studies should investigate the optimal timing of "semi-elective" circuit changes to balance costs and clinical risks.

Severity of thrombocytopenia, bleeding risk, and considerations for transfusions

We found a strong association between absolute platelet count during ECMO and bleeding risk. Given the established link between bleeding and mortality in ECMO patients, strategies to prevent or mitigate moderate to severe thrombocytopenia are almost certainly essential. While baseline factors such as immunosuppression and severity of illness were associated with thrombocytopenia and may be difficult to modify [11], we identified CRRT and septic shock as key risk factors for moderate to severe thrombocytopenia during ECMO.

Further research is needed to determine whether patients with risk factors, such as septic shock or renal replacement therapy, could benefit from platelet-modifying or -stimulating agents, such as thrombopoietin receptor agonists, to prevent clinically relevant thrombocytopenia during ECMO. In this context, the platelet-modifying agent prostaglandin E_1 has shown promising results as add-on therapy to low-dose unfractionated heparin in patients receiving VV ECMO, and might be particularly beneficial for those with high-levels of inflammation, such as in septic shock [29].

Notably, one-third of our patients received at least one platelet transfusion, with more than half receiving transfusions before their first bleeding event. The median platelet count before transfusion was just above $50{\cdot}10^9$/L, aligning with the current Extracorporeal Life Support Organization (ELSO) transfusion guidelines [30]. However, practices vary largely among centers, and data supporting an optimal platelet transfusion threshold are currently limited [31]. Additionally, we currently lack adequate tools to monitor platelet function to guide appropriate transfusions.

While a low platelet count is clearly associated with bleeding, it is still uncertain whether transfusion alone is effective in the absence of a targeted treatment of the underlying cause of thrombocytopenia. On the other hand, prophylactic platelet transfusion has a limited ability to reduce the risk of first bleeding, reinforcing the importance of preventive strategies focused on circuit care and compatibility to mitigate thrombocytopenia,

subsequent bleeding [28, 32], and associated mortality. Retrospective data on intracranial hemorrhage during VV ECMO identified a clinically meaningful platelet cut-off of $56{\cdot}10^9$/L, supporting the currently recommended transfusion threshold [10]. This study additionally reported that a platelet count above $100{\cdot}10^9$/L prevented the occurrence of intracranial hemorrhage, with very high sensitivity and specificity [10]. This aligns with the significant increase in bleeding events with platelet counts below $100{\cdot}10^9$/L observed in our study. This finding may suggest that patients who develop new-onset thrombocytopenia with platelet counts < $100{\cdot}10^9$/L, particularly those with additional bleeding risk factors (e.g., high positive end-expiratory pressure levels), could benefit from higher transfusion thresholds and/or lower anticoagulation targets [10]. However, this remains hypothesis-generating, as there are currently no data on individualized anticoagulation targets or on the efficacy of platelet transfusion to prevent bleeding events during ECMO. In this context, transfusion refractoriness must also be considered, as ECMO patients are at risk for both nonimmune causes (including infection, sepsis, and accelerated platelet consumption) and immune-mediated causes [33].

Strengths and limitations

This sub-study provides a large, contemporary dataset of prospectively collected VV ECMO patient data, with minimal missing data for the primary outcome. The multicenter design further strengthens its generalizability.

The main limitation of this study is its observational design, which limits causal inference. However, one strength that this longitudinal study offers is the precise temporal evaluation of exposure and outcome variables. Therefore, even though causal inference cannot be reached, the association level is more precise, since it is not based on aggregated data. Nonetheless, the comprehensive documentation of events and patient characteristics allows for robust association analyses, and establishes a valuable database for future research comparing different management strategies.

The unique case mix of our cohort needs to be considered when interpreting and comparing our findings to prior and future studies. One in five patients was immunocompromised, contributing to a high prevalence of baseline thrombocytopenia. Furthermore, as this study was partly conducted during the COVID-19 pandemic, one third of patients had COVID-19-associated acute respiratory distress syndrome, which was linked to a lower risk of baseline thrombocytopenia.

Conclusion

Thrombocytopenia is highly prevalent in VV ECMO patients, and strongly associated with bleeding risk. However, platelet transfusions do not appear to significantly reduce bleeding risk, emphasizing the need for targeted prevention strategies. Future research should focus on optimizing anticoagulation, transfusion protocols, and defining the optimal timing for circuit exchange to mitigate thrombocytopenia-related complications.

Abbreviations

COVID-19	Coronavirus disease 2019
ECMO	Extracorporeal membrane oxygenation
GEE	General estimating equations
HIT	Heparin-induced thrombocytopenia
ICH	Intracranial hemorrhage
ICU	Intensive care unit
PRBCs	Packed red blood cells
VA	Venoarterial
VV	Venovenous

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05569-3.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions

N.B., F.T., and G.M. conceived and designed the study. C.A., A.H., J.R., P.S., M.S., R.R., M.B., L.B., K.S., W.D.G., V.F., B.T., H.B., S.B., and M.G. acquired the data. N.R.

and F.T. performed the statistical analysis. N.B., K.T., G.G., A.A., D.B., R.L., and G.M. interpreted the data. N.B. and G.M. drafted the first version of the manuscript. All authors critically revised the manuscript for important intellectual content. All of the authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Data availability
Data are available upon reasonable request from the corresponding author.

Declarations

Ethics approval and consent to participate
The study was approved by the local institutional review boards of all participating centers according to local regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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