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Contribution of Coagulopathy on the Risk of Bleeding After Central Venous Catheter Placement in Critically Ill Thrombocytopenic Patients

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OBJECTIVES: Critically ill patients often undergo central venous catheter placement during thrombocytopenia and/or coagulopathy. It is unclear whether severe coagulopathy increases the risk of postprocedural bleeding in critically ill patients with severe thrombocytopenia.

DESIGN: Single-center retrospective cohort study.

SETTING: Academic mixed ICU in Amsterdam, the Netherlands.

PATIENTS: Consecutive severely thrombocytopenic (platelet count $\leq 50 \times 10^9$/L) patients who underwent central venous catheter placement between February 2016 and February 2020.

INTERVENTIONS: Central venous catheter placement in patients with both severe thrombocytopenia and severe coagulopathy (international normalized ratio $>$ 1.5 and/or activated partial thromboplastin time $>$ 45 s) versus patients with severe thrombocytopenia and normal or mildly prolonged international normalized ratio and activated partial thromboplastin time.

MEASUREMENTS AND MAIN RESULTS: We included 289 central venous catheter placements in 175 patients, 112 in patients with and 172 in patients without severe coagulopathy. Median (interquartile range) platelet count was 27 (16–38) and equal for both groups. There were 44 bleeding episodes at the central venous catheter insertion site (15.5%), of which four (1.4%) were grade 2 and two (0.7%) were grade 3. There were 19 bleeding episodes (17.0%) versus 25 bleeding episodes (14.5%) in the coagulopathy and noncoagulopathy groups, of which one and five were of grade 2 or higher, respectively. After correction for confounders, coagulopathy had no effect on bleeding: odds ratio (95% CI) 0.96 (0.24–3.88). Before central venous catheter placement, 116 (40.8%) patients received platelet transfusion. Bleeding at the central venous catheter insertion site occurred in 19 of 116 patients (16.4%) and 25 of 168 patients (14.9%) who did and did not receive platelet transfusion. After correction for confounders, platelet transfusion had no effect on bleeding: odds ratio (95% CI) 0.73 (0.18–2.83).

CONCLUSIONS: Coagulopathy was not associated with an increased bleeding risk in severely thrombocytopenic ICU patients undergoing ultrasound guided central venous catheter placement. Prophylactic platelet transfusion in patients with severe thrombocytopenia was not associated with a reduced risk of bleeding.

KEY WORDS: central venous catheter; coagulopathy; critical illness; hemorrhage; platelet transfusion; thrombocytopenia

Patients in the ICU frequently undergo central venous catheter (CVC) placement for the administration of vasoactive drugs or for continuous venovenous hemofiltration (1). As any invasive procedure, CVC placement carries a risk of periprocedural bleeding complications, for which

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landmark technique (as opposed to ultrasound guidance) and lower operator experience are the most important risk factors (1–4). Additionally, thrombocytopenia and coagulopathy are considered to increase bleeding risk after CVC placement, which is why guidelines advise on platelet count thresholds for safe CVC placement (5–8). However, we previously reviewed that preprocedural coagulation tests, such as prothrombin time (PT), activated partial thromboplastin time (APTT), and platelet count, are inconsistent predictors of bleeding complications (9).

The most common causes of thrombocytopenia in critically ill patients include disseminated intravascular coagulation (DIC) and posttrauma coagulopathy, also resulting in prolonged clotting times (10). Most evidence concerning bleeding after CVC placement originates from studies with few patients with severe thrombocytopenia and/or coagulopathy (11–13). Furthermore, even in studies in which thrombocytopenia and/or coagulopathy was more prevalent, only a limited number of patients suffered from both simultaneously (14–16). Two studies that did report substantial overlap between patients suffering from thrombocytopenia and coagulopathy used broad definitions of thrombocytopenia ($< 100 \times 10^9$/L and $< 150 \times 10^9$/L, respectively) (17, 18). There is one randomized controlled trial (RCT) published on bleeding risk after CVC placement and other invasive procedures in critically ill patients with coagulopathy (international normalized ratio [INR] between 1.5 and 3.0) (19). This study showed no benefit of prophylactic plasma transfusion but failed to meet its intended sample size due to slow inclusion. Furthermore, the study excluded patients with severe thrombocytopenia (platelet count $\leq 30 \times 10^9$/L). There is one RCT on the effect of prophylactic platelet transfusion on bleeding complications after CVC placement in severely thrombocytopenic patients (platelet count $\leq 50 \times 10^9$/L). However, this study excludes patients with severe coagulopathy and is still recruiting patients (20). In the current retrospective study, we aim to investigate the added bleeding risk of prolonged INR and APTT in critically ill patients with severe thrombocytopenia undergoing CVC placement.

MATERIALS AND METHODS

Study Design

This is a single-center, retrospective cohort study that was conducted in Amsterdam University Medical Centers, location Academic Medical Centre (AMC), Amsterdam, The Netherlands. All consecutive thrombocytopenic patients undergoing CVC placement were included between February 2016 and February 2020. Data were collected between October 2020 and August 2021. The medical-ethical committee of the AMC waived the necessity of informed consent under the Medical Research Involving Human Subjects Act on March 31, 2020 (reference number W20_104 number 20.139). Informed consent was not required under article 458 of the Medical Treatment Agreement Act. A hospital wide opt-out procedure was in place for patients not wishing to participate in retrospective studies.

CVC Placement

All catheters were placed using the Seldinger technique. Standard catheter sizes were 14F double-lumen hemodialysis catheters and 8F three- or four-lumen regular catheters. The use of ultrasound guidance was standard procedure but not mandatory. After needle insertion and prior to dilation, a small incision could be made in the skin, according to operator preference.

Inclusion and Exclusion Criteria

All adult (18+) ICU patients with a platelet count less than or equal to 50×10^9/L within 24 hours prior to CVC placement were eligible. Patients were excluded if they subsequently had a last platelet count prior to CVC placement greater than 50×10^9/L, unless this was due to a platelet transfusion. Patients were allowed to participate multiple times. Patients were considered to have coagulopathy with an INR greater than 1.5 and/or APTT greater than 45 seconds (upper limit of normal was 30 s).

Outcome Measures

The primary endpoint for this study was the occurrence of any postprocedural bleeding within 24 hours after CVC placement. Bleeding was assessed according to the bleeding scale previously used by Zeidler et al (16), an adaptation of the Common Terminology Criteria for Adverse Events (**Table 1**) (21). Secondary endpoints included platelet and plasma transfusions within 6 hours prior to CVC placement and their efficacy in preventing bleeding.

TABLE 1.
Bleeding Scale

Grade	Criteria
0	No bleeding
1	Oozing. Hematoma. Bleeding that requires < 20 min of manual compression to stop.
2	Bleeding that requires minor interventions to stop, such as sutures or prolonged manual compression (≥ 20 min).
3	Bleeding requiring radiologic, or elective operative interventions, red cell transfusion without hemodynamic instability.
4	Bleeding associated with severe hemodynamic instability (hypotension: > 50 mm/Hg fall or > 50% decrease in either systolic or diastolic blood pressure, with associated tachycardia (heart rate increase of > 20% for 20 min) and requiring RBC transfusion over routine transfusion needs or fatal bleeding).

This scale was previously used by Zeidler et al (16) and is derived from the Common Terminology Criteria for Adverse Events.

Data Collection

Demographic, disease, treatment, and outcome data were derived from electronic patient records and retrospectively entered into the electronic Case Registry Form (Castor Electronic Data Capture). Bleeding and transfusion data were entered independently by a second investigator, after which conflicts were resolved by a third investigator (**Appendix 1**, http://links.lww.com/CCX/A899). Although all outcome measures were restricted to 24 hours after CVC placement, patient records were searched up to 48 hours after CVC placement, to account for clinical observations recorded at a later moment.

Statistical Considerations

It was assumed that missing variables (e.g., baseline laboratory results) would not be missing completely at random, as the availability of data was likely to be related to disease severity. Therefore, multiple imputation was used to handle missing data, equalizing the number of imputations with the overall percentage of missing data as previously described (22). Primary outcome data were not imputed but rather handled by listwise deletion if missingness occurred.

Inverse probability of treatment weighting (IPTW) was used to account for confounding variables. A propensity score for prolonged clotting time was calculated, based on predefined confounder variables. Cases were then weighted according to the inverse of this probability score. Balance of baseline characteristics was assessed prior to and after weighting using the standardized mean difference (SMD). An SMD greater than 0.1 is by convention considered an indication for significant imbalance (23).

Predefined confounder variables were based on the directed acyclic graph (DAG) presented in **Appendix 2** (http://links.lww.com/CCX/A899). Based on this theoretical framework, adjustment was needed for platelet count, fibrinogen level, CVC type, and underlying disease. Unweighted differences of the other variables in the DAG were assessed between bleeding and nonbleeding groups, and possible confounders were added if they were associated with the primary outcome ($p < 0.2$).

Statistical Analysis

Continuous data were described as mean (SD) if normally distributed or as median (interquartile range [IQR]) if not normally distributed. Categorical data were described as number (%), and odds ratios (ORs) were calculated with a 95% CI. The primary analysis was conducted using univariable logistic regression on the IPTW sample. Two sensitivity analyses were performed: 1) an unweighted logistic regression model with the confounders as covariates and 2) a logistic regression model with PT and APTT as continuous variables instead of the binary predictor coagulopathy. All statistical analyses were performed on the multiply imputed dataset, using R (Version 4.0.3), with packages mice and survey.

RESULTS

Baseline Characteristics

Within the study period, 427 patients suffered from severe thrombocytopenia during their ICU admission, of whom 175 patients received a total of 289 CVCs with a platelet count less than or equal to 50×10^9/L (**Appendices 3** and **4**, http://links.lww.com/CCX/A899).

Coagulopathy could not be evaluated for five CVC placements due to missing data. One-hundred twelve CVC placements were performed during combined thrombocytopenia and coagulopathy, and 172 were performed during thrombocytopenia only. Median (IQR) platelet count was similar for patients with and without coagulopathy (26 [17–36] vs 27 [15–38]). Groups with and without coagulopathy differed significantly on Sequential Organ Failure Assessment (SOFA) score, Child-Pugh score, International Society on Thrombosis and Hemostasis (ISTH) DIC score, fibrinogen levels, hematological diagnosis, catheter type, insertion site, and plasma transfusion (Table 1) (**Appendix 5**, http://links.lww.com/CCX/A899). After IPTW, groups still differed in SOFA score, Child-Pugh score, ISTH-DIC score, and insertion site, but not in the predefined confounders (**Appendix 6**, http://links.lww.com/CCX/A899). SMDs were smaller after IPTW and at most 0.11 for all continuous and binary predictors (**Appendix 7**, http://links.lww.com/CCX/A899).

CVC Placement

In accordance with local guidelines, the vast majority of CVCs were placed using ultrasound guidance. Only one CVC (0.5%) was placed using landmark technique, which resulted in a grade 1 bleeding event (no coagulopathy group). Of all CVCs placed, 113 (39.0%) were hemodialysis catheters, whereas the rest were regular CVCs. Preferred entry sites were the internal jugular (48.2% vs 64.1% in patients with and without coagulopathy) and the femoral vein (49.1% vs 32.9% in patients with and without coagulopathy). Hemodialysis catheters were placed more often in the femoral vein (60%) compared with regular CVCs (25%) and were placed more often in patients with coagulopathy. CVC placement was usually successful after 1 attempt (n = 184, 78%), with a maximum of four attempts.

Missing Data

The mean percentage of missing data was 7.2%, resulting in eight imputations. The highest percentages of missing data were in laboratory values (D-dimer, fibrinogen, albumin), disease severity scores dependent on these laboratory values (Child-Pugh score and DIC score), ultrasound guidance, and operator specialty (**Appendix 8**, http://links.lww.com/CCX/A899).

Postprocedural Bleeding

In the univariable analysis, the number of attempts, arterial puncture, catheter type, operator specialty, bleeding elsewhere, fibrinogen level, and administration of clotting factors were associated with bleeding with p value of less than 0.2 and therefore added as potential confounders to the prespecified IPTW model (**Appendix 9**, http://links.lww.com/CCX/A899).

Overall 44 CVC placements (15.5%; 95% CI, 11.5–19.8) were followed by bleeding at the insertion site. Bleeding rate was 19 (17.0%) and 25 (14.5%) in the groups with and without coagulopathy, respectively. Notably, only two episodes (0.7%; 95% CI, 0.2–2.5) of grade 3 bleeding occurred, both in the group without coagulopathy. Similarly, of four grade 2 bleeding events (1.4%; 95% CI, 0.5–3.5), one occurred in the group with and three in the group without coagulopathy, respectively (**Appendix 10**, http://links.lww.com/CCX/A899).

After IPTW, there was no association between coagulopathy and postprocedural bleeding, OR (95% CI), 0.96 (0.24–3.88) (**Table 2**). Both sensitivity analyses yielded similar results: 0.98 (0.40–2.41) for coagulopathy as binary predictor (**Appendix 11**, http://links.lww.com/CCX/A899) and 1.58 (0.81–3.08) and 0.99 (0.96–1.01) for INR and APTT, respectively, as separate predictors (**Appendix 12**, http://links.lww.com/CCX/A899). In both sensitivity analyses, the only predictor associated with bleeding ($p < 0.05$) was concurrent bleeding elsewhere.

There were two instances of grade 3 bleeding, one with and one without prophylactic platelet transfusion, both in patients without coagulopathy. The first patient had a platelet count of 13×10^9/L, INR of 1.0, and APTT of 41 seconds, and the second patient had a platelet count of 23×10^9/L, INR of 1.1, and APTT of 41 seconds. Both underwent multiple additional CVC placements during their ICU stay, none of which resulted in grade 2 or higher bleeding complications.

Platelet and Plasma Transfusion

Platelet transfusions within 6 hours prior to CVC placement were given equally in the groups with and without coagulopathy: 43 (38.4%) versus 73 (42.4%), respectively. Reasons for transfusion were similar between the groups (**Table 3**). Both platelet count and hemoglobin level were lower for patients who received platelet

TABLE 2.
Baseline Characteristics

Characteristics	Total	Normal Coagulation	Abnormal Coagulation	Statistical Significance
N	289	172	112	
Female, *n* (%)	121 (41.9)	78 (45.3)	39 (34.8)	
Age (yr), median (IQR)	57 (43–64)	58 (51–63)	53 (39–64)	
Sequential Organ Failure Assessment score, mean (SD)	12.8 (4.3)	11.6 (4.2)	14.5 (4.0)	[c]
Child-Pugh score, median (IQR)	9 (7–10)	7 (7–9)	10 (8–11)	[c]
Charlson Comorbidity Index, median (IQR)	3 (2–5)	3 (2–5)	3 (2–5)	
International Society on Thrombosis and Hemostasis- Disseminiated Intravascular Coagulation score, median (IQR)	7 (6–7)	7 (5–7)	7 (7–7)	[c]
Concurrent bleeding elsewhere, *n* (%)	151 (52.2)	87 (50.6)	62 (55.4)	
Platelets (× 10^9/L), median (IQR)	27 (16–38)	27 (15–38)	26 (17–36)	
Hemoglobin (mmol/L), median (IQR)	5.1 (4.6–5.9)	5.1 (4.6–5.7)	5.1 (4.6–6.0)	
International normalized ratio, median (IQR)	1.3 (1.1–1.6)	1.2 (1.1–1.3)	1.7 (1.5–2.2)	[c]
Activated partial thromboplastin time (s), median (IQR)	35 (29–46)	31 (28–36)	50 (40–61)	[c]
Fibrinogen (g/L), median (IQR)	3.4 (1.8–5.5)	4.2 (2.7–6.4)	2.0 (1.3–3.7)	[c]
ICU admission diagnosis, *n* (%)				
Sepsis	132 (45.7)	80 (46.5)	48 (42.9)	
Pulmonary	54 (18.7)	34 (19.8)	19 (17.0)	
Cardiac	13 (4.5)	3 (1.7)	10 (8.9)	
Routine postcardiac surgery	15 (5.2)	11 (6.4)	4 (3.6)	
Surgery (other)	28 (9.7)	14 (8.1)	14 (12.5)	
Other	47 (16.3)	30 (17.4)	17 (15.2)	
Any hematologic diagnosis, *n* (%)	149 (51.6)	105 (61.0)	40 (35.7)	[b]
Number of tries, median (IQR)	1 (1–1)	1 (1–1)	1 (1–2)	
Continuous venovenous hemofiltration catheter, *n* (%)	113 (39.4)	58 (34.1)	55 (49.1)	[a]
Insertion site, *n* (%)				[a]
Internal jugular vein	167 (58.2)	109 (64.1)	54 (48.2)	
Subclavian vein	8 (2.8)	5 (2.9)	3 (2.7)	
Femoral vein	112 (39.0)	56 (32.9)	55 (49.1)	
Operator specialty, *n* (%)				
Anesthesiology	123 (64.4)	76 (63.3)	47 (68.1)	
Internal medicine	32 (16.8)	22 (18.3)	9 (13.0)	
Neurology	16 (8.4)	10 (8.3)	6 (8.7)	
Cardiology	10 (5.2)	5 (4.2)	4 (5.8)	
Other	10 (5.2)	7 (5.8)	3 (4.3)	
Clotting factors, *n* (%)	41 (14.2)	19 (11.0)	22 (19.6)	
Platelet transfusion, *n* (%)	117 (40.5)	73 (42.4)	43 (38.4)	
Plasma transfusion, *n* (%)	8 (2.8)	1 (0.7)	7 (6.5)	[a]

IQR = interquartile range.
[a]$p < 0.05$.
[b]$p < 0.01$.
[c]$p < 0.001$.

TABLE 3.
Frequency of Bleeding in Normal and Abnormal Coagulation Groups

Group	Abnormal Coagulation	Normal Coagulation	Total	OR (95% CI)
N	112	172	284	
Overall bleeding, *n* (%)	19 (17.0)	25 (14.5)	44 (15.5)	
Grade 1 bleeding	18 (16.1)	20 (11.6)	38 (13.4)	
Grade 2 bleeding	1 (0.9)	3 (1.7)	4 (1.4)	
Grade 3 bleeding	–	2 (1.2)	2 (0.7)	
After multiple imputation and inverse probability of treatment weighing[a]				
n	108.1	172.0	280.1	
Overall bleeding, *n* (%)	17.1 (15.8)	28.2 (16.4)	45.3 (16.2)	0.96 (0.24–3.88)

OR = odds ratio.
Data presented as *n* (%).
[a]Data were multiply imputed (8 imputations, 20 iterations) and then inverse probability of treatment weighing (IPTW) was performed on each dataset separately. Bleeding frequencies in this table were obtained after taking the mean IPTW for each individual and weighing the unimputed dataset. OR and 95% CI were obtained after pooling results from the multiply imputed datasets according to Rubin's rules.
Dash indicates no observations of this bleeding grade within this group.

transfusions, whereas SOFA score was higher, and hematologic diagnosis and internal jugular placement were more likely (**Appendix 13**, http://links.lww.com/CCX/A899). The median (IQR) corrected count increment 1 hour after platelet transfusion was 14×10^9/L ($8–25 \times 10^9$/L) and was not different between the groups with and without coagulopathy (**Appendix 14**, http://links.lww.com/CCX/A899).

Overall, plasma transfusions were rarely given, but they were more frequently administered in the group with coagulopathy compared with the group without coagulopathy (9 [8.0%] vs 3 [1.7%], respectively). Plasma transfusions were given prophylactically before CVC placement ($n = 2$), for bleeding elsewhere ($n = 9$), or therapeutically for purpura fulminans, as shown in Table 3.

There was no difference in CVC-related bleeding between patients who did (19/116; 16.4%) and did not (25/168; 14.9%) receive a platelet transfusion within 6 hours prior to CVC placement (**Tables 4** and **5**). An IPTW analysis yielded an OR (95% CI) of 0.73 (0.18–2.83), and a regression analysis yielded an OR (95% CI) of 1.20 (0.27–5.30).

DISCUSSION

In our study, we found no relation between severe coagulopathy and CVC-related bleeding complications in critically ill patients with severe thrombocytopenia, which held in several sensitivity analyses. Importantly, there were no major bleeding events in the group of patients with severe coagulopathy.

Existing literature is ambivalent about the predictive value of traditional coagulation variables for CVC-related bleeding. In a recent review of 21 observational studies of CVC placement (including 13,256 CVC insertions, of which 4,213 in patients with abnormal coagulation parameters), bleeding rate varied between 0% and 32%, and only 13 major bleeding events were reported. Of these, eight were in patients with abnormal coagulation variables (although definitions of both hemostatic abnormality and major bleeding differed between studies), corresponding with a 0.2% major bleeding rate (9).

Notably, Fisher and Mutimer (17) prospectively studied 658 CVC placements in patients with liver disease, of whom 88% had an INR greater than or equal to 1.5, 81% had a platelet count of less than or equal to 150×10^9/L, and 67% had both. There was 1 hemothorax reported, in a patient with INR 1.5 and a platelet count of 68×10^9/L. Superficial hematoma occurred in 7.0% and oozing in 2.3% of CVC placements. Foster et al (14) retrospectively studied 259 CVC placements in liver transplant patients, of whom 202 had either a platelet count less than 80×10^9/L, a PT activity less than or equal to

TABLE 4.
Reasons for Platelet and Plasma Transfusion

Group	Prior to CVC Placement		After CVC Placement	
	Abnormal Coagulation, *n* (%)	Normal Coagulation, *n* (%)	Abnormal Coagulation, *n* (%)	Normal Coagulation, *n* (%)
N	112	172	112	172
Platelet transfusion	43 (38.4)	73 (42.4)	45 (40.2)	59 (34.3)
Reason for transfusion:				
Prophylactic (CVC)	17 (15.2)	44 (25.6)	2 (1.8)	1 (0.6)
Prophylactic (other procedure)	6 (5.4)	4 (2.3)	11 (9.8)	12 (7.0)
Prophylactic (no procedure)	13 (11.6)	19 (11.0)	19 (17.0)	32 (18.6)
Bleeding (CVC)	1 (0.9)	–	–	3 (1.7)
Bleeding (other)	6 (5.4)	6 (3.5)	13 (11.6)	11 (6.4)
Other	–	–	–	–
Plasma transfusion	9 (8.0)	3 (1.7)	10 (8.9)	5 (2.9)
Reason for transfusion:				
Prophylactic (CVC)	2 (1.8)	–	1 (0.9)	–
Prophylactic (other procedure)	–	–	3 (2.7)	1 (0.6)
Prophylactic (no procedure)	–	–	–	–
Bleeding (CVC)	–	–	–	1 (0.6)
Bleeding (other)	7 (6.3)	2 (1.2)	4 (3.6)	3 (1.7)
Purpura fulminans	–	1 (0.6)	2 (1.8)	–
Other	–	–	–	–

CVC = central venous catheter.
Platelet and plasma transfusion within 6 hr prior to and within 24 hr after CVC placement.
Dashes indicate no observations of this reason for transfusion within this group.

40%, and/or an APTT greater than or equal to 77 seconds. No bleeding complications were found. Zeidler et al (16) retrospectively studied 604 CVC placements in patients with acute leukemia, of whom 39% had a platelet count less than 50×10^9/L. An overall bleeding rate of 32% was found, mostly self-limiting grade 1 bleeding events and eight (prolonged) grade 2 bleeding events. No grade 3 or 4 bleeding events were found. Vinson et al (18) retrospectively studied 936 CVC placements in septic patients presenting at the emergency

TABLE 5.
Frequency of Bleeding by Platelet Transfusion

Group	Platelet Transfusion			No Platelet Transfusion		
	Abnormal Coagulation	Normal Coagulation	Total	Abnormal Coagulation	Normal Coagulation	Total
N	43	73	116	69	99	168
Bleeding overall, *n* (%)	9 (20.1)	10 (13.7)	19 (16.4)	10 (14.5)	15 (15.2)	25 (14.9)
Bleeding grade, *n* (%)						
Grade 1	8 (18.6)	8 (11.0)	16 (13.8)	10 (14.5)	12 (12.1)	22 (13.1)
Grade 2	1 (2.3)	1 (1.4)	2 (1.7)	–	2 (2.0)	2 (1.2)
Grade 3	–	1 (1.4)	1 (0.9)	–	1 (1.0)	1 (0.6)

Dashes indicate no observations of this bleeding grade within this group.

department, of whom 71 had a platelet count less than or equal to 50×10^9/L, 475 had an INR greater than or equal to 1.5, and 17 had an APTT greater than 50 seconds. An overall bleeding rate of 4% was found with one major bleeding event, a hemothorax in a patient with a platelet count of 207×10^9/L and INR 1.4. Haas et al (15) studied 3,170 ultrasound-guided CVC placements in the interventional radiology department, of whom 300 had a platelet count less than or equal to 50×10^9/L, 282 had an INR greater than or equal to 1.5, and 44 had both. An overall bleeding rate of 0.1% was observed, and none of those events were found in patients with severe thrombocytopenia and/or coagulopathy.

In our study, an overall bleeding rate of 15% was found with a frequency of grade 3 bleeding events of 0.7%, which is higher than most of the studies mentioned above. However, comparison of bleeding rates between studies is complicated by differences in definitions, methodology, and population (24). Different from previous studies, all patients in our population were severely thrombocytopenic, and 39% also had coagulopathy. Given these characteristics, the frequency of clinically significant bleeding as a result of CVC placement remained low.

With respect to predicting CVC-related bleeding complications, previous studies have identified several risk factors, like insertion site, lower operator experience, landmark technique, multiple attempts, arterial puncture, ascites, and lower fibrinogen (9). In the current study, we consistently found that patients suffering from CVC-related bleeding were more likely to simultaneously have other bleeding events as well. Although this suggests that patient characteristics are more important than procedural factors in developing bleeding complications, the lack of evidence for procedural factors could be due to very high standards in the consistent use of ultrasound guidance and experienced operators. During the study period, ultrasound guidance was the standard of care in our center, resulting in only one CVC placement using the landmark technique. This placement was complicated by a (grade 1) bleeding event, confirming the importance of the routine use of ultrasound guidance as shown by others (2–4). Our results do suggest that a history of bleeding can be helpful in predicting bleeding complications, in line with observations from the surgical theater (25–27).

In order to prevent periprocedural bleeding, sometimes platelet and/or plasma transfusions are administered. In this cohort, the preprocedural use of plasma products was very low, which is in line with national recommendations in the Netherlands on CVC placement and previous publications indicating a lack of efficacy of plasma products in preventing bleeding complications after CVC placement (8, 19). In this cohort, prophylactic platelet transfusion before CVC placement was used more often. Remarkably, the coexistence of severe coagulopathy besides thrombocytopenia did not affect the decision to administer prophylactic platelet concentrate in our study, indicating that physicians did not consider coagulopathy to increase the risk of CVC-related bleeding. Our results showed no significant effect of platelet transfusion on bleeding risk. This supports recent platelet transfusion guidelines that have moved toward lower transfusion thresholds. However, a definitive answer from an RCT is eagerly awaited (5–8).

There are several limitations to our study observations. First, the retrospective nature of this study may have resulted in missing minimal bleeding episodes, since those complications are often not registered in clinical records, especially in critically ill patients. However, we separated the bleeding events into grades and found that most severe bleeding complications, which are clinically most relevant and least likely to be underreported, occurred in patients without coagulopathy. Second, the retrospective assessment of bleeding complications involves the interpretation of large amounts of patient files, which is prone to both subjectivity and human error. In order to prevent this, we used two independent assessors and an adjudicator for all outcome data. Third, subclavian CVC placements were underrepresented in our study. According to national guidelines, subclavian placement is relatively contraindicated in patients with increased bleeding risk, due to difficulty applying local pressure in case of hemorrhage (8). Furthermore, previous observational studies found evidence both in favor of and against subclavian placement or found no difference (16–18). One randomized trial found no difference in mechanical complications between insertion sites (28). We therefore consider it unlikely that this selection bias influenced the results of our study. The use of multiple imputation to account for missing data introduces the least possible risk of bias. Furthermore, IPTW allows for estimation of the marginal treatment effect in observational data, similar to an RCT (29). Although this balances all measured confounders, some unmeasured confounding may persist.

CONCLUSIONS

In conclusion, in this retrospective cohort study, severe coagulopathy was not associated with an increased risk of CVC-related bleeding in critically ill patients with severe thrombocytopenia. Furthermore, the use of prophylactic transfusion of platelet and plasma products was not associated with a reduced bleeding risk. We conclude that a CVC can be placed safely in critically ill patients with both severe thrombocytopenia and coagulopathy without the prophylactic administration of blood products, provided the use of ultrasound guidance and experienced operators.

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