

ICU-acquired infections and thrombo-embolic events in critically ill patients receiving platelet transfusion: a prospective multicenter observational study

Florian Reizine^{1,2}, Sarah Le Marec³, Zoe McQuilten⁴, Anthony Le Meur⁵, Maëlys Consigny⁶, Florian Berteau⁷, Laetitia Bodenes³, Marie Geslain⁸, Catherine Le Niger⁹, Julien Huntzinger², Yoann Launey¹⁰, Jean-Baptiste Thibert¹¹, Jean Reignier¹², Pierre-Yves Egreteau⁷, Jean-Marc Tadié¹, Olivier Huet¹³, Francois Beloncle¹⁴, Stephan Ehrmann¹⁵, Cécile Aubron³



¹Maladies Infectieuses et Réanimation Médicale, CHU de Rennes, Rennes, France;

²Service de Réanimation Polyvalente, CH de Vannes, Vannes, France;

³Service de Médecine Intensive Réanimation, Université de Bretagne Occidentale, Centre Hospitalo-Universitaire de Brest, Brest, France;

⁴Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), Monash University, Melbourne, Australia;

⁵Service de Médecine Intensive Réanimation, CHU de Nantes, Nantes, France;

⁶Service de Biostatistiques, CHU de Brest, Brest, France;

⁷Service de Réanimation Polyvalente, CH de Morlaix, Morlaix, France;

⁸Département d'Anesthésie-Réanimation, Université de Bretagne Occidentale, CHU de Brest, Brest, France;

⁹Unité d'Hémovigilance, CHU de Brest, Brest, France;

¹⁰Service de Réanimation Chirurgicale, CHU de Rennes, Rennes, France;

¹¹Etablissement Français du Sang Bretagne, Rennes, France;

¹²Service de Médecine Intensive Réanimation, Centre Hospitalier Universitaire Hotel-Dieu, Nantes, France;

¹³UFR de médecine de Brest, Université de Bretagne Occidentale, Brest, France;

¹⁴Service de Médecine Intensive Réanimation, CHU d'Angers, Angers, France;

¹⁵Service de Médecine Intensive Réanimation, INSERM CIC 1415, CRICS-TriggerSEP F-CRIN Research Network, CHU de Tours et Centre d'Études des Pathologies Respiratoires, INSERM U1100, Université de Tours, Tours, France

Background - Platelet transfusion is relatively common in patients hospitalized in intensive care units (ICU). Both ICU-acquired infections and thromboembolic events have been reported after platelet transfusion. We sought to explore risk-factors of these complications.

Materials and methods - We conducted an ancillary analysis of a multicenter prospective observational study including critically ill patients who received at least one platelet transfusion in one of the 9 participating ICUs. Patients' characteristics were compared according to the occurrence of post platelet transfusion ICU-acquired infections (blood stream infections and ventilator-associated pneumonia) and thromboembolic events. Factors associated with those outcomes were assessed by univariable and multivariable Fine and Gray regression.

Results - Of the 310 included patients, 64 patients (20.6%) and 14 patients (4.5%) experienced at least one ICU-acquired infection and a thromboembolic event after platelet transfusion, respectively. Fifty patients (78.1%) developed blood stream infection (BSI), 32 (50%) experienced ventilator associated pneumonia (VAP) and 18 (28.1%) had both VAP and BSI. Independent risk factors for post platelet transfusion ICU-acquired infection included a platelet count at ICU admission $<10^9/L$ (protective) (subdistribution Hazard Ratio (sHR) 0.52 95% CI [0.31-0.89] $p=0.016$), multiple platelet transfusion prior to infection occurrence (sHR 2.15 [1.25-3.71] $p=0.005$) and a Simplified Acute Physiology Score (SAPS) II >50 (sHR 3.67 [2.16-6.25] $p<0.001$). While, the unique variable independently associated with thrombotic event occurring after platelet transfusion in adjusted Fine-Gray regression was a SAPS II >50 (sHR 4.27 [1.18-15.39] $p=0.027$).

Discussion - In this prospective multicenter study, the risk of hospital-acquired infection after platelet transfusion increased in patients receiving multiple platelet transfusions and with patient severity at ICU admission.

Keywords: platelet transfusion, ICU-acquired infection, thrombosis.

Arrived: 30 April 2025

Revision accepted: 31 August 2025

Correspondence: Florian Reizine

e-mail: florian.reizine@gmail.com

INTRODUCTION

Platelet transfusion is a relatively common procedure in patients admitted to intensive care units (ICU), with an incidence varying between 9 to 24% depending on platelet count, platelet transfusion indication and associated bleeding risk¹⁻³. Platelets are given to prevent bleeding in thrombocytopenic patients, including prior to invasive procedures, and to treat active bleeding. Little is known about the benefit-risk balance of platelet transfusion in critically ill patients and guidelines are either supported by studies conducted in non-ICU patients and/or by very low level of evidence^{4,5}. Although, severe thrombocytopenia is associated with an increased risk of bleeding^{2,6}, there is a lack of high-level evidence to guide when prophylactic platelet transfusion must be given, except for patients with very low platelet count ($<10 \times 10^9/L$). This is important as 1) firstly, platelets are a scarce life-saving resource at risk of shortage due to their short shelf-life duration, 2) secondly, there are accumulating data on poor platelet transfusion response in critically ill patients questioning the clinical significance of such response and 3) finally, platelet transfusion has been associated with adverse events including hospital-acquired infections and an increased risk of thrombotic events^{3,7}. The risk of hospital-acquired infection after platelet transfusion has been reported previously to be twice more frequent than in non-transfused patients³. This higher susceptibility to hospital-acquired infection might be due to transfusion related immunomodulation^{8,9}. Similarly, an increased thrombotic risk after platelet transfusion has also been found¹⁰⁻¹².

Therefore, we conducted a secondary analysis of the RECCIP prospective multicenter observational study⁷ to describe ICU-acquired infections and thromboembolic events in ICU patients receiving platelet transfusion and to identify factors associated with those outcomes.

MATERIALS AND METHODS

Study design and population

This is a secondary analysis of the RECCIP prospective multicenter observational study conducted from June 2018 to November 2019 in 9 French ICUs of 7 hospitals (5 university-affiliated hospitals and 2 community hospitals) that enrolled adult patients (>18 years) who received at least one platelet transfusion in ICU⁷. The primary outcome

of the RECCIP study, as registered at ClinicalTrials.gov (NCT03325140), was the post-transfusion platelet count increment. The present analysis, focusing on ICU-acquired infections and thromboembolic events, was specified in the internal statistical analysis plan before the end of patient recruitment but was not included in the public trial registry or in the initial primary results publication.

Ethics approval and consent to participate

The study protocol was reviewed and approved by the *Comité de Protection des Personnes*, Tours-Ouest 1 (approval number 2017T3-22). Patients or their next of kin if patients were unable to consent, received oral and written information about the study, and verbal consent was obtained before inclusion.

Data collection and definitions

Demographic characteristics including age, gender and patients' comorbidities with immunosuppression, cirrhosis, chronic kidney disease, obesity (defined as a body mass index >30), cardiovascular disease, diabetes mellitus, hematological malignancies, solid neoplasia, and chronic respiratory disease were recorded. The severity of illness at ICU admission was assessed using the Simplified Acute Physiology Score II (SAPS II)¹³. Primary ICU admission diagnosis and type of admission (medical vs surgical), hemoglobin concentration, platelet count and prothrombin time at ICU admission were collected. Multiple platelet transfusion was defined as at least two platelet transfusions. Thromboembolic events occurring after platelet transfusion (including stroke, myocardial infarction, pulmonary embolism and deep vein thrombosis) as well as ICU-acquired infections (including blood stream infections [BSI] and ventilator associated pneumonia [VAP]) were also recorded.

Infections and thromboembolic events were considered to be postplatelet transfusion when they were diagnosed 24 hours or later after the first platelet transfusion episode. ICU-acquired infections were defined as infections occurring after the first 48 hours of ICU stay. BSI was defined as a positive blood culture yielding a typical pathogen or 2 positive blood cultures drawn on separate occasions regarding common skin contaminants. VAP were defined in accordance with the international guidelines¹⁴. In addition, clinical course data comprised the occurrence of multiple platelet transfusion episodes, the need for red blood cells (RBC) and fresh frozen plasma

(FFP) transfusion, surgery during ICU stay, need for mechanical ventilation, mechanical ventilation duration, hospital and ICU length of stay as well as ICU and hospital mortality rates.

Objectives

We aimed to assess prevalence of post platelet transfusion ICU-acquired infections and thromboembolic events. Secondary objectives included the description of characteristics of post platelet transfusion infections and thromboembolic events in ICU and the identification of their risk factors.

Statistical analysis

Continuous variables are reported as median (interquartile ranges [IQRs]) and categorical variables as proportions (%). Patient's characteristics were compared according to both post platelet transfusion ICU-acquired infections or thromboembolic events occurrences using the Mann-Whitney test for quantitative data and the Chi-square or Fisher test for qualitative data, as appropriate. Given the time-dependent nature of the primary outcomes, the Fine-Gray competing risk regression, considering death in ICU as a competing event, was used to assess factors associated with the occurrence of post platelet transfusion ICU-acquired infection and thromboembolic events. Hazard ratio (HR) with their 95% confidence interval (95% CI) were estimated using the Fine and Gray sub distribution hazard function. When assessing the impact of multiple platelet transfusions and of FFP and RBC transfusions on post platelet transfusion ICU-acquired infection and thromboembolic events, only transfusion occurring before either infections or thromboembolic events onset were considered. In addition, platelet count at ICU admission and the SAPS II score were converted into binary variables. Covariables achieving a p-value <0.2 in

the univariable analyses were entered in the multivariable analyses of risk factors for post platelet transfusion ICU-acquired infections and thromboembolic events. Multiple backward stepwise procedures with an exit threshold set at $p=0.05$ were performed to select variables of the final models. Using the "MICE" R package (R Foundation for Statistical Computing, Vienna, Austria) and assuming that missing data were randomly missing, multiple imputation using Monte Carlo Markov chained equations was used to generate 5 data sets without missing values. Only variables available at ICU admission (outcome variables not included) were used for the imputation process. Two-sided tests were performed and were considered to reach statistical significance when the p-value was <0.05.

RESULTS

Study population

Overall, 310 patients were included in the present analysis. The median age was 61 years (IQR 50-68) and 62.6% of them were male. The median SAPS II score at ICU admission, assessing illness severity, was 50 (IQR 37-63). The most common primary ICU admission diagnosis was sepsis (28.4%) and the overall ICU mortality rate was 33.9% (105/310).

Post platelet transfusion ICU-acquired infection occurred in 64/310 patients (20.6%) and post platelet transfusion thromboembolic events occurred in 14/310 patients (4.5%). Of the 64 patients who developed post platelet transfusion ICU-acquired infection, 50 (78.1%) had BSI, while 32 (50%) experienced VAP and 18 (28.1%) had both VAP and BSI. Microorganisms isolated from respiratory and blood samples are presented in **Figures 1 and 2**. When considering post platelet transfusion thromboembolic events, the overall incidence was 18 events occurring in 14 patients. Of these, 4 patients (28.6%) had pulmonary embolism, 9 patients (64.3%) had

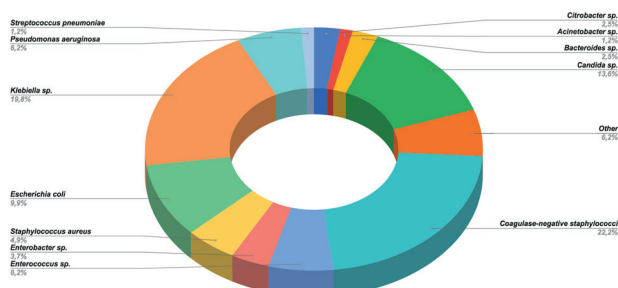


Figure 1 - Microorganisms responsible for bloodstream infections

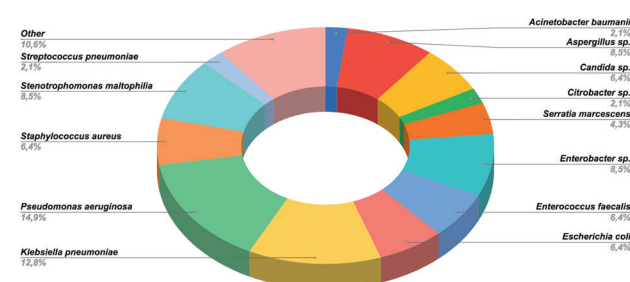


Figure 2 - Microorganisms responsible for ventilator associated pneumonia

distal vein thrombosis. Stroke occurred in 4 patients (28.6%) and myocardial infarction in 1 patient (7.1%). The median delays between the first platelet transfusion and ICU-acquired infections or thromboembolism events were 6 days (2-13) and 8 days (2-13), respectively.

Baseline features and outcomes according to post platelet transfusion ICU-acquired infections

Table I reports the demographic characteristics of the patients according to post platelet transfusion ICU-acquired infections occurrence. Patients with post platelet

transfusion ICU-acquired infections were more severely ill at ICU admission, with a higher median SAPS II score (58 [48-71] vs 46 [36-61]; $p<0.001$). A higher proportion of these patients required mechanical ventilation and received multiple platelet transfusion (90.6% vs 56.5%; $p<0.001$ and 68.8% vs 45.5%; $p=0.002$, respectively). Hospital and ICU length of stay were longer in those patients (34 days [11-70] vs 27 days [14-46]; $p=0.009$ and 21 days [12-45] vs 7 days [4-14]), respectively. Finally, both ICU and hospital mortality rates were higher in patients developing

Table I - Comparison of baseline characteristics, clinical course and outcomes of patients with and without post platelet transfusion ICU-acquired infection

Characteristics	All patients No.=310	Patients without post platelet ICU-acquired infection No.=246	Patients with post platelet ICU-acquired infection No.=64	p-value
Demographic characteristics				
Age, years (median [IQR])	61 (50-68)	61 (49-68)	60 (51-68)	0.974
Male sex, No. (%)	194 (62.6)	143 (62.2)	51 (65.4)	0.710
Obesity (BMI>30) ^a , No. (%)	56 (18.8)	40 (16.9)	16 (25.8)	0.160
Diabetes mellitus, No. (%)	51 (16.4)	39 (15.9)	12 (18.8)	0.713
Cardiovascular disease, No. (%)	110 (35.5)	85 (34.6)	25 (39.1)	0.600
Hematological disease, No. (%)	124 (40.0)	105 (42.7)	19 (29.7)	0.081
Solid neoplasia, No. (%)	53 (17.1)	42 (17.1)	11 (17.2)	1.000
Chronic respiratory disease, No. (%)	37 (11.9)	31 (12.6)	6 (9.4)	0.622
Chronic kidney disease, No. (%)	18 (5.8)	12 (4.9)	6 (9.4)	0.284
Antiplatelet agents, No. (%)	57 (18.4)	48 (19.5)	9 (14.1)	0.411
Chemotherapy, No. (%)	121 (39.0)	102 (41.5)	19 (29.7)	0.115
Immunocompromised, No. (%)	147 (47.4)	123 (50.0)	24 (37.5)	0.100
Type of admission: medical admission, No. (%)	236 (76.1)	191 (77.6)	45 (70.3)	0.289
Primary ICU admission diagnosis				0.685
Respiratory distress, No. (%)	38 (12.3)	29 (11.8)	9 (14.1)	
Sepsis, No. (%)	88 (28.4)	67 (27.2)	21 (32.8)	
Trauma, No. (%)	16 (5.2)	13 (5.3)	3 (4.7)	
Neurologic, No. (%)	21 (6.8)	17 (6.9)	4 (6.2)	
Cardiovascular, No. (%)	16 (5.2)	12 (4.9)	4 (6.2)	
Hematologic, No. (%)	24 (7.7)	21 (8.5)	3 (4.7)	
Hemorrhage, No. (%)	41 (13.2)	36 (14.6)	5 (7.8)	
Metabolic, No. (%)	8 (2.6)	6 (2.4)	2 (3.1)	
Acute kidney injury, No. (%)	5 (1.6)	4 (1.6)	1 (1.6)	
Uro-digestive, No. (%)	9 (2.9)	8 (3.3)	1 (1.6)	
Other, No. (%)	44 (14.2)	33 (13.4)	11 (17.2)	

continues on next page

Table I - Comparison of baseline characteristics, clinical course and outcomes of patients with and without post platelet transfusion ICU-acquired infection (continued from previous page)

Characteristics	All patients No.=310	Patients without post platelet ICU-acquired infection No.=246	Patients with post platelet ICU-acquired infection No.=64	p-value
Patient ABO Group ^b				0.558
A, No. (%)	122 (41.1)	101 (42.8)	21 (34.4)	
O, No. (%)	133 (44.8)	103 (43.6)	30 (49.2)	
B, No. (%)	33 (11.1)	26 (11.0)	7 (11.5)	
AB, No. (%)	9 (3.0)	6 (2.5)	3 (4.9)	
Clinical and laboratory findings at ICU admission				
Platelet count (×10 ⁹ /L, median [IQR])	47 (22-99)	43 (22-87)	79 (23-150)	0.055
Platelet count <50×10 ⁹ /L, No. (%)	161 (51.9)	134 (54.5)	27 (42.2)	0.107
Hemoglobin (g/dL), No. (%)	9.1 (7.6-11.1)	9.1 (7.8-11.1)	9.1 (7.5-11.4)	0.936
PT ^c (%), No. (%)	58 (37-73)	59 (38-71)	57 (34-75)	0.856
SAPS II ^d , No. (%)	50 (37-63)	48 (36-61)	58 (48-71)	<0.001
Clinical course and outcomes				
Multiple platelets units transfused, No. (%)	156 (50.3)	112 (45.5)	44 (68.8)	0.002
At least one RBC transfusion, No. (%)	145 (46.8)	100 (40.7)	45 (70.3)	<0.001
At least one FFP transfusion, No. (%)	188 (60.6)	143 (58.1)	45 (70.3)	0.102
Thrombo-embolic events, No. (%)	14 (4.5)	6 (2.4)	8 (12.5)	0.002
Surgery during ICU stay, No. (%)	98 (31.6)	69 (28.0)	29 (45.3)	0.013
ICU LOS, days, (median [IQR])	9 (4-20)	7 (4-14)	21 (12-45)	<0.001
Need for mechanical ventilation, No. (%)	197 (63.5)	139 (56.5)	58 (90.6)	<0.001
Mechanical ventilation duration, days, (median [IQR])	3 (0-12)	2 (0-8)	13 (7-33)	<0.001
Hospital LOS, days, (median [IQR])	29 (15-49)	27 (14-46)	34 (21-70)	0.009
ICU mortality rate, No. (%)	76 (24.5)	48 (19.5)	28 (43.8)	<0.001
Hospital mortality rate, No. (%)	105 (33.9)	72 (29.3)	33 (51.6)	0.001

p-values comparing patients are tested by Mann-Whitney (continuous variables) and Chi² or Fisher tests (categorical variables). *13 missing data; ^b13 missing data; ^c16 missing data; ^d2 missing data. BMI: body mass index; FFP: fresh frozen plasma; LOS: length of stay; ICU: Intensive Care Unit; PT: prothrombin time; RBC: red blood cells; SAPS II: simplified acute physiology score II.

post platelet transfusion ICU-acquired infections (43.8% vs 19.5%; $p < 0.001$ and 51.6% vs 29.3%; $p = 0.001$).

Risk-factors for post platelet transfusion

ICU-acquired infections

The Fine-Gray risk regression analysis identified a platelet count $<10^9/L$ at ICU admission to be protective against post platelet transfusion ICU-acquired infections (sHR 0.52 95% CI [0.31-0.89] $p = 0.016$). While, multiple platelet transfusion before infection (sHR 2.15 [1.25-3.71] $p = 0.005$) and a SAPS II >50 (sHR 3.67 [2.16-6.25] $p < 0.001$) were found to be independently associated with post platelet transfusion

ICU-acquired infections (**Table II**). Conversely, RBC transfusion and immunosuppression were not associated with post platelet transfusion ICU-acquired infection.

General characteristics and outcomes according to thromboembolic events

Baseline characteristics did not differ according to the occurrence of post platelet transfusion thromboembolic events as presented in **Table III**. Multiple platelet transfusion episodes and RBC transfusions were more common in patients with post platelet transfusion thromboembolic events (85.7% vs 48.6%; $p = 0.015$ and 78.6%

Table II - Risk factors of developing ICU-acquired infections
(unadjusted and adjusted analysis, Fine-Gray model considering death as competing risk events)

Variables	Unadjusted analysis			Adjusted analysis		
	sHR	95% CI	p-value	sHR	95% CI	p-value
Age (years)	1.00	0.99-1.02	0.02			
Male sex	1.54	0.90-2.65	0.12			
Obesity (BMI>30)	1.47	0.85-2.55	0.17			
Diabetes mellitus	1.12	0.61-2.07	0.71			
Cardiovascular disease	1.20	0.84-1.96	0.48			
Hematological disease	0.61	0.36-1.04	0.072			
Solid neoplasia	1.01	0.53-1.94	0.98			
Chronic respiratory disease	0.70	0.31-1.58	0.40			
Chronic kidney disease	1.84	0.79-4.29	0.16			
Antiplatelet agents	0.75	0.37-1.54	0.43			
Chemotherapy	0.66	0.38-1.12	0.12			
Immunocompromised	0.65	0.39-1.07	0.09			
Medical admission	0.73	0.43-1.23	0.24			
Primary ICU admission diagnosis: sepsis	1.24	0.74-2.10	0.42			
Platelet count at ICU admission <50×10 ⁹ /L	0.66	0.41-1.09	0.10	0.52	0.31-0.89	0.016
Hemoglobin at ICU admission (g/dL)	1.03	0.93-1.15	0.53			
Multiple platelet transfusions before IAI	1.91	1.16-3.14	0.011	2.15	1.25-3.71	0.005
At least one RBC transfusion before IAI	1.53	0.87-2.72	0.14			
At least one FFP transfusion before IAI	1.31	0.79-2.16	0.29			
PT at ICU admission (%)	1.00	0.98-1.01	0.56			
SAPS II >50	3.70	2.15-6.38	<0.001	3.67	2.16-6.25	<0.001

BMI: body mass index; FFP: fresh frozen plasma; IAI: ICU-acquired infection; ICU: Intensive Care Unit; PT: prothrombin time; RBC: red blood cells; SAPS II: simplified acute physiology score II.

Table III - Comparison of baseline characteristics, clinical course and outcomes of patients with and without post platelet transfusion thrombo-embolic event

Characteristics	All patients No.=310	Patients without post platelet transfusion thrombo-embolic event No.=296	Patients with post platelet transfusion thrombo-embolic event No.=14	p-value
Demographic characteristics				
Age, years (median [IQR])	61 (50-68)	61 (50-68)	60.5 (47-67.5)	0.857
Male sex, No. (%)	194 (62.6)	187 (63.2)	8 (57.1)	0.862
Obesity (BMI>30) ^a , No. (%)	56 (18.8)	54 (19.0)	2 (14.3)	0.927
Diabetes mellitus, No. (%)	51 (16.4)	49 (16.6)	2 (14.3)	1.000
Cardiovascular disease, No. (%)	110 (35.5)	103 (34.8)	7 (50.0)	0.381
Hematological disease, No. (%)	124 (40.0)	120 (40.5)	4 (28.6)	0.539
Solid neoplasia, No. (%)	53 (17.1)	50 (16.9)	3 (21.4)	0.938
Chronic respiratory disease, No. (%)	37 (11.9)	34 (11.5)	3 (21.4)	0.484
Chronic kidney disease, No. (%)	18 (5.8)	16 (5.4)	2 (14.3)	0.422
Antiplatelet agents, No. (%)	57 (18.4)	55 (18.6)	2 (14.3)	0.958
Chemotherapy, No. (%)	121 (39.0)	116 (39.2)	5 (35.7)	1.000
Immunocompromised, No. (%)	147 (47.4)	142 (48.0)	5 (35.7)	0.533

continues on next page

Table III - Comparison of baseline characteristics, clinical course and outcomes of patients with and without post platelet transfusion thrombo-embolic event (continued from previous page)

Characteristics	All patients No.=310	Patients without post platelet transfusion thrombo-embolic event No.=296	Patients with post platelet transfusion thrombo-embolic event No.=14	p-value
Type of admission: medical admission, No. (%)	236 (76.1)	226 (76.4)	10 (71.4)	0.919
Primary ICU admission diagnosis				0.433
Respiratory distress, No. (%)	38 (12.3)	34 (11.5)	4 (28.6)	
Sepsis, No. (%)	88 (28.4)	86 (29.1)	2 (14.3)	
Trauma, No. (%)	16 (5.2)	16 (5.4)	0 (0.0)	
Neurologic, No. (%)	21 (6.8)	21 (7.1)	0 (0.0)	
Cardiovascular, No. (%)	16 (5.2)	14 (4.7)	2 (14.3)	
Hematologic, No. (%)	24 (7.7)	23 (7.8)	1 (7.1)	
Hemorrhage, No. (%)	41 (13.2)	40 (13.5)	1 (7.1)	
Metabolic, No. (%)	8 (2.6)	7 (2.4)	1 (7.1)	
Acute kidney injury, No. (%)	5 (1.6)	5 (1.7)	0 (0.0)	
Uro-digestive, No. (%)	9 (2.9)	9 (3.0)	0 (0.0)	
Other, No. (%)	44 (14.2)	41 (13.9)	3 (21.4)	
Patient ABO Group ^b				0.889
A, No. (%)	122 (41.1)	116 (39.2)	6 (42.9)	
O, No. (%)	133 (44.8)	128 (43.2)	5 (35.7)	
B, No. (%)	33 (11.1)	31 (10.5)	2 (14.3)	
AB, No. (%)	9 (3.0)	9 (3.0)	0 (0.0)	
Clinical and laboratory findings at ICU admission				
Platelet count ($\times 10^9/L$), (median [IQR])	47 (22-99)	45 (22-97)	105 (39-173)	0.094
Platelet count $<50 \times 10^9/L$, No. (%)	161 (51.9)	157 (53.0)	4 (28.6)	0.129
Hemoglobin (g/dL), (median [IQR])	9.1 (7.6-11.1)	9.1 (7.6-11.1)	9.8 (7.8-11.7)	0.610
PT ^c (%), (median [IQR])	58 (37-73)	58 (37-73)	61 (38-79)	0.839
SAPS II ^d , No. (%)	50 (37-63)	49 (37-63)	61 (51-71)	0.051
Clinical course and outcomes				
Multiple platelets units transfused, No. (%)	156 (50.3)	144 (48.6)	12 (85.7)	0.015
RBC transfusion, No. (%)	145 (46.8)	134 (45.3)	11 (78.6)	0.030
FFP transfusion, No. (%)	188 (60.6)	180 (60.8)	8 (57.1)	>0.990
ICU-acquired infections, No. (%)	64 (20.6)	56 (18.9)	8 (57.1)	0.002
Surgery during ICU stay, No. (%)	98 (31.6)	92 (31.1)	6 (42.9)	0.527
ICU LOS (days), (median [IQR])	9 (4-20)	9 (4-18)	27 (13-56)	<0.001
Need for mechanical ventilation, No. (%)	197 (63.5)	184 (62.2)	13 (92.9)	0.041
Mechanical ventilation duration, (median [IQR])	3 (0-12)	3 (0-11)	18 (8-39)	<0.001
Hospital LOS, days, (median [IQR])	29 (15-49)	28 (14-48)	45 (31-76)	0.033
ICU mortality rate, No. (%)	76 (24.5)	68 (23.0)	8 (57.1)	0.010
Hospital mortality rate, No. (%)	105 (33.9)	96 (32.4)	9 (64.3)	0.030

p-values comparing patients are tested by Mann-Whitney (continuous variables) and Chi² or Fisher tests (categorical variables). ^a13 missing data; ^b13 missing data; ^c16 missing data; ^d2 missing data. BMI: body mass index; FFP: fresh frozen plasma; LOS: length of stay; ICU: Intensive Care Unit; PT: prothrombin time; RBC: red blood cells; SAPS II: simplified acute physiology score II.

Table IV - Risk factors of developing post platelet transfusion thrombo-embolic events (unadjusted and adjusted analysis, Fine-Gray model considering death as competing risk events)

Variables	Unadjusted analysis			Adjusted analysis		
	sHR	95% CI	p-value	sHR	95% CI	p-value
Age (years)	1.00	0.97-1.03	0.99			
Male sex	0.79	0.28-2.25	0.66			
Obesity (BMI>30)	0.70	0.16-3.12	0.64			
Diabetes mellitus	0.79	0.18-3.46	0.75			
Cardiovascular disease	1.87	0.66-5.28	0.24			
Hematological disease	0.63	0.20-2.00	0.44			
Solid neoplasia	1.34	0.37-4.85	0.65			
Chronic respiratory disease	1.95	0.56-6.79	0.29			
Chronic kidney disease	2.55	0.61-10.60	0.20			
Antiplatelet agents	0.76	0.17-3.35	0.71			
Chemotherapy	0.91	0.31-2.70	0.87			
Immunocompromised	0.63	0.21-1.88	0.41			
Medical admission	0.82	0.26-2.59	0.73			
Primary ICU admission diagnosis: sepsis	0.41	0.09-1.83	0.24			
Platelet count at ICU admission <50×10 ⁹ /L	0.38	0.12-1.21	0.10	0.39	0.12-1.26	0.120
Hemoglobin at ICU admission (g/dL)	1.06	0.87-1.20	0.56			
Multiple platelet transfusions	1.47	0.68-4.26	0.47			
At least one RBC transfusion before thromboembolic event	-	-	-			
At least one FFP transfusion before thromboembolic event	0.84	0.27-2.68	0.77			
PT at ICU admission (%)	1.00	0.98-1.02	0.96			
SAPS II >50	4.36	1.21-15/70	0.024	4.27	1.18-15.39	0.027

BMI: body mass index; FFP: fresh frozen plasma; IAI: ICU-acquired infection; ICU: Intensive Care Unit; PT: prothrombin time; RBC: red blood cells; SAPS II: simplified Acute physiology score II.

vs 45.3%; $p=0.03$). Need for mechanical ventilation was also more common (92.9% vs 62.2%; $p=0.041$) and mechanical ventilation duration was higher in those patients (18 days [8-39] versus 3 days [0-11]; $p<0.001$). Those patients had more frequently post platelet transfusion ICU-acquired infection (57.1% vs 18.9%; $p=0.002$). Finally, they had higher ICU mortality than patients without post platelet transfusion thromboembolic events (57.1% vs 23%; $p=0.01$). The unique variable independently associated with those thromboembolic events in adjusted Fine-Gray regression was a SAPS II >50 (sHR 4.27 [1.18-15.39] $p=0.01$) (**Table IV**).

Sensitivity analysis

When comparing patients according to the platelet count at ICU admission, we observed that patients with a platelet count <50×10⁹/L at ICU appeared younger (median age 59 years [48-67] vs 63 [48-67]; $p=0.013$), more commonly suffering from hematological diseases (62.7% vs 15.4%;

$p<0.001$). In addition, they received more frequently multiple platelet transfusion (61.5% vs 38.3%; $p<0.001$). Conversely, they required less frequently mechanical ventilation (53.4% vs 74.5%; $p<0.001$) and had both shorter ICU length of stay and duration of mechanical ventilation (7 days [3-14] vs 12 days [6-24]; $p<0.001$ and 1 day [0-8] vs 7 days [0-15]; $p<0.001$, respectively) as exposed in *Online Supplementary Content, Table SI*.

DISCUSSION

In this secondary analysis of a prospective multicenter observational study on platelet transfusion in critically ill patients (the RECCIP study), 20.6% of patients developed ICU-acquired infections, either BSI or VAP, after platelet transfusion. Independent risk factors for these events included admission patient severity and multiple platelet transfusion prior to infection occurrence. Venous

thromboembolism rate was 4.5% and the only independent risk factors for these thromboembolic events was admission patient severity. Our study supports a negative impact of platelet transfusion on the risk of ICU-acquired infection reinforcing the need to avoid unnecessary platelet transfusion.

The independent increased risk of hospital-acquired infection, including BSI and bacteriuria, in patients who received one or more platelet transfusions has been previously described in a large multicenter observational study of 18,965 critically ill patients that evidenced a rate of ICU acquired infection of 7.7% with transfused patients presenting higher illness severity scores than non-transfused ones³. It has also been reported by Mansour et al. in the setting of cardiac surgery¹⁵. In this recently published large-scale (7,662 included patients) retrospective study, patients who underwent cardiac surgery and who received intra-operative platelet transfusion were significantly and independently at higher risk of BSI even after adjustment for confounders using propensity score matching compared to patients without platelet transfusion (OR3.04, [1.51-6.1] $p=0.002$)¹⁵. Although this association might reflect the patient's severity, adjustment for important confounders including illness severity, administration of other blood components and additional risks of infections, along with propensity score matched analyses, supported the findings. Similarly, in a large multicenter study (No.=3,502), Engle et al. also found an independent association between platelet transfusion and nosocomial infections, including various types of infections¹⁶. Keeping with our findings, those authors did not report any independent association between RBC or plasma administration and post-transfusion nosocomial infections¹⁶. Our observed rate (20.6%) is thus consistent with these large-scale prospective data, with similar risk factors identified, notably high illness severity at admission and repeated platelet transfusions. The comparability of these findings across settings reinforces the external validity of our results.

Platelets develop changes during the collection, preparation and storage process. These changes lead to the accumulation of biological response modifiers, including cytokines which impact on inflammation and immune response¹⁷. Accordingly, several biological

mechanisms may plausibly link platelet transfusion to an increased risk of ICU-acquired infections. Platelet concentrates accumulate a variety of biologically active mediators during collection and storage (including soluble CD40L [sCD40L], chemokines [e.g., PF4/CXCL4, RANTES], pro-inflammatory cytokines and platelet-derived microparticles) that can modulate both innate and adaptive immune responses. These biological response modifiers have been shown to prime neutrophils and monocytes, alter dendritic cell maturation, and influence T-cell responses, potentially impairing host pathogen clearance and promoting an immunodysregulated state after transfusion^{17,19,20}. Platelet microparticles and mitochondria-associated DAMPs carried in platelet products can also act as pro-inflammatory and pro-coagulant stimuli in the recipient, further linking transfusion to both infectious and thrombotic complications^{21,22}. In addition, platelets express MHC class I molecules and toll-like receptors and can directly interact with antigen presenting cells, thereby modulating antigen presentation and adaptive immunity (a mechanism shown experimentally to affect susceptibility to infection after platelet transfusion)^{8,9}. Taken together, these data support that platelet transfusion is not biologically neutral and that storage (and product-related factors) may contribute to the increased incidence of nosocomial infections observed in transfused critically ill patients.

Although being common in this particular population, particularly for BSI as compared with global ICU population with BSI rates ranging from 5 to 7%²³, microorganisms recovered from both blood culture and respiratory samples in our study did not differ from those evidenced in previous studies focusing on those infectious complications²⁴.

In contrast to previous reports^{10,25}, the rate of thromboembolic event in patients receiving platelet transfusion remained low. However, there was no systematic screening for those complications. In addition, our study was limited to patients who had received platelet transfusion and was also likely to be underpowered for this outcome. Along these lines, such a small number of thromboembolic events (No.=14) limits the statistical power of our analysis for this outcome, and the results of the related analysis should therefore be interpreted with caution.

In the present study, although a low platelet count on ICU admission appeared to protect against post

platelet transfusion ICU-acquired infection, multiple platelet transfusion was found to be a risk-factor for such an event. One explanation for this finding may be the difference between patients (in baseline characteristics or outcomes) according to platelet count on admission to the ICU, with a higher proportion of patients with low platelet counts on admission to the ICU more frequently suffering from hematological disease. It is possible that these patients received antibiotic therapy more often, which could have had an influence on ICU-acquired infections. In addition, they were less likely to require mechanical ventilation and had shorter lengths of stay in the ICU and shorter duration of mechanical ventilation, which may have reduced the risk of ICU-acquired infection (notably ventilator-associated pneumonia).

Studies investigating the optimal strategy for platelet transfusion in critically ill patients should also perform safety evaluation in thoroughly investigating infections occurring after platelet transfusion. Experimental research on immunologic changes after platelet transfusion should also be conducted for a better understanding of the underlying mechanisms of this observed association.

Our findings have important clinical implications for ICU practice. Given the observed association between multiple platelet transfusions and the risk of ICU-acquired infections, platelet transfusions should be restricted to situations where the benefits outweigh the risks. When feasible, alternative strategies (including correction of reversible causes of thrombocytopenia, postponement of non-urgent procedures, or optimization of coagulation parameters) should be considered before initiating transfusion. Avoiding repeated transfusion episodes unless strictly necessary may help reduce the risk of nosocomial infections and thromboembolic complications, while preserving platelet resources.

This study analyzed prospectively collected data. The multicenter design supports the study external validity. The time dependent nature of both post transfusion ICU-acquired infection and thrombotic events were taken into account when assessing risk factors for those events by performing competing risk analysis. Granular assessment of post platelet transfusion ICU-acquired infections including microbiological features are provided.

However, this study suffers limitations. Firstly, by

including only patients who received at least one platelet transfusion, our study precludes comparison with non-transfused ICU patients and therefore does not allow estimation of the absolute excess risk attributable to platelet transfusion. This design choice may introduce selection bias, as transfused patients are likely to be more severely ill or have underlying conditions that themselves increase the risk of infections or thromboembolic events, potentially confounding the observed associations despite multivariable adjustment. Secondly, although platelet storage duration was recorded, it varied across transfusion episodes and therefore constituted a repeated, time-dependent exposure variable. Our analysis used a Fine-Gray competing risk model, selected because of the time-dependent nature of the outcomes, but this approach is limited to baseline covariates and does not accommodate repeated measures. Properly accounting for transfusion-specific characteristics, such as storage duration or platelet preparation process, would require alternative statistical methods (e.g., multi-event or joint models), which were beyond the scope of this study. Future research should specifically explore the impact of platelet storage and preparation processes on post-transfusion complications, as these factors may impact on the immunological profile of platelet concentrates and potentially influence the risk of post-transfusion infections or thromboembolic events. Additionally, data on concomitant antibiotic or antithrombotic prophylaxis, pre-existing risk factors for infection or thrombosis were not collected. The absence of these variables may have introduced residual confounding, as the absence of consideration for platelet transfusion prior ICU admission. Thirdly, we did not take into account the potential platelet transfusion given prior to ICU admission. Fourthly, there was no systematic screening for thromboembolic events, which therefore may have been underdiagnosed and the date of their diagnosis might be different to the date to the event itself. In addition, the small number of thromboembolic events (No.=14) in our cohort considerably limits the statistical power to detect any potential associations. As a result, our study may have failed to identify other relevant risk factors for this outcome. Fifthly, although patients with post platelet transfusion ICU acquired infection appeared more severe on ICU admission and had a higher mortality rate,

our study was not designed to properly assess the impact of these infectious events on such a critical outcome. This type of analysis would have required a causal model along with the identification of possible collider bias. We are therefore unable to draw any definitive conclusions on the impact of these events on mortality. In addition, due to limited data availability, we were unable to assess several relevant covariates such as the Charlson's comorbidity index or the use of central venous catheter. Consequently, residual confounding factors may persist.

CONCLUSIONS

In this secondary analysis of a multicenter prospective observational study on platelet transfusion in critically ill patients, 20% of patients developed hospital-acquired infection including BSI and VAP after platelet transfusion with multiple PLT transfusion and patient severity at the ICU admission to be independently associated with those events. In light of these results, clinicians should carefully evaluate the indication for each platelet transfusion in critically ill patients, avoid repeated transfusions when possible and be aware of the infectious risk associated with platelet transfusion.

Availability and data materials

The datasets used and/or analysed during the current study are available from the corresponding Author on reasonable request.

Authorship contribution

FR, SLM, ALM and CA were involved in the conception and supervision of the study. FR performed the statistical analysis. FR, ZM and CA performed the primary results analysis. FR, SLM, ALM and FB were involved in data collection. FR, ZM and CA were involved in the writing of the first draft of the manuscript. All Authors made substantial changes in the manuscript and approved the final manuscript.

The Authors declare no conflicts of interest.

REFERENCES

- Stanworth SJ, Walsh TS, Prescott RJ, Lee RJ, Watson DM, Wyncoll DLA, et al. Thrombocytopenia and platelet transfusion in UK critical care: a multicenter observational study. *Transfusion*. 2013; 53: 1050-1058. doi: 10.1111/j.1537-2995.2012.03866.x.
- Anthon CT, Pène F, Perner A, Azoulay E, Puxty K, Van De Louw A, et al. Thrombocytopenia and platelet transfusions in ICU patients: an international inception cohort study (PLOT-ICU). *Intensive Care Med*. 2023; 49(11): 1327-1338. doi: 10.1007/s00134-023-07225-2.
- Aubron C, Flint AW, Bailey M, Pilcher D, Cheng AC, Hegarty C, et al. Is platelet transfusion associated with hospital-acquired infections in critically ill patients? *Crit Care*. 2017; 21: 2. doi: 10.1186/s13054-016-1593-x.
- Vlaar AP, Oczkowski S, de Bruin S, Wijnberge M, Antonelli M, Aubron C, et al. Transfusion strategies in non-bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine. *Intensive Care Med*. 2020; 46: 673-696. doi: 10.1007/s00134-019-05884-8.
- Vlaar APJ, Dionne JC, de Bruin S, Wijnberge M, Raasveldt SJ, van Baarle FEHP, et al. Transfusion strategies in bleeding critically ill adults: a clinical practice guideline from the European Society of Intensive Care Medicine. *Intensive Care Med*. 2021; 47: 1368-1392. doi: 10.1007/s00134-021-06531-x.
- Strauss R, Wehler M, Mehler K, Kreutzer D, Koebeck C, Hahn EG. Thrombocytopenia in patients in the medical intensive care unit: bleeding prevalence, transfusion requirements, and outcome. *Crit Care Med*. 2002; 30: 1765-1771. doi: 10.1097/00003246-200208000-00015.
- Reizine F, Le Marec S, Le Meur A, Consigny M, Berteau F, Bodenes L, et al. Prophylactic platelet transfusion response in critically ill patients: a prospective multicentre observational study. *Crit Care*. 2023; 27: 373. doi: 10.1186/s13054-023-04650-z.
- Aslam R, Speck ER, Kim M, Freedman J, Semple JW. Transfusion-related immunomodulation by platelets is dependent on their expression of MHC Class I molecules and is independent of white cells. *Transfusion*. 2008; 48: 1778-1786. doi: 10.1111/j.1537-2995.2008.01791.x.
- Ki KK, Faddy HM, Flower RL, Dean MM. Platelet concentrates modulate myeloid dendritic cell immune responses. *Platelets*. 2018; 29: 373-382. doi: 10.1080/09537104.2017.1306045.
- Goel R, Ness PM, Takemoto CM, Krishnamurti L, King KE, Tobian AAR. Platelet transfusions in platelet consumptive disorders are associated with arterial thrombosis and in-hospital mortality. *Blood*. 2015; 125: 1470-1476. doi: 10.1182/blood-2014-10-605493.
- Refaai MA, Phipps RP, Spinelli SL, Blumberg N. Platelet transfusions: impact on hemostasis, thrombosis, inflammation and clinical outcomes. *Thromb Res*. 2011; 127: 287-291. doi: 10.1016/j.thromres.2010.10.012.
- von Meijenfildt FA, van den Boom BP, Adelmeijer J, Roberts LN, Lisman T, Bernal W. Prophylactic fresh frozen plasma and platelet transfusion have a prothrombotic effect in patients with liver disease. *J Thromb Haemost*. 2021; 19: 664-676. doi: 10.1111/jth.15185.
- Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA*. 1993; 270: 2957-2963. doi: 10.1001/jama.270.24.2957.
- Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis*. 2016; 63: e61-e111. doi: 10.1093/cid/ciw353.
- Mansour A, Massart N, Gouin-Thibault I, Seite T, Cognasse F, Anselmi A, et al. Impact of intraoperative allogeneic platelet transfusion on healthcare-associated infections in cardiac surgery: insights from a large single-center cohort study. *J Cardiothorac Vasc Anesth*. 2024; 38: 1650-1658. doi: 10.1053/j.jvca.2024.02.031.
- Engel LJ, Straat M, van Rooijen IHM, de Vooght KMK, Cremer OL, Schultz MJ, et al. Transfusion of platelets, but not of red blood cells, is independently associated with nosocomial infections in the critically ill. *Ann Intensive Care*. 2016; 6: 67. doi: 10.1186/s13613-016-0173-1.
- Cognasse F, Hally K, Fauteux-Daniel S, Eyraud M-A, Arthaud C-A, Fagan J, et al. Effects and side effects of platelet transfusion. *Hamostaseologie*. 2021; 41: 128-135. doi: 10.1055/a-1347-6551.
- McQuillen ZK, French CJ, Nichol A, Higgins A, Cooper DJ. Effect of age of red cells for transfusion on patient outcomes: a systematic review and meta-analysis. *Transfus Med Rev*. 2018; 32: 77-88. doi: 10.1016/j.tmr.2018.02.002.
- Cognasse F, Duchez AC, Audoux E, Ebermeyer T, Arthaud CA, Prier A, et al. Platelets as key factors in inflammation: focus on CD40L/CD40. *Front Immunol*. 2022; 13: 825892. doi: 10.3389/fimmu.2022.825892.
- Cognasse F, Boussoulade F, Chavarin P, Acquart S, Fabrigli P, Lamy B, et al. Release of potential immunomodulatory factors during platelet storage. *Transfusion*. 2006; 46: 1184-1189. doi: 10.1111/j.1537-2995.2006.00869.x.
- Marcoux G, Magron A, Sut C, Laroche A, Laradi S, Hamzeh-Cognasse H, et al. Platelet-derived extracellular vesicles convey mitochondrial DAMPs in platelet concentrates and their levels are associated with adverse reactions. *Transfusion*. 2019; 59: 2403-2414. doi: 10.1111/trf.15300.
- Boudreau LH, Duchez A-C, Cloutier N, Soulet D, Martin N, Bollinger J, et al. Platelets release mitochondria serving as substrate for bactericidal group IIA-secreted phospholipase A2 to promote inflammation. *Blood*. 2014; 124: 2173-2183. doi: 10.1182/blood-2014-05-573543.
- Timis J-F, Ruppé E, Barbier F, Tabah A, Bassetti M. Bloodstream infections in critically ill patients: an expert statement. *Intensive Care Med*. 2020; 46: 266-284. doi: 10.1007/s00134-020-05950-6.
- Tabah A, Buetti N, Staiquily Q, Ruckly S, Akova M, Aslan AT, et al. Epidemiology and outcomes of hospital-acquired bloodstream infections in intensive care unit patients: the EURO-BACT-2 international cohort study. *Intensive Care Med*. 2023; 49: 178-190. doi: 10.1007/s00134-022-06944-2.
- Schmidt AE, Henrichs KF, Kirkley SA, Refaai MA, Blumberg N. Prophylactic preprocedure platelet transfusion is associated with increased risk of thrombosis and mortality. *Am J Clin Pathol*. 2017; 149: 87-94. doi: 10.1093/ajcp/aqx151.