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Duration of platelet storage and outcomes of critically ill patients

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Abstract

Background

The storage duration of platelet units is limited to 5-7 days. This study investigates whether platelet storage duration is associated with patient outcomes in critically ill patients.

Study Design and Methods

Retrospective analysis of critically ill patients admitted to the intensive care unit (ICU) of two hospitals in Australia who received one or more platelet transfusions from 2008-2014. Storage duration was approached in several different ways. Outcome variables were hospital mortality and ICU-acquired infection. Associations between platelet storage duration and outcomes were evaluated using multiple logistic regression and also by Cox regression.

Results

Among 2250 patients who received one or more platelet transfusions while in ICU, the storage duration of platelets was available for 64% of patients (1430). In-hospital mortality was 22.1% and ICU infection rate 7.2%. When comparing patients who received platelets of a maximum storage duration of ≤3, 4 or 5 days, there were no significant differences in baseline characteristics. After adjusting for confounders, the storage duration of platelets was not independently associated with mortality (4 versus ≤3 days OR 0.88 [95% CI 0.59-1.30], 5 versus ≤3 days OR 0.97 [95% CI 0.68-1.37]) or infection (4 versus ≤3 days OR 0.71 [95% CI 0.39-1.29], 5 versus ≤3 days OR 1.11 [95% CI 0.67-1.83]). Similar results were obtained regardless of how storage duration of platelets was approached.

Conclusions

In this large observational study in a heterogeneous ICU population, storage duration of platelets was not associated with an increased risk of mortality or infection.

Keywords

Platelets, transfusion, storage duration, outcomes, mortality, infection, critically ill patients

List of Abbreviations

ICU = Intensive Care Unit; HR = Hazard Ratio; OR = Odds Ratio; IQR = Interquartile Range; SD = Standard Deviation; CI = Confidence Interval; RBC = Red Blood Cell; FFP = Fresh Frozen Plasma

Introduction

Approximately 10% of all patients receive at least one platelet transfusion while in the Intensive Care Unit (ICU).[1] Platelet transfusions are often administered to bleeding patients or as bleeding prophylaxis[2] in many of the 35-45% of ICU patients who are thrombocytopenic.[1,3]

Platelets must be stored in specific conditions at room temperature as their circulating time post-transfusion is markedly reduced when cooled.[4-6] However, room temperature storage increases the risk of bacterial proliferation and is one of the main limitations of the maximum storage duration.[7,8] Additionally, over their storage lifetime, platelets undergo deleterious changes in their structure and function, thought to correspond with reduced haemostatic efficacy,[9] and these changes are often referred to as the platelet storage lesion.[4] Due to these two main factors (bacterial contamination and the development of a storage lesion), platelets only have a usable shelf life of up 5 days in Australia, and up to 7 days in other parts of the world.[10] However, despite these in vitro indices, the clinical impact of storage duration on clinical outcomes remains unknown. We hypothesised that patients with critical illness (with its accompanying reduced physiological reserve and high mortality) might, logically, be at a higher risk of adverse outcomes if prolonged platelet storage is detrimental. Only two previous studies have been conducted in critically ill patient populations and the results are conflicting.[11,12]

Over the last decade there has been a substantial increase in demand for platelets around the world.[13] The short duration of platelet storage creates a difficult to manage trade-off between minimising wastage of expired platelets and having sufficient supply to meet demand. Consequently, platelet wastage due to outdating can be as high as 15-30% of all platelet stocks.[8,14] ICU patients are the third largest consumer of platelets behind haematology and cardiac surgery patients.[13] If the storage duration of platelets can be extended without impacting patient outcomes, better use could be made of this scarce resource.

Accordingly, the purpose of this study is to investigate the association of platelet storage duration with mortality and ICU acquired infection in a large heterogeneous population of critically ill patients at two teaching hospitals in Australia. If storage for up to five days has no impact on clinical outcomes, investigation of the effects of more

prolonged storage would be justified, especially as platelets of up to 7 days storage duration are already in use in some countries.[10]

Materials and Methods

Study design

We performed a retrospective study of patients admitted to the ICUs of the Alfred and Austin Hospitals (Melbourne, Australia) between January 2008 and September 2013. The Austin Hospital has a 29-bed multidisciplinary ICU specialising in spinal trauma and liver transplant. The Alfred Hospital multidisciplinary ICU has an average occupancy of 39 patients and specialises in trauma, heart and lung transplantation and extra-corporeal membrane oxygenation. Patients who received a platelet transfusion during ICU admission were included in the study. For patients with multiple ICU admissions during that hospital admission, only the first admission was considered.

Data Collection

Data were obtained from prospectively maintained clinical databases and blood transfusion databases. Clinical data were extracted from local ICU databases used to collect and submit data to the Australian and New Zealand Intensive Care Society (ANZICS) Adult Patient Database. This included gender, date of birth, co-morbidities, ICU admission diagnosis, ICU and hospital admission and discharge dates, Acute Physiology and Chronic Health Evaluation (APACHE) III score, requirement for mechanical ventilation or renal replacement therapy, and ICU and hospital mortality.

Data on transfused blood components came from the hospital laboratory information system (LIS) at each hospital. This included the type of product issued (platelets, red blood cells (RBC), fresh frozen plasma (FFP) and cryoprecipitate), a unique donation identification number, and date and time of issue from the blood bank. The date of donation and platelet manufacture was provided by the Australian Red Cross Blood Service using the unique donation identification number. The age of the platelet component was calculated using the date of issue and transfusion from the hospital laboratory and date of manufacture.

Platelet units are manufactured by two methods in Australia: either by apheresis from anti-coagulated blood separated into components to produce apheresis platelets; or from the buffy coats of whole blood from four donors of identical ABO blood type to produce pooled platelets.[15] Both apheresis and pooled platelets are resuspended in Platelet Additive Solution and are leucodepleted before being stored for up to 5 days at 20-24°C with gentle continuous agitation.[15]

Infection data was obtained from the microbiology laboratory records at the Austin hospital and from the Alfred Hospital's prospectively maintained infectious disease database. This included the dates of positive blood cultures and positive urine cultures, and their isolated pathogens. If a known contaminant was isolated, only results with two or more positive blood cultures were included.

Data analysis

The primary outcomes were hospital mortality and ICU-acquired infection. Hospital mortality was defined as death while an inpatient in the hospital. ICU-acquired infection was defined as bacteraemia and/or bacteriuria occurring 48 hours after ICU admission until ICU discharge. The storage duration of platelets was considered in four different ways: the maximum (oldest unit), minimum (youngest unit), and median storage duration of all platelets transfused, and the storage duration of the first platelet transfused. We hypothesised that the maximum storage duration would be the most likely to be associated with outcomes if a relationship was to be found. The median storage duration was analysed because storage duration distribution was skewed towards more prolonged storage and the cumulative storage duration may be important for multiple platelet unit ages. The minimum storage duration and the storage duration of the first unit transfused were included for comparison. A secondary analysis was performed analysing patients who received only one platelet transfusion; we did this to facilitate comparison with previous studies.

Statistical analysis

Descriptive statistics are reported according to data distribution as either mean (standard deviation (SD)) or median (inter-quartile range (IQR)). Hypothesis testing was performed using Student's t-test and Analysis of Variance (ANOVA) for normally distributed variables, Kruskal-Wallis test for non-normally distributed data, and Chi-square or Fisher's Exact test for categorical variables. The relationship between storage duration and outcomes were analysed using a logistic regression with the treatment variable being a categorical variable of $\leq$3 days, 4 days or 5 days.

Results are reported using odds ratios (ORs) (95% confidence interval (CI)). Multivariate analysis was performed adjusting for the following confounders: gender, APACHE III Score, site, diagnosis category, year, requirement for renal replacement therapy, requirement for mechanical ventilation, and whether another type of transfusion (red blood cell, fresh frozen plasma or cryoprecipitate) had been given prior to the platelet transfusion. A two-sided significance level of P=0.05 was considered to indicate significance. Survival time was estimated using the Kaplan Meier method, and the log rank test used to compare survival between groups. Association between platelet storage and survival was modelled using Cox regression, adjusting for gender, APACHE III Score, site, diagnosis category, year, requirement for renal replacement therapy, requirement for mechanical ventilation, and blood components (RBC, FFP or cryoprecipitate) treated as time varying variables. All analyses were performed using STATA version 12.1.[16] The study was approved by the Human Research Ethics Committees at both sites.

Results

Out of the 19 101 patients admitted to the ICUs of the two hospitals between January 2008 and September 2013, there were complete data (ICU, transfusion and microbiology) for 18 965 (99%) patients. Of these, 2 250 (12%) patients received at least one platelet transfusion in ICU, and the storage duration of platelets was available for 1 430 (64%) patients (Figure 1). Table 1 shows comparison demographics between those where platelet storage duration was known versus those where platelet storage duration was unavailable.

In total, 4 238 platelets were transfused during the study period for which the storage duration was known. The platelet storage duration ranged from 2 to 5 days, with mean storage duration of 4 days (SD 1 day), median storage duration of 4 days (IQR 3 to 5 days), and most common storage duration of 5 days (41% of transfusions) (Figure 2). The donor ABO and Rhesus group was recorded for 57% of transfusions, of which 36% were blood type A, 3% type B, 61% type O and 70% were Rhesus D positive. 3 599 (85%) of all platelet units transfused were pooled platelets manufactured from whole blood and 649 (15%) were apheresis platelets. Of the first platelet unit transfused, 87% were pooled platelets.

Maximum storage duration of platelets

Table 2 shows demographics, ICU admission diagnosis, pre-ICU comorbidities and ICU treatment variables for patient groups by the maximum storage duration of platelets transfused and for all patients. The mean age of patients was 58 (SD 19) years. The population was predominantly male (67%) and the average APACHE III Score was 66 (SD 29).

There were no significant differences between patient groups except that patients receiving fresher platelets were more likely to be insulin dependent diabetics (p = 0.02).

Seventy-nine percent of patients received at least one RBC transfusion, 67.8% received FFP, and 29.2% received cryoprecipitate (Table 3). There were no significant differences in the median units of any blood products between platelet age groups.

The overall in-hospital mortality was 22.1% and ICU-acquired infection rate was 7.2% (Table 4). Hospital mortality and infection rates were similar in platelet storage categories in the univariate analysis, with no significant difference between groups for mortality (p = 0.47) and infection (p = 0.44).

After adjusting for confounders, there was no significant difference in mortality between platelet storage groups (4 versus ≤3 days OR 0.88 [95% CI 0.59-1.30], 5 versus ≤3 days OR 0.97 [95% CI 0.68-1.37]). Similarly, no significant differences were found in the rates of infection (bacteraemia and/or bacteriuria) in both the univariate analysis (p = 0.44) and after adjusting for confounders (4 versus ≤3 days OR 0.71 [95% CI 0.39-1.29], 5 versus ≤3 days OR 1.11 [95% CI 0.67-1.83]), and no differences when individually considering bacteraemia (4 versus ≤3 days OR 0.90 [95% CI 0.43-1.87], 5 versus ≤3 days OR 1.04 [95% CI 0.54-2.02]) or bacteriuria (4 versus ≤3 days OR 0.75 [95% CI 0.32-1.75], 5 versus ≤3 days OR 1.33 [95% CI 0.67-2.64]). Similar findings were obtained when comparing outcomes against the storage duration of platelets first transfused, the minimum and median storage duration, and when considering only patients who received one platelet unit.

Figures 3 and 4 show Kaplan Meier estimates for mortality and infection up to 50 days and 20 days respectively, when 75% of outcomes had occurred. Cox proportional hazard modelling for mortality (4 versus ≤3 days adjusted Hazard Ratio (HR) 0.92 [95% CI 0.67-1.25], and 5 versus ≤3 days adjusted HR 1.04 [95% CI 0.79-1.35]) and infection (4 versus ≤3 days adjusted HR = 0.69 [95% CI 0.40-1.19], and 5 versus ≤3 days adjusted HR 1.11 95% [CI 0.71-1.75]) showed no association with storage duration of platelets transfused after adjusting for confounders.

Subgroup analyses

To confirm that these findings were consistent across different patient groups, subgroup analyses were performed on trauma patients, haematology patients, non-haematology patients, those receiving other transfusions, those not receiving other transfusions, stratified between the most critically ill 50% and the least critically ill 50% as measured by the APACHE III Score, and considering post-operative cardiac patients as a proxy for cardiac surgery patients. The storage duration of platelets was not associated with an increased risk of mortality or infection in any of these subgroups, with the exception that in the post-operative cardiac subgroup, platelets of 4-day storage duration were associated with a lower risk of mortality compared to 3 days but not observed for 5 days compared to 3 days. A subgroup analysis of infection in haematology patients was not performed due to insufficient outcomes.

Discussion

We found that the storage duration of platelets (up to 5 days) was not associated with hospital mortality or infection in a large population of critically ill patients. These results were independent of the platelet storage duration variable used (the maximum, minimum, median or first storage duration of platelets transfused), independent within the subgroup analyses, and in those who received only a single platelet transfusion.

Comparison with existing literature

There have only been two studies examining the effect of platelet storage duration on patient outcomes in critical care. In a retrospective study of 2 578 cardiac surgery patients receiving platelets, Welsby et al.[12] concluded storage duration was not associated with adverse short-term outcomes, long-term survival or infection. In a retrospective study of trauma patients receiving platelets, Inaba et al.[11] found storage duration was not associated with mortality, however there was a step-wise increase in the rates of sepsis with increasing storage duration. Our findings do not support an association between platelet storage up to 5 days and infection as in Inaba et al.[11], who investigated a more homogeneous population of 381 trauma patients at a single centre with higher rates of infection overall, reporting sepsis rates of 10.8% compared to an overall infection of 7.2% in our study. In a post hoc analysis of the Platelet Dose (PLADO) study[17] of haematology-oncology patients, Kaufman, et al. [18] found that the storage duration of platelets up to 5 days was not associated with an increased risk of transfusion-related adverse events including infection.

The impact of storage duration on other outcomes such as bleeding, corrected platelet count increments and time to next transfusion remains uncertain. In one retrospective cohort study of haematology patients, shorter storage duration was associated with increased corrected count increments and lower bleeding events.[19] In a randomised non-inferiority crossover trial of haematology patients, MacLennan et al.[10] found that 6-7 day old platelets were not inferior to 2-5 day old platelets as measured by post-transfusion corrected count increments, bleeding events and the time to next transfusion. While our study did not examine corrected count increments or bleeding events, the observation that the total units transfused to patients receiving older platelets was not significantly more than those receiving platelets of shorter storage duration supports other study findings that the efficacy of prolonged storage platelets is comparable.

Strengths and limitations

Our study has a number of strengths including its large sample size, multi-centre design and inclusion of both whole blood derived and apheresis platelets, which contribute to the generalisability of our findings. In addition, to our knowledge it is the first study to investigate the storage duration of platelets in a heterogeneous critically ill population and we were able to adjust for important confounders thought to be associated with outcomes. Our results were consistent regardless of how we defined the storage duration of platelets (maximum, minimum, median or the storage duration of the first unit), and there were no differences in effects in clinically-relevant subgroups. Landmark outcomes and survival analyses reached similar conclusions.

Limitations of this study include its retrospective and observational design. However, data came from prospectively maintained databases, so issues of bias should be minimal. While we did not find a significant association between platelet storage duration and outcomes, it is possible that our study was not sufficiently powered to detect significant benefit or harm. There was a proportion of platelet units for which we were unable to obtain donation date, and although patients excluded from the analysis due to missing platelet age data were similar with respect to illness severity, there were differences in age and co-morbidities. Whilst we adjusted for a range of important determinants of the outcomes of interest, we may have omitted other important confounders which were not available in our data. Infection data was limited to infections while in the ICU, so it is possible that we did not capture some infections occurring after ICU discharge. Furthermore, our definition of infection was limited to

positive culture results; many patients with culture-negative clinically-apparent infection would not have been identified. Finally, we had no data about platelets and blood products received prior to ICU admission, and so could not analyse the potential effect of these pre-ICU transfusions on outcomes.

Implications of the study findings

Our study implies that, up to day 5, duration of platelet storage may not affect clinical outcomes. However, as with the previous studies investigating the impact of storage duration of platelets on outcomes, this study only investigated association and not causality. Prospective research is warranted to determine whether storage duration of platelets is associated with clinical centred outcomes and therefore whether extending the storage duration could be achieved without adversely impacting on patient outcomes.

Conclusions

In this observational study of a heterogeneous population of critically ill patients, the storage duration of platelets up to 5 days was not found to be associated with mortality or infection. Investigating the clinical effect of more prolonged storage is justified.

Acknowledgments

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Table 1: Comparing patient characteristics according to availability of platelet age

	Platelet storage duration available (n = 1 430)	Platelet storage duration not available (n = 820)	P-value
Age (years), mean (SD)	57.5 (18.1)	61.5 (16.0)	<0.001
Gender (male), number (%)	964 (66.7%)	547 (67.4%)	0.73
Comorbidity, number (%)	484 (33.9%)	218 (26.6%)	<0.001
APACHE III Score, mean (SD)	65.8 (29.0)	63.4 (27.7)	0.06

SD standard deviation

Table 2: Patient characteristics by the maximum storage duration of platelets transfused

	All patients (N = 1 430)	≤3 days (n = 433)	4 days (n = 387)	5 days (n = 610)	P-value*
Demographics					
Age (years), mean (SD)	57.5 (18.5)	58.1 (18.1)	56.4 (17.7)	57.8 (18.4)	0.35
Gender (male), number (%)	964 (67.4%)	294 (67.9%)	257 (66.4%)	413 (67.7%)	0.88
APACHE III Score, mean (SD)	66 (29.0)	66.5 (29.3)	64.3 (26.4)	66.5 (29.3)	0.48
ICU admission diagnosis					
Cardiovascular, number (%)	507 (35.5%)	151 (34.9%)	127 (32.8%)	229 (37.5%)	0.30
Gastrointestinal, number (%)	200 (14.0%)	55 (12.7%)	52 (13.4%)	93 (15.3%)	0.47
Haematological, number (%)	73 (5.1%)	29 (6.7%)	18 (4.7%)	26 (4.3%)	0.20
Neurological, number (%)	67 (4.7%)	24 (5.5%)	12 (3.1%)	31 (5.1%)	0.20
Renal/Genitourinary, number (%)	58 (4.1%)	19 (4.4%)	16 (4.1%)	23 (3.8%)	0.87
Respiratory, number (%)	105 (7.3%)	32 (7.4%)	35 (9.0%)	38 (6.2%)	0.26
Sepsis, number (%)	56 (3.9%)	12 (2.8%)	16 (4.1%)	28 (4.6%)	0.30
Trauma, number (%)	316 (22.1%)	93 (21.5%)	98 (25.3%)	125 (20.5%)	0.19

Other, number (%)†	48 (3.4)	18 (4.2%)	13 (3.4%)	17 (2.8%)	0.47
Comorbidities					
Cancer ‡	140 (9.8%)	48 (11.1%)	38 (9.8%)	54 (8.9%)	0.49
Hepatic disease (hepatic failure, cirrhosis or chronic liver disease), number (%)	112 (7.8%)	34 (7.9%)	27 (7.0%)	51 (8.4%)	0.73
IDDM, number (%)	50 (3.5%)	24 (5.5%)	12 (3.1%)	14 (2.3%)	0.02
Chronic respiratory disease, number (%)	81 (5.7%)	30 (6.9%)	23 (5.9%)	28 (4.6%)	0.26
Chronic CVD, number (%)	117 (8.2%)	35 (8.1%)	27 (7.0%)	55 (9.0%)	0.52
Chronic renal failure, number (%)	40 (2.8%)	9 (2.1%)	12 (3.1%)	19 (3.1%)	0.55
Immuno-compromised (immuno-suppress	235 (16.4%)	85 (19.6%)	57 (14.7%)	93 (15.3%)	0.10

ed or immune disease), number (%)					
Treatment					
Requirement for Mechanical Ventilation, number (%)	1,235 (86.4%)	366 (84.5%)	338 (87.3%)	531 (87.1%)	0.41
Requirement for Renal Replacement Therapy, number (%)	295 (20.6%)	76 (17.6%)	87 (22.5%)	132 (21.6%)	0.16

SD standard deviation

*P-value comparing ≤3 days, 4 days and 5 day groups

† Other includes undefined, metabolic, musculoskeletal or skin, and gynaecological

‡ Cancer includes leukaemia, myeloma, lymphoma or metastases

Table 3: Transfusion characteristics by the maximum storage duration of platelets transfused

	All patients (N = 1 430)	≤3 days (n = 433)	4 days (n = 387)	5 days (n = 610)	P-value*
Platelets					
Median units	2	2	2	2	0.06
(IQR)	(1-3)	(1-3)	(1-3)	(1-3)	
Total units	4,238	1,169	1,215	1,854	
Red blood cells					
Median units	5	4	5	5	0.75
(IQR)	(1-10)	(1-10)	(1-11)	(2-10)	
Number of patients (%)	1,135 (79.4%)	345 (79.7%)	303 (78.3%)	487 (79.8%)	
Total units	11,629	3,306	3,346	4,977	
Cryoprecipitate					
Median units	0	0	0	0	0.28
(IQR)	(0-1)	(0-1)	(0-1)	(0-1)	
Number of patients (%)	418 (29.2%)	127 (29.3%)	129 (33.3%)	162 (26.6%)	
Total units	1,886	530	440	916	

IQR interquartile range

*P-value comparing ≤3 days, 4 days and 5 day groups

Table 4: Outcomes by the maximum storage duration of platelets transfused

	All patients (N = 1 430)	≤3 days (n = 433)	4 days (n = 387)	5 days (n = 610)	P-value*
Hospital mortality, deceased (%)	316 (22.1%)	100 (23.1%)	77 (19.9%)	139 (22.8%)	0.47
Positive blood culture and/or urine culture, number (%)	103 (7.2%)	29 (6.7%)	24 (6.2%)	50 (8.2%)	0.44
Positive blood culture, number (%)	60 (4.2%)	16 (3.7%)	17 (4.4%)	27 (4.4%)	0.82
Positive urine culture, number (%)	52 (3.6%)	14 (3.2%)	11 (2.8%)	27 (4.4%)	0.44

*P-value comparing ≤3 days, 4 days and 5 day groups

Legends for Illustrations

Figure 1: Final patient population included after exclusions

Figure 2: The number of platelet units transfused for each storage duration

Figure 3: Kaplan-Meier estimates of survival to 50 days (p = 0.36)

Figure 4: Kaplan-Meier estimates of infection to 20 days (p = 0.22)

Figure 1

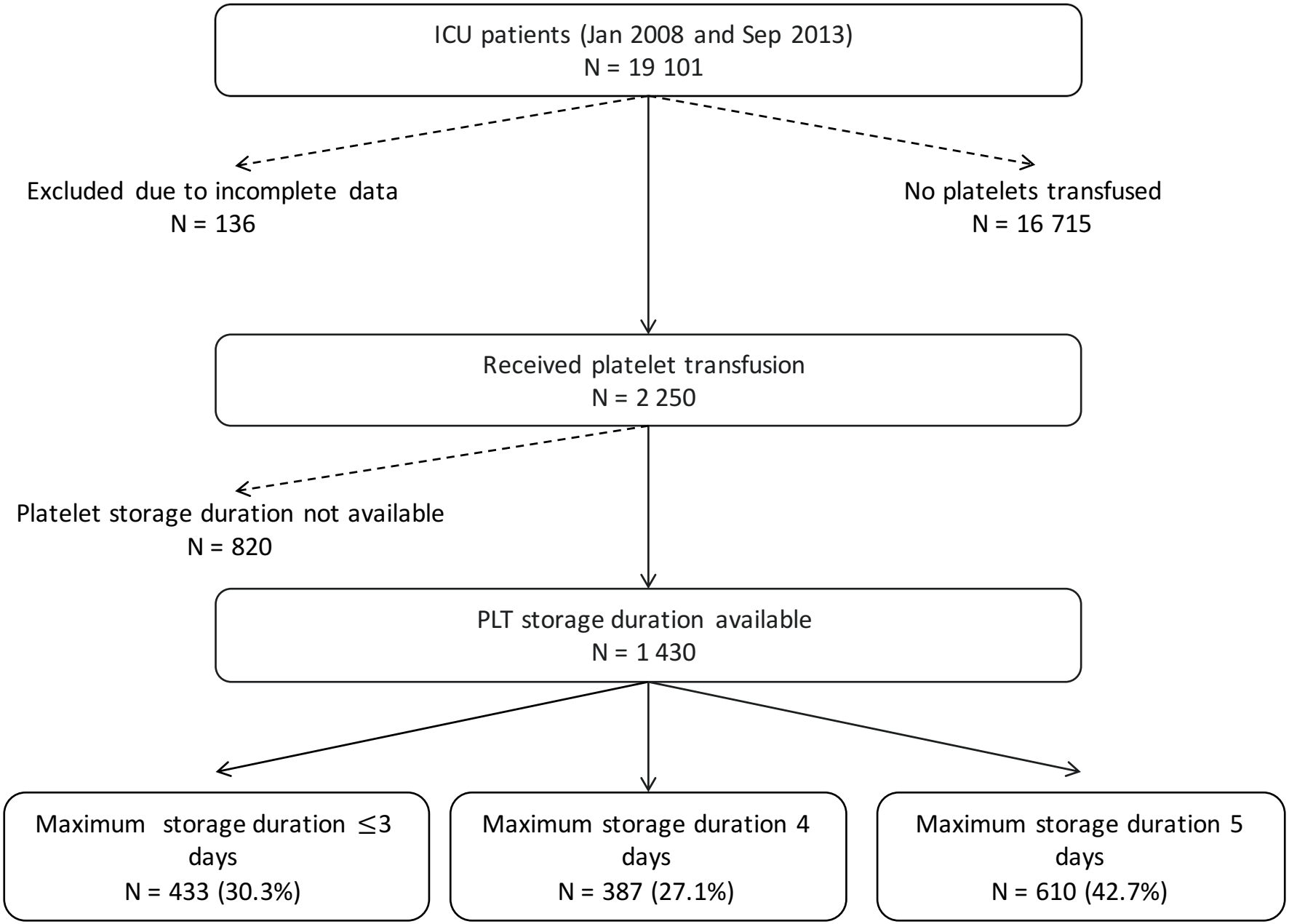
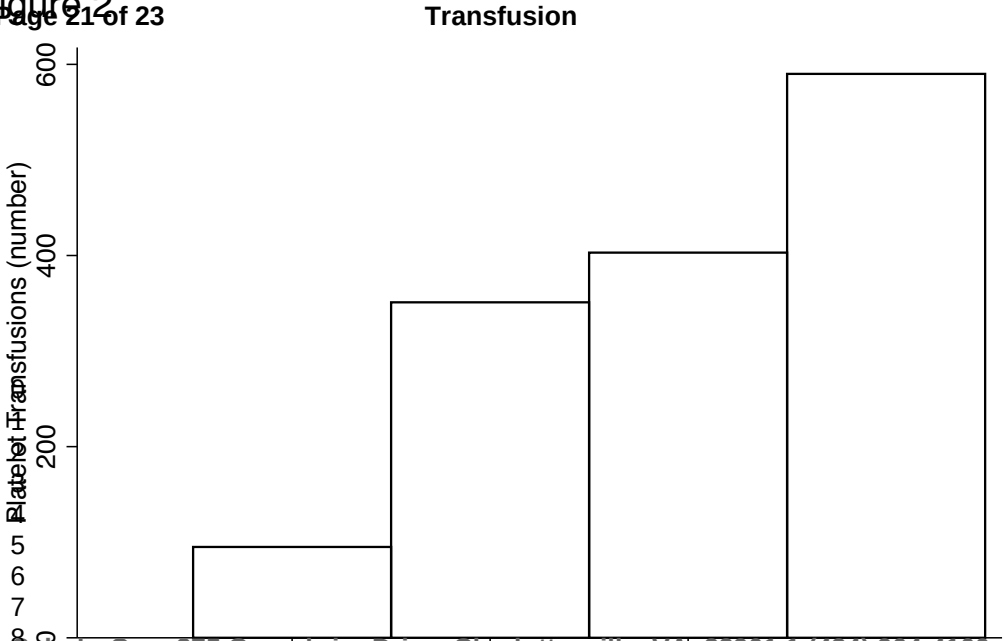


Figure 2



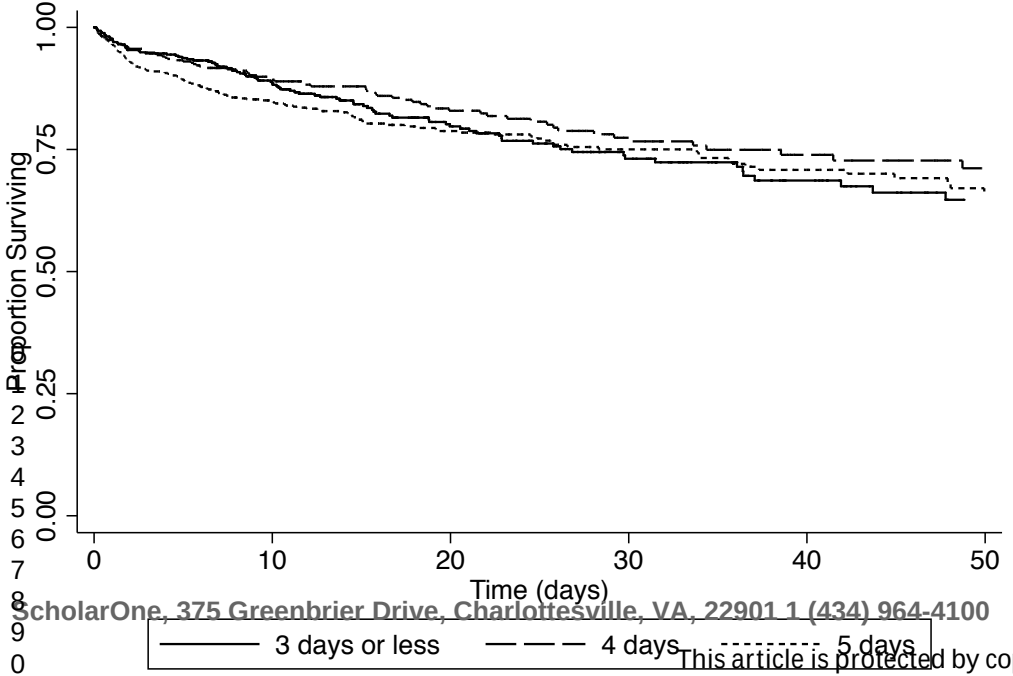


Figure 4