

Indications and effects of plasma transfusions in critically ill children

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At a Glance Commentary:

Scientific Knowledge on the Subject: Plasma transfusions are frequently prescribed for critically ill children, although most clinical uses of plasma are not evidence-based.

What This Study Adds to the Field: Our data indicate that a third of transfused patients were not bleeding and had no planned procedure. Furthermore, plasma transfusion only corrected coagulation tests for patients with severe coagulopathy.

1 **Abstract**

2 **Rationale:** Plasma transfusions are frequently prescribed for critically ill children,
3 although their indications lack strong evidence base. Plasma transfusions are largely
4 driven by physician conceptions of need and these are poorly documented in
5 pediatric intensive care patients.

6 **Objective:** To identify patient characteristics and characterize indications leading to
7 plasma transfusions in critically ill children and to assess the effect of plasma
8 transfusions on coagulation tests.

9 **Methods:** Point-prevalence study in 101 pediatric intensive care units in 21
10 countries, on six pre-defined weeks. All critically ill children admitted to a participating
11 unit were included if they received at least one plasma transfusion.

12 **Main results:** During the six study weeks, 13192 children were eligible among whom
13 443 (3.4%) receiving at least one plasma transfusion were included. The primary
14 indications for plasma transfusion were critical bleeding in 22.3%, minor bleeding in
15 21.2%, planned surgery or procedure in 11.7%, and high risk of post-operative
16 bleeding in 10.6%. No bleeding or planned procedures were reported in 34.1%. Prior
17 to plasma transfusion, the median International Normalized Ratio (INR) and activated
18 Partial Thromboplastin Time (aPTT) values were 1.5 and 48, respectively. After
19 plasma transfusion, the median INR and aPTT changes were -0.2 and -5,
20 respectively. Plasma transfusion significantly improved INR only in patients with a
21 baseline INR >2.5.

22 **Conclusions:** A third of transfused patients were not bleeding and had no planned
23 procedure. Additionally, in most patients, coagulation tests are not sensitive to
24 increases in coagulation factors resulting from plasma transfusion. Studies assessing
25 appropriate plasma transfusion strategies are urgently needed.

26 Abstract: 250 words

1 Introduction

2 Although plasma transfusions are frequently prescribed worldwide, the indications for
3 their use remain unclear. In 2011, 3,882,000 plasma units were transfused in the
4 United States in adults and children (1). According to US pediatric health information
5 administrative databases, nearly 3% of all recorded pediatric admissions receive a
6 plasma transfusion during their hospital stay (2). In France, administration of plasma
7 has increased by more than 40% over the last ten years, often in clinical situations
8 where the biological and/or clinical criteria do not seem to justify its use (3). Experts
9 recommend plasma transfusions mainly in the context of massive transfusion and in
10 case of bleeding associated with documented abnormal coagulation tests(4, 5).

11

12 In massively bleeding patients, observational data suggest that early use of plasma
13 and platelets seems to be associated with improved outcomes in patients with life-
14 threatening bleeding (6). However, in a less critical clinical context, adult and
15 pediatric epidemiological studies have shown an independent association between
16 plasma transfusion and development of nosocomial infections (7, 8), acute
17 respiratory distress syndrome (9-11), multiple organ failure (8, 11) and mortality (12).
18 Therefore, it might seem important to determine when the benefits outweigh the side
19 effects, especially as previous studies have already shown that plasma transfusions
20 failed to correct mildly abnormal coagulation tests (13-15). There is no specific
21 pediatric data on this issue. However, the increased morbidity associated with
22 plasma transfusions in observational studies might be due to unrecognized biases,
23 as plasma might be given to sicker patients.

24

25 Plasma transfusions are frequently administered to correct abnormal coagulation
26 tests (16) which are often viewed as predicting a risk of bleeding although Segal et al

1 have shown that abnormal coagulation tests are not associated with increased risk of
2 bleeding in most procedures (17). In 2007, Lauzier et al reported that plasma
3 transfusions were often administered to critically ill adults who were not bleeding and
4 who did not required an invasive procedure/surgery (18). In 2011, Stanworth et al
5 reported that half of the plasma transfused in the UK was given to non-bleeding
6 patients (15). These practices are not in accordance with the guidelines for the use of
7 frozen plasma published by expert committees (4, 5). This might lead to a significant
8 waste, especially as blood availability is already a major concern.

9

10 There are few published reports of the reasons for plasma transfusion in children. A
11 recent pediatric international survey showed an important heterogeneity in plasma
12 transfusion thresholds and strategies (19), with two-thirds of responding pediatric
13 critical care physicians stating that they prescribe plasma transfusions for non-
14 bleeding critically ill children. This marked heterogeneity in plasma transfusion
15 patterns might be due to the absence of randomized controlled trials (RCTs) that
16 could guide plasma transfusion strategies (20).

17

18 This point-prevalence study is part of a larger undertaking that aims to design a RCT
19 to address optimal plasma transfusion strategies in critically ill children (8, 19, 20).

20 Our primary objectives were to identify the characteristics and clinical situations
21 resulting in plasma transfusion and to evaluate changes in coagulation laboratory
22 values resulting from the initial plasma transfusion in critically ill children.

23

24 **Methods**

25 *Study sites and population*

1 This point-prevalence study is an international multicenter cross-sectional
2 observational study carried out in 101 Pediatric Intensive Care Units (PICUs) in 21
3 countries. Clinical sites were recruited through several research networks including
4 BloodNet of the Pediatric Acute Lung Injury and Sepsis Investigators Network
5 (PALISI), the Canadian Critical Care Trials Group (CCCTG), the European Society of
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8 (GFRUP), and the Australian and New Zealand Intensive Care Society (ANZICS), as
9 well as through personal contacts made by the study investigators. For each study
10 site, six one-week periods were randomly predefined over six consecutive months
11 (April to September 2014). Within each week, screening was done and data were
12 collected on 5 days (Monday to Friday, from midnight to midnight).

13 All critically ill children aged 3 days to 16 years old admitted to a participating PICU
14 on one of the 30 study days were considered eligible. Any eligible patient for whom at
15 least one plasma transfusion was administered on any study day was included
16 unless one of the exclusion criteria (i.e. plasmapheresis and gestational age less
17 than 37 weeks at the time of PICU admission) was present. If a patient was
18 readmitted within 24 hours of PICU discharge, this was considered part of the same
19 admission.

20

21 *Outcome definitions*

22 The *primary outcome* was the primary indication for the first plasma transfusion and
23 the coagulation tests prior to that transfusion. We only considered plasma
24 transfusions, but not cryoprecipitate, albumin, or infusions of specific coagulation
25 factors.

26 Clinical indications were categorized as follows:

1 *A) Critical bleeding:* massive bleeding (transfusion of all blood products > 80
2 ml/kg within 24 hours), bleeding in specific sites (intra-cranial, intra-ocular,
3 retroperitoneal, intra-spinal, pericardial, non-traumatic intra-articular);or
4 bleeding requiring a surgical intervention or drainage (e.g. hemothorax
5 requiring drainage) (21)

6 *B) Minor bleeding:* minor surgical bleeding (wound, drain, etc.) or minor non-
7 surgical bleeding (endotracheal tube secretions, nasogastric tube, urine, etc.)

8 *C) Planned surgery or procedures* (central venous catheter, pleural drain, etc.)

9 *D) High risk of post-operative bleeding* (as defined by the intensivist)

10 *E) No bleeding, no planned procedure* (hypovolemia, abnormal coagulation
11 tests, factor or component replacement, at high risk of bleeding due to non-
12 surgical reasons, etc.)

13 The *secondary outcome* was the changes in coagulation tests that occurred after the
14 first plasma transfusion.

15 We also collected data on the transfusion itself, such as the product that had been
16 used [Fresh-Frozen Plasma (FFP), Frozen Plasma (FP), Mirasol-treated Plasma,
17 Solvent/Detergent Plasma (SD plasma)] (22), the rate and volume of the transfusion.

18 Description and clinical outcome of the population was studied using daily Pediatric
19 Logistic Organ Dysfunction (PELOD)-2 score (23), length of mechanical ventilation,
20 PICU length of stay, and PICU mortality. Because the PELOD-2 score is predictive of
21 mortality when measured on certain specific days, we collected patient data on days 1
22 (first transfusion), 2, 5, 8, and 12 of PICU stay (24). Length of mechanical ventilation,
23 PICU length of stay, and PICU mortality were censored 28 days after the end of the
24 enrollment period.

25

26 *Ethics approval*

1 This study was approved by ethics committees or boards at all sites. Five centers
2 (two in Canada, one in Denmark, Italy and Norway) required to obtain individual
3 patient written consent. French and Belgian sites provided study information in the
4 PICU waiting room, with an opt-out (or passive) consent. The ethics committees or
5 boards of all other sites did not require individual consent.

6

7 *Sample size*

8 The sample size was calculated to attain a precision of $\pm 5\%$ of the proportion of
9 patients in whom plasma was transfused despite the fact they were non-bleeding and
10 without planned invasive procedures. The estimated proportion was 34%, based on
11 previously reported data in critically ill adults (18). Based on these assumptions, the
12 study aimed to enroll 339 critically ill children who received at least one plasma
13 transfusion.

14

15 *Statistical analysis*

16 Descriptive statistics are reported as mean \pm standard deviation (SD), median and
17 interquartile range (IQR), or proportions with their 95%CI.

18 We assessed the association between the indication for plasma transfusion and the
19 different variables (demographic data, coagulation tests, clinical outcome measures)
20 with a Pearson Chi-Square test (for dichotomous variables) and a one-way ANOVA
21 test for continuous variables. We assessed the difference between coagulation test
22 results drawn before and after plasma transfusion using the Wilcoxon signed rank
23 test. Coagulation test cut-offs were determined incrementally, using the Wilcoxon
24 signed rank test, by steps of 0.5 and 5 for International Normalized Ratio (INR) and
25 activated partial thromboplastin time (aPTT), respectively. We also assessed the
26 association between plasma transfusion dose and change in coagulation tests using

1 a one-way ANOVA, after categorizing the doses. Correlations between non-normally
2 distributed variables were assessed with Spearman's correlation test.
3 All tests were 2-sided, with an alpha level of 0.05. All statistical analyses were
4 performed with SPSS version 20 for Mac (SPSS, Chicago, IL, USA).

5

6

7 **Results**

8 *Frequency and description of the population*

9 One hundred and one PICUs from 21 countries participated in this study, from April
10 to September 2014. Fifty-six centers were in Europe, 35 in North America, 5 in
11 Oceania, 3 in Asia, and 2 in South America. The median number of beds per PICU
12 was 13 (IQR 10-22).

13 Over the 30 study days, 13,192 patients were admitted and hence eligible. Per PICU,
14 the median number of patients already admitted at the beginning of a study week
15 was 9 (IQR 5-13) and the median number of new admissions on each study day was
16 2 (IQR 1-3).

17 Only one patient was not enrolled because written consent was not obtained. Plasma
18 transfusions were observed in 443 patients (3.4%, 95%CI 3.1-3.7). The median
19 length of PICU stay prior to the first plasma transfusion was 1 day (IQR 0-5).

20 Table 1 describes the baseline characteristics of included patients. The median age
21 and weight were 1 year (IQR 0.2-6.4) and 9.1 kg (IQR 4.0-21.0), respectively. 43%
22 were males. The median PELOD-2 score was 7 (IQR 5-10).

23 The center which included the largest number of patients contributed 11.1% of the
24 results. Fifteen centers (15/101, 14.8%) did not transfuse plasma during their six
25 study weeks.

26

1 *Indications for plasma transfusion*

2 The primary indication for plasma transfusion was critical bleeding in 22.3% of
3 patients (95%CI 18.7-26.5), minor bleeding in 21.2% (95%CI 17.78-25.3), planned
4 surgery or procedure in 11.7% (95%CI 9.1-15.7), and high risk of post-operative
5 bleeding in 10.6% (95%CI 8.0-14.0). No bleeding or planned procedures were
6 reported in 34.1% of patients (95%CI 29.8-38.6) (Fig.1). Among the latter, 68.3%
7 (95%CI 60.4-75.1) were transfused to correct abnormal coagulation tests, 13.2%
8 (95%CI 8.7-19.6) were considered at high risk of bleeding due to their medical
9 condition, 12.6% (95%CI 8.2-18.8) were transfused to treat hypovolemia, and 6.0%
10 (95%CI 3.2-10.9) were transfused to replace losses (ascites, chylothorax or
11 antithrombin deficiency).

12 Forty-eight patients received plasma while on Extracorporeal Life Support (ECLS); 12
13 of these (25%) received plasma for critical bleeding. Six (13%) received plasma as
14 part of an ongoing trial (NCT01903863).

15

16 *Coagulation tests before plasma transfusion*

17 Coagulation tests were performed prior to the first plasma transfusion in 96.4% of the
18 patients. Prothrombin Time (PT) was measured in seconds and in percentage in
19 59.1% and 23.3% of the patients, respectively. INR and aPTT were measured in
20 74.0% and 90.3% of patients, respectively. The median time between sampling for
21 coagulation tests and initiation of plasma transfusion was 3.5 hours (IQR 1.7-6.5).
22 The median results for INR and aPTT were 1.5 (IQR 1.3-2.0) and 48 (IQR 36-75),
23 respectively. Thirty percent of patients transfused were not bleeding, had no planned
24 procedure, and had an INR < 1.5.

25 Thromboelastography (TEG) was performed in seven centers (located in three
26 countries: Denmark, United Kingdom and USA) on 13 (2.9%) patients. Rotational

1 Thromboelastometry (ROTEM) was performed in four centers (located in Belgium,
2 France, Italy, and Switzerland) on 7 (1.6%).

3

4 *Plasma transfusions*

5 At the time of the first plasma transfusion, Fresh-Frozen Plasma was given to 75% of
6 the patients, whereas Solvent/Detergent Plasma and Frozen Plasma were given in
7 14% and 6%, respectively. Physicians were not aware of the type of plasma in 5% of
8 transfusions. The median dose of plasma was 11 ml/kg (IQR 9.7-15.1). Plasma was
9 transfused over a median time of 60 minutes (IQR 30-104). The median dose and
10 median transfusion rate were not significantly higher for patients with critical bleeding
11 ($p=0.10$).

12

13 *Coagulation tests after plasma transfusion*

14 Coagulation tests were performed after the first plasma transfusion in 89.4% of
15 patients. The median time between the end of the plasma transfusion and sampling
16 for coagulation tests was 4.0 hours (IQR 1.7-8.2).

17 The median results for INR and aPTT were 1.4 (IQR 1.2-1.7) and 41 (IQR 33-59),
18 respectively. The median INR and aPTT changes are -0.2 (IQR -0.4 to 0, $n=281$,
19 $p<0.001$) and -5 (IQR -17 to 2, $n=356$, $p<0.001$), respectively (Fig. 2).

20 After plasma transfusions, TEG and ROTEM were performed in 7 (1.6%) and 4
21 (0.9%) patients, respectively.

22 Changes in INR and aPPT values compared to baseline are shown in Figures 3A
23 and 3B. The median INR change after transfusion was -0.1 (IQR -0.3 to 0) for 273
24 children (83%) with a baseline INR value < 2.5 and -1.1 (IQR -2.0 to -0.4) for 55
25 children (17%) with a baseline INR value ≥ 2.5 ($p<.0001$). The median aPTT change
26 after transfusion was -2 (IQR -7 to -3) for 249 children (62%) with a baseline aPTT

1 value < 60 sec and -22 (IQR -44 to -5) for 151 children (38%) with a baseline aPTT
2 value \geq 60 sec ($p < .0001$).

3

4 *Effect of plasma dose*

5 Figure 4 shows how the plasma dose transfused modified INR and aPTT values
6 according to baseline. A dose-response relationship was observed only in children
7 with a baseline INR \geq 2.5 (Spearman's Rho coefficient -0.47, $p < 0.001$).

8

9 *Clinical outcome*

10 Median length of mechanical ventilation was 5 days (IQR 1-16) and median PICU
11 length of stay was 10 days (IQR 4-24) in our study population. Table 2 shows that
12 there were no statistically significant variations according to the primary indication for
13 plasma transfusion. PICU mortality was 26.9% (119/443, 95%CI 23-31).

14

15 **Discussion**

16 In this large international observational study, we examined the indications of plasma
17 transfusions in critically ill children and their effects on coagulation tests. We found
18 that 34% of patients who receive plasma were neither bleeding nor being prepared
19 for a procedure, whereas only 22% receive plasma for critical bleeding.

20 Clinically significant decrease in INR and aPTT values were only noted for INR
21 values > 2.5 or aPTT values > 60 sec. These findings underscore that when the INR
22 is only mildly prolonged, the assay is not sensitive to the increase in coagulation
23 factors resulting from transfusion. It must be recognized that coagulation tests may
24 not be the most appropriate measure of plasma transfusion efficacy, as they fail to
25 predict bleeding (17). Unfortunately, alternative laboratory measures to better
26 ascertain this do not exist at the present time.

1

2 In 2004, Dzik et al reported that the most common purpose of plasma transfusion in
3 adults was to «prepare» a patient with an elevated INR for invasive procedures (16).

4 In 2007, Lauzier et al also showed that plasma transfusions were often administered
5 to critically ill adults who were not bleeding; 33.7% of plasma orders were for non-
6 bleeding patients with no planned invasive procedures (18). Our study shows very
7 similar results; 34.1% of patients transfused with plasma were not bleeding and had
8 no planned invasive procedures.

9

10 The effect of plasma transfusions on coagulation tests has been described in adults.
11 In 121 patients with moderately abnormal coagulation tests (INR < 1.85), the post-
12 transfusion INR value decreased to below 1.1 in only 0.8% of this mixed surgical and
13 medical intensive care patient population (13). In another study, Holland et al showed
14 that plasma transfusion did not correct INR levels < 2.0-2.5 in 103 adult patients who
15 received 174 transfusions (14). These studies demonstrate the inability of the INR to
16 document the effect of plasma infusions at INR values commonly encountered in
17 critical care patients. Similar results have also been reported by Stanworth et al (15).
18 Our study shows that only severely abnormal coagulation tests are improved by
19 plasma transfusions and that this association was non-linear. This is likely due to the
20 exponential relationship between coagulation factor concentration and coagulation
21 test results (25). Our results suggest that a mild to moderate elevation of the INR in a
22 non-bleeding patient is not a worthwhile target for intervention.

23

24 Despite improvements in the management of blood products, some modeling
25 suggests that blood availability could become a major concern in the next 5-10 years
26 due to increasing demand in certain patient populations (26) which in turn justifies the

1 rationalization of blood product (including plasma) transfusions. More specifically, in
2 order to ensure the best use of blood products and to reduce unnecessary
3 transfusion, it is important to ascertain whether transfusing critically ill but non-
4 bleeding patients with a baseline INR < 2.5 is appropriate. Indeed, it is possible that
5 there are some benefits, which are not measured by coagulation tests. Furthermore,
6 these cut-offs are based on observational data, and might not truly reflect the efficacy
7 of plasma transfusions, which could only be tested in a randomized controlled trial.
8 Nonetheless, it seems obvious that a more restrictive transfusion strategy could
9 considerably reduce the unnecessary use of plasma, which would allow for more
10 appropriate resource utilization where truly needed.

11

12 This is the largest prospective observational study on plasma transfusions in critically
13 ill children, both in terms of number of patients and in terms of PICUs. Worldwide
14 enrollment enhances external validity. This study also avoided selection bias, as all
15 but one eligible patients were enrolled. Definitive conclusions cannot be drawn but
16 meaningful hypotheses have been generated. Our findings reveal certain very
17 striking observations that suggest overuse of plasma in certain clinical contexts. The
18 data will allow us to design a future RCT to evaluate these hypotheses.

19

20 Some limitations must be recognized. The design of our study does not permit
21 comparison between patients transfused and not transfused with plasma. This was
22 not the purpose of our study as data collection was limited only to patients who
23 received plasma (prevalent cases) and not to the much larger group of patients who
24 did not receive plasma. The patients in our study were sicker than those in a general
25 PICU population, as our median PELOD-2 score and mortality rate were 7 (IQR 5-10)
26 and 26.6%, respectively, compared to 4 (2-7) and 6.0% in a large PICU population

1 (23). This may reflect the fact that plasma was given mainly to sicker patients.
2 Although we enrolled virtually all patients admitted in the participating PICUs, there
3 might have been a selection bias for centers themselves, as some sites with specific
4 transfusion strategies might have been less keen to participate. The limited data
5 collected did not include information on co-interventions, such as heparin,
6 antithrombin, coagulation factor concentrates, vitamin K, or platelet administration.
7 Finally, mortality was higher than anticipated in our patient cohort. It is therefore
8 possible we underestimated the burden of rapidly fatal disease, as we did not
9 measure ventilator-free days but only the length of mechanical ventilation.

10

11 This international observational study shows that non-bleeding patients represent
12 more than half of the critically ill children receiving plasma transfusions. Commonly
13 used coagulation tests are not sensitive to the effects of plasma transfusion for the
14 majority of patients transfused. Studies assessing appropriate plasma transfusion
15 strategies are urgently needed.

16

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1 **Tables****Table 1:** Demographic data according to primary indication for plasma transfusion

	Critical bleeding (n=99)	Minor bleeding (n=94)	Planned procedure (n=52)	High risk of post- operative bleeding (n=47)	No bleeding, no procedure (n=151)	p
Gender [male], n (%)	40 (40%)	39 (41%)	20 (38%)	15 (32%)	75 (50%)	0.21
Age [years], median (IQR)	4.0 (0.25-11.1)	1.7 (0.25-7.6)	2.0 (0.5-6.1)	0.5 (0.1-1.9)	0.5 (0.1-4.4)	<0.001
Weight [kg], median (IQR)	15.1 (4.7-35.0)	9.7 (4.5-20.0)	12.0 (6.0-27.8)	6.1 (3.6-11.9)	6.9 (3.5-17.5)	0.001
Reasons for PICU admission* (n, %)						
respiratory	35 (35%)	21 (22%)	18 (35%)	8 (17%)	61 (40%)	0.006
septic shock	5 (5%)	9 (10%)	11 (21%)	1 (2%)	39 (26%)	<0.001
hemorrhagic shock	26 (26%)	2 (2%)	4 (8%)	0 (0%)	4 (3%)	<0.001
other shock	9 (9%)	4 (4%)	4 (8%)	6 (13%)	11 (7%)	0.46
trauma	19 (19%)	3 (3%)	1 (2%)	0 (0%)	6 (4%)	<0.001
traumatic brain injury	15 (15%)	1 (1%)	2 (4%)	0 (0%)	8 (5%)	<0.001
burn	0 (0%)	1 (1%)	1 (2%)	1 (2%)	2 (1%)	0.75
cardiac surgery (bypass)	30 (30%)	47 (50%)	1 (2%)	19 (40%)	36 (24%)	<0.001
cardiac surgery (no bypass)	0 (0%)	3 (3%)	1 (2%)	7 (15%)	6 (4%)	<0.001
cardiac non-surgical	7 (7%)	10 (11%)	7 (14%)	3 (6%)	23 (15%)	0.24

emergency surgery	29 (29%)	2 (2%)	6 (12%)	9 (19%)	13 (9%)	<0.001
elective surgery	16 (16%)	47 (50%)	3 (6%)	22 (47%)	19 (13%)	<0.001
seizure	5 (5%)	2 (2%)	4 (8%)	1 (2%)	11 (7%)	0.32
encephalopathy	6 (6%)	5 (5%)	3 (6%)	0 (0%)	9 (6%)	0.57
meningitis	2 (2%)	0 (0%)	2 (4%)	0 (0%)	5 (3%)	0.29
renal failure	8 (8%)	10 (11%)	10 (19%)	1 (2%)	16 (11%)	0.07
hepatic failure	10 (10%)	5 (5%)	11 (21%)	1 (2%)	18 (12%)	0.01
post-operative liver transplantation	2 (2%)	0 (0%)	2 (4%)	4 (9%)	3 (2%)	0.04
other reason [†]	11 (11%)	2 (2%)	8 (15%)	9 (19%)	17 (11%)	0.24
Severity at inclusion (plasma transfusion)						
(median, IQR)						
PELOD-2 score	8 (6-11)	7 (5-8)	7 (4-11)	7 (5-9)	7 (5-10)	0.05
Worst lactate	3.2 (1.6-5.3)	2.4 (1.7-4.1)	2.2 (1.2-4.9)	2.7 (1.9-5.4)	2.1 (1.4-5.1)	0.54
Support (n, %)						
Mechanical ventilation	87 (88%)	82 (87%)	38 (73%)	42 (89%)	122 (81%)	.08
ECLS	12 (12%)	7 (7%)	1 (2%)	11 (23%)	17 (11%)	0.1
CRRT	5 (5%)	7 (7%)	6 (12%)	5 (11%)	12 (8%)	0.63
MARS	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	-
Intermittent dialysis	1 (1%)	1 (1%)	1 (2%)	0 (0%)	2 (1%)	0.92

1 *Some patients had more than one reason for admission.

2 †The main other reasons for admission were oncologic-hematologic disease (19 patients),
3 neurosurgery (5 patients), and metabolic disorders (4 patients).

4 CRRT: Continuous Renal Replacement Therapy; ECLS: Extracorporeal Life Support; MARS:

5 Molecular Adsorbent Recirculating System; PELOD-2 score: Pediatric Logistic Organ Dysfunction 2

6 score (23); PICU: Pediatric Intensive Care Unit.

Table 2: Patient outcomes according to primary indication for plasma transfusion

	Critical bleeding (n=99)	Minor bleeding (n=94)	Planned procedure (n=52)	High risk of post- operative bleeding (n=47)	No bleeding, no procedure (n=151)	p
PELOD-2 score						
Day 2* (n=402)	8 (5-10)	6 (5-8)	8 (4-11)	8 (5-9)	8 (5-10)	0.37
Day 5* (n=296)	7 (5-9)	6 (3-9)	8 (4-10)	7 (4-10)	8 (4-10)	0.43
Day 8* (n=227)	6 (4-9)	5 (3-9)	8 (4-10)	7 (5-9)	6 (3-9)	0.69
Day 12* (n=162)	6 (3-7)	6 (2-9)	7 (3-10)	6 (3-8)	7 (3-9)	0.79
Duration of mechanical ventilation (days)	5 (1-15)	2 (1:8)	9 (2-25)	7 (3-13)	6 (2-17)	0.20
PICU length of stay (days)	11 (3-23)	7 (3-14)	18 (5-32)	11 (6-25)	12 (4-26)	0.46
Mortality, n (%)	34 (35%)	14 (16%)	16 (32%)	9 (19%)	46 (31%)	0.01

1 Results are provided as median and interquartile range (IQR), except for mortality.

2 * Days after the first plasma transfusion.

3 PELOD-2 score: Pediatric Logistic Organ Dysfunction 2 score (23); PICU: Pediatric Intensive Care

4 Unit.

1 **Figure legends**

2 **Figure 1:** Proportion of the different primary indications to plasma transfusion. The
3 indications were categorized as *critical bleeding* (massive bleeding, bleeding in
4 specific sites, or bleeding requiring a surgical intervention or drainage, in red), *minor*
5 *bleeding* (in orange), *preparation for surgery or procedures* (in yellow), *at high risk of*
6 *post-operative bleeding* (in gray), and *no bleeding, no planned procedure* (in green).

7

8 **Figure 2:** Changes in International Normalized Ratio (INR, panel A) and activated
9 Partial Thromboplastin Time (aPTT, panel B) after plasma transfusion, according to
10 the indications for transfusion: *critical bleeding* (in red), *minor bleeding* (in orange),
11 *preparation for surgery or procedures* (in yellow), *at high risk of post-operative*
12 *bleeding* (in gray), and *no bleeding, no planned procedure* (in green). The median
13 INR change was -0.2 (IQR -0.4 to 0, n=281 pairs of tests) and the median aPTT
14 change was -5 (IQR -17 to 2). Mild outliers ($< 1.5 * \text{IQR}$) and extreme outliers ($> 1.5 *$
15 IQR) are marked with a circle (O) and asterisk (*) on the boxplot.

16

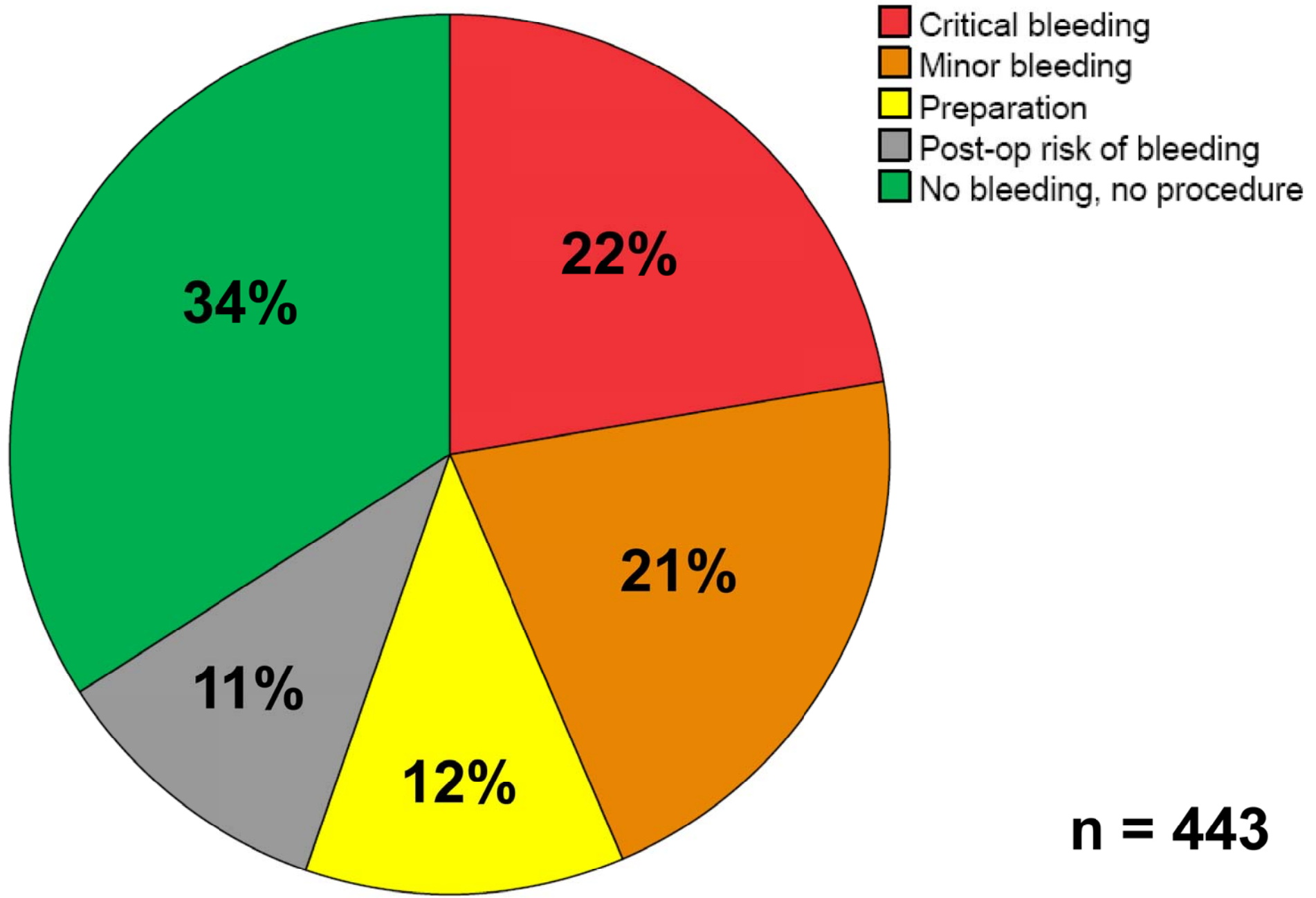
17 **Figure 3:** Boxplot of the changes in International Normalized Ratio (INR, panel A)
18 and activated Partial Thromboplastin Time (aPTT, panel B) after plasma transfusion,
19 according to the coagulation test prior to transfusion (n=281 and n=360 pairs of INR
20 and aPTT, respectively). Mild outliers ($< 1.5 * \text{IQR}$) and extreme outliers ($> 1.5 * \text{IQR}$)
21 are marked with a circle (O) and asterisk (*) on the boxplot.

22

23 **Figure 4:** Boxplot of the changes in International Normalized Ratio (INR, panel A)
24 and activated Partial Thromboplastin Time (aPTT, panel B) after plasma transfusion,
25 according to the dose of plasma transfusion in ml/kg and according to the baseline
26 coagulation test (n=281 and n=360 pairs of INR and aPTT, respectively). Mild outliers

- 1 ($< 1.5 * IQR$) and extreme outliers ($> 1.5 * IQR$) are marked with a circle (O) and
- 2 asterisk (*) on the boxplot.

Primary indication to plasma transfusion



n = 443

