Sharma and Padhi
Egyptian Pediatric Association Gazette (2024) 72:64
https://doi.org/10.1186/s43054-024-00302-1

Egyptian Pediatric Association Gazette

RESEARCH

Open Access

Pediatric demographic association with hospital mortality in platelets- and plasma-transfused young pediatric patients — a mixed cohort study

Sankalp Sharma[1*] and Phalguni Padhi[2]

Abstract

Background Demographic and biochemical variations in newborn children as compared to adults are attributable to variable prognosis to blood transfusions. Aims of this mixed cohort study of Platelets with/without Plasma (PLT/PZ); only Plasma (PZ) transfusions in ≤ 24 months children is as follows: An Association of demography towards hospital mortality, and an association of laboratory investigations (LI) with hospital mortality.

Methods PLT/PZ ($n=72$) and PZ ($n=79$) children ≤ 24 months were followed up for a total length of hospital stay (LOS(D)). We calculated the Odds Ratio (OR) of demographic, and laboratory parameters for mortality, survival studies of demographic, laboratory parameters , Kaplan Meier Survival curve, Log-Rank significance (KMLR) and Multivariable regression (r^2) with outcome as death.

Results The present study is in 2019–2022. Higher OR for hospital-based mortality for PLT/PZ and PZ cohort were age ≤ 1 m, weight ≤ 1500 g, preterm, gestational age ≤ 34 weeks, hospital length of stay {LOS(D)} 0–7 days, APGAR score ≤ 5, and Hb ≤ 7 g/dl. High OR, mortality was observed with Female gender, Length of stay before first transfusion {LOS(F)}, 0-7d, WHO Grade of bleeding (GOB) 4, *PT*>50 sec, *INR*>1·7, *aPTT* >75sec, PLT counts (µl) ≤25000/µl (PLT/PZ) and GOB 3, 4 (PZ). Higher OR for mortality was also observed with a lower derangement of coagulative parameters *PT*≤50s, *INR* ≤1·7, *aPTT* ≤75s (PZ).

Higher survival was observed for (PLT/PZ) LOS(F) 0–7 days across age (m), weight (g) ($P=0{\cdot}002;<0{\cdot}01$), and *INR* ≤ 1·7; *aPTT* ≤ 75 s across LOS(D) ($P<0{\cdot}01,0{\cdot}018$); (PZ) LOS(D) ≤ 7 days across age (m) and weight (g) ($P=0{\cdot}036$, 0·001); and GOB across LOS(D) (PLT/PZ; PZ) ($P=0{\cdot}052$, 0·005). Demography (PLT/PZ) $r^2=50{\cdot}36\%$ ($P=0{\cdot}021$), laboratory investigations $r^2=10{\cdot}44\%$ ($P=0{\cdot}47$), LOS(F) ($P=0{\cdot}010$), LOS(D) ($P=0{\cdot}003$), and GOB ($P=0{\cdot}03$) were the predictors. Demography (PZ) r^2 ($P=0{\cdot}095$), investigations $r^2=8{\cdot}79\%$ ($P=0{\cdot}254$), LOS(D) ($P=0{\cdot}026$), and GOB ($P=0{\cdot}012$) were the predictors.

Conclusions PLT/PZ, demographic parameters, were significant cause of mortality with LOS(F), LOS(D), and GOB as predictors. PZ, demography attributed to mortality with LOS(D), and GOB as predictors. A higher OR of morality with lower derangement of laboratory profile is indicative of unnecessary transfusions in the age group. Laboratory investigations by themselves are not significant predictors of mortality.

*Correspondence:
Sankalp Sharma
sankalpsharma@aiimsraipur.edu.in; sunray2077@gmail.com
Full list of author information is available at the end of the article

Keywords Demographic, Age groups, Hospital stays, Length of stay before first transfusion, Frozen plasma, Fresh, Transfusions, Platelet

Background

Newborn and young children are vulnerable to transfusion therapy in the form of fresh-frozen plasma (PZ) and platelets (PLT) due to developmental variations in biochemical values from adults [1]. Diverse clinical practices are also attributable to variable prognoses towards bleeding and coagulopathy in the age group [2, 3].

A physiological prolongation is seen in the newborns of both prothrombin time (PT) and activated partial thromboplastin time (aPTT); however, the ratio of coagulation factor and their respective inhibitors (AT-III, proteins C and S) is maintained [4–7]. During the fetal period (10 to 12 weeks), PT, INR, and aPTT are significantly prolonged with a shortening of these laboratory parameters from 30 to 38 weeks [8, 9]. PT of premature infants is comparable to the adults' levels, whereas aPTT is prolonged in premature full-term newborns as compared to adults [7, 9, 10].

Developmental, acquired predictor of bleeding in newborn

Patients requiring PLT and PZ transfusions are influenced by demographic parameters or the clinical state of patients [11–15]. Demographic predictors of deranged coagulation profile during early childhood are preterm birth (age < 34-week gestation), early thrombocytopenia after birth, and Apgar score (1 min and 5 min) [11, 12]. Acquired coagulation abnormalities (acute systemic infection, liver disease, sepsis) in newborns cause direct endothelial injury which may manifest as coagulation factor consumptive coagulopathy [13, 15–17].

PLT counts generally attain adult levels after the second trimester [11]. PLT deficiency generally seen in preterm infants usually resolves by day 10 of life [17]. PLT insufficiency could be due to defect in platelet production due to hypoplastic bone marrow or increased sequestration in peripheral circulation [18]. Incidence of neonatal thrombocytopenia is estimated at 0·7–0·9% with a higher incidence in the neonatal ICU (NICU) setting (22% + / − 5%) [9, 11, 12].

Rationale and knowledge gap

In this mixed cohort study of children ≤ 24 months transfused with platelets with/without plasma transfusions (PLT/PZ) ($n = 72$) or only plasma transfusions PZ ($n = 79$), we tried to ascertain whether during early childhood (≤ 24 months) the prognosis of PLT or PZ subjects could be influenced by demographic factors, laboratory values.

Objective

The study specifically had the following aims and objectives:

- To determine an association of demographic parameters in PLT, PZ transfused pediatric patients (≤ 24 months) for mortality during a hospital stay.
- To measure an association of laboratory variables towards patient mortality in PLT- and PZ-transfused patients during hospitalization.

Methods

This (mixed cohort) study was carried out at a tertiary level center on hospitalized pediatric patients ≤ 24 months (December 2018 to June 2022). We classified patients ($n = 151$) into those who received PLT/PZ ($n = 72$) or PZ ($n = 79$), followed up until "length of hospital stays" (days) {LOS(D)} for death or discharge from the hospital. Patient-related variables and study algorithm are summarized in Table 1 and Fig. 1.

The present study had institute research ethics approval (IEC proposal number: IEC/2019/308).

Study acronyms

We defined the patient groups as follows:

- PLT/PZ cohort: PLT with/without PZ transfusions ($n = 72$)
- PZ cohort: Plasma-transfused subjects ($n = 79$)
- LOS(F): Length of stay (in days) before first transfusion
- LOS(D): Length of stay in hospital (number of days) before death/discharge
- PLT(T): Average PLT at which PLT transfusion was initiated
- Preterm patients with preterm listed in the patient case records
- GOB defined as WHO grade of bleeding (1 to 4) and no bleeding (0)

The patient-related independent (predictor) variables were categorized as follows:

- Age (months) (≤ 1 m, > 1 m), gender (male, female), and weight (g) (≤ 1500, > 1500)

Table 1 Demographic and laboratory parameters

S. no	Patient variable	Total subjects ($n=151$)	PLT/PZ mean (SD) ($n=72$)	PZ mean (SD) ($n=79$)
1.	Age (months)	5·8 (8·2)	6·8 (9·1)	4·9 (7·3)
2.	Weight (g)	3929 (3125)	4097 (3268)	3776 (3002)
3.	BSA (m^2)	0·25 (0·14)	0·25 (0·164)	0·24 (0·132)
4.	Gestational age (weeks)	35·8 (3·6)	35·5 (3·59)	36·0 (3·7)
5.	APGAR (5 min)	7·4 (2·0)	7·1 (2·4)	7·6 (1·76)
6.	LOS(F)	5·7 (7·6)	6·6 (6·6)	5·06 (8·4)
7.	LOS(D)	18·7 (18·3)	20·40 (17·85)	17·1 (18·8)
8.	Av. Hb values	11·3 (3·7)	10·9 (3·8)	11·7 (3·74)
9.	Av. PT values	28·7 (26·12)	25·20 (22·98)	31·3 (28·03)
10.	INR	2·5 (2·6)	2·1 (2·1)	2·7 (2·9)
11.	Av. aPTT	58·1 (36·2)	55·15 (31·71)	60·4 (39·5)
12.	Platelets (T)	–	32,869 (46,343)	–
13.	WHO bleeding score	1·5 (1·3)	1·4 (1·3)	2·0 (1·4)

- Gestational age at birth (weeks) ($\leq 34, > 34$)
- APGAR score (5 min) ($\leq 5, > 5$)
- LOS(F) (≤ 7 days, > 7 days)
- Hospital LOS(D) (≤ 7 days, 8–14 days, ≥ 15 days)
- Hb (g/dl) ($\leq 7, > 7$)
- No bleeding and GOB score (1–4)
- PLT count at transfusion {PLT(T)} ($\leq 25{,}000, > 25{,}000$)
- PT (s) ($\leq 50, > 50$), INR ($\leq 1{\cdot}7, > 1{\cdot}7$), and aPTT (s) ($\leq 75, > 75$) respectively

The dependent (response) variables of the study were as below:

- Age (in months), weight (g), and LOS(D) in PLT/PZ and PZ subgroup

We recruited the study population according to the following criteria:

- Inclusion criteria: Hospitalized pediatric patient's age ≤ 24 months ($n=151$) requiring PLT/PZ ($n=72$) and PZ ($n=79$) transfusions
- Exclusion criteria: Children > 24 months of age, children without PLT and/or PZ transfusions, and patients lost to follow-up

Sample size estimation

A total of 51% of transfusions from our blood center to pediatric patients were of PLT and PZ units. The mean total pediatric (0–14 years) and neonatal transfusions from 2019 to 2022 at our institution (total blood units issued $n=3528$) were estimated as 882. Assuming ≤20% of total transfusions in the pediatric age group to be ≤ 24 months, sample size of both PLT/PZ, (n=72) and PZ, (n=79) transfusions were considered adequate for the study. The results were reported as associations due to a smaller number of patients in a certain subgroup of interest. The missing data was not included in the overall calculations. Patients lost to follow-up were not included in the eligible list as per the inclusion criteria.

Statistical methods

The statistical analysis included the following:

- We performed calculations with the licensed version of 2023-Minitab, LLC, all rights reserved. The factorial analysis of categorical variables of nonparametric data was performed on the trial version of the SPSS. We evaluated the effects of covariates (categorical parameters) towards mortality using a binary logistic model for determining "OR" of categorical variables during a hospital stay. We used coding information displaying reference parameter of categorical variable for depicting OR for mortality with 95% confidence interval (Table 2).
- We performed a comparison of survival by Kaplan–Meier log rank with chi-square (non-parametric) P-value $\leq 0{\cdot}05$ as significant, categorical variables as a predictor on the y-axis, and dependent variables on the x-axis.· Null hypothesis, no difference in the survival between the two categories, and· censored events were surviving hospitalized patients.

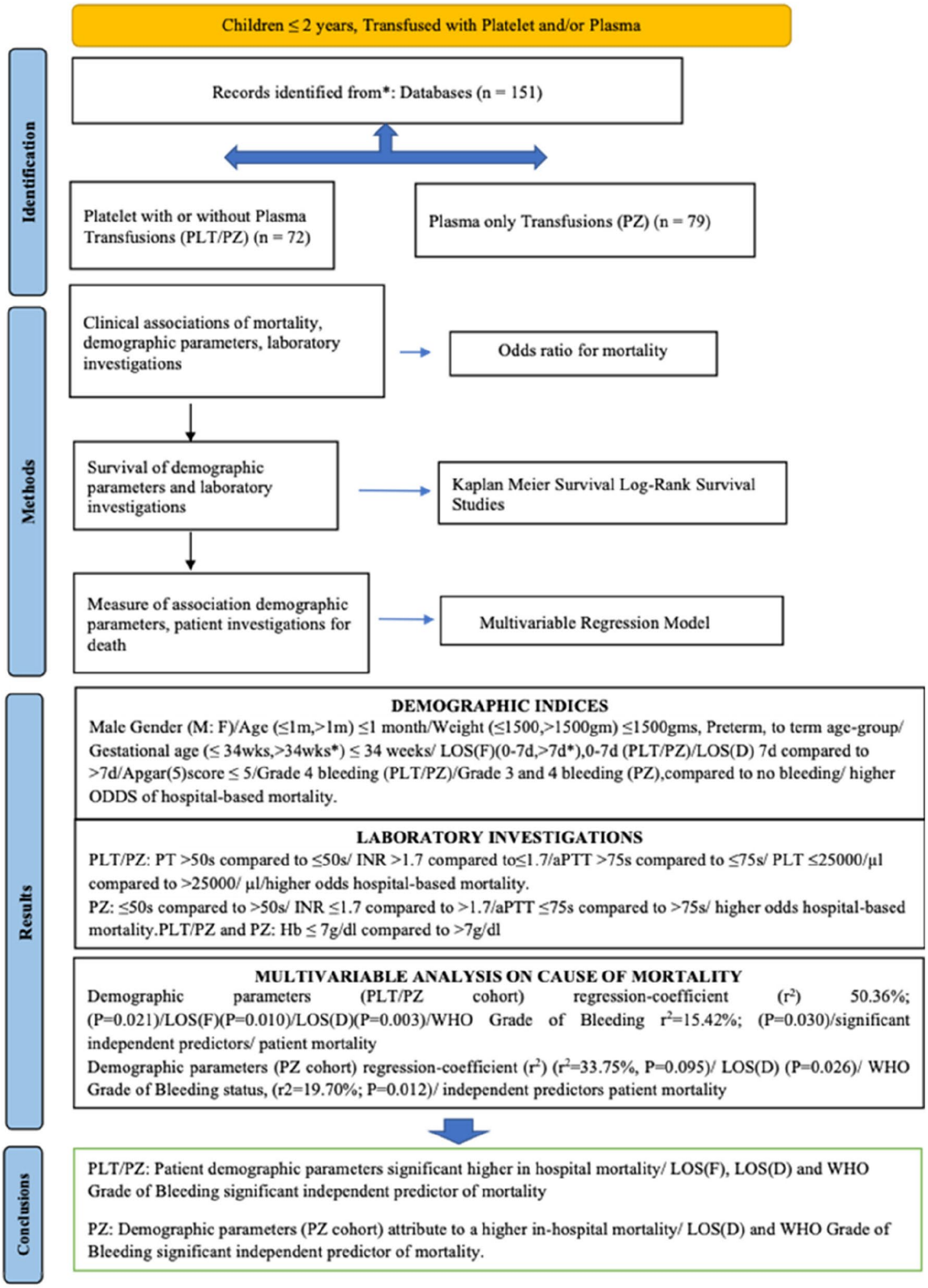


Fig. 1 Flow diagram of the study

Table 2 Odds ratio analysis of categorical demographic variables

	Platelets with or without plasma transfusions (*n* = 72)			**Plasma only transfusions (*n* = 79)**	
S. no	**Parameter**	***OR***	**95% *CI***	**Parameter Odds ratio**	**95% *CI***
1.	Gender (M[a]:F)	1·5	0·6–4·0	0·9	0·36–2·2
2.	Age (≤ 1 m, > 1 m[a])	2·5	0·95–6·8	2·9	1·7–7·4
3.	Weight (≤ 1500 g, > 1500 g[a])	6·8	2·2–21·08	1·56	0·50–4·84
4.	Preterm/term[a]	4·7	1·7–13·4	1·5	0·58–4·15
5.	Gestational age (≤ 34 weeks; > 34 weeks[a])	3·12	1·08–8·9	2·7	0·85–8·55
6.	LOS(F) (0–7 days; > 7 days[a])	3·8	1·2–12·07	1·0	0·27–3·6
7.	LOS(D) (0–7 days; ≥ 15 days[a])	1·7	0·52–5·8	3·5	1·2–9·8
8.	LOS(D) (0–7 days; 8–14 days[a])	1·9	0·49–7·7	8·0	1·8–34·9
9.	APGAR (5) (≤ 5, > 5[a])	4·5	0·77–26·8	11·5	1·2–107·5
10.	PT (≤ 50[a], > 50)	2·8	0·47–17·12		0·56–7·33
11.	[b]PT (≤ 50, > 50[a])	0·35	0·05–2·12	[b]2·03	
12.	INR (≤ 1·7[a], > 1·7)	4·5	1·3–15·2		0·47–3·05
13.	[b]INR (≤ 1·7, > 1·7[a])	0·22	0·06–0·73	[b]1·2	
14.	aPTT (≤ 75 s[a], > 75 s)	2·5	0·53–12·0		0·76–19·6
15.	[b]aPTT (≤ 75 s, > 75 s[a])	0·39	0·08–1·86	[b]3·8	
16.	Hb (≤ 7 g/dl; > 7 g/dl[a])	4·17	1·07–16·3	3·5	0·38–33·6
17.	Platelet (T) (≤ 25,000, > 25,000[a])	2·6	0·57–11·8	–	–
18.	*Bleeding grade (WHO)*				
	Bleeding status				
	(WHO): no bleeding, grades I to IV	0·20 0·18 0·64 3·0	0·04–0·81 0·03–1·10 0·15–2·5 0·28–31·6	0·44 0·4 2·9 8·8	0·06 –2·8 0·10–1·6 0·59–14·7 0·92–85·6

[a] Reference level of categorical parameters (OR)

[b] Reference level of categorical parameter (plasma transfusions)

GOB (WHO) Plt/Pz cohort; the number of subjects: 0 = 21, 1 = 10, 2 = 10, 3 = 13, 4 = 5

GOB (WHO) PZ cohort; number of subjects: 0 = 19, 1 = 7, 2 = 18, 3 = 11, 4 = 9

- We compared the demographic parameters of the PLT/PZ and PZ cohorts by performing the Mann–Whitney nonparametric test, null hypothesis, no difference between variables, alternate hypothesis significant difference between two medians, and 95% confidence interval $P \leq 0{\cdot}05$ as significant (if the difference between the medians is statistically significant, reject the null hypothesis).
- We evaluated the significant difference between the median of > 2 categorical parameters of interest by Kruskal–Wallis's testing; in 95% two-sided confidence interval, results displayed as a difference of medians, assuming all medians as equal $\alpha = 0{\cdot}05$; and alternate hypothesis at least one median is different for all categorical parameters.
- In multivariable regression model (r^2) with death as an outcome during hospitalization, we examined the strength of association of death during hospitalization as an outcome for demographic and laboratory variables and GOB separately.

Outcome measures

We classified the outcome measures of PLT- and PZ-transfused subjects as follows:

- OR (95% confidence interval) for determining a change in mortality compared to a unit change in reference parameter
- Survival differences of demographic parameters and laboratory investigations for each transfusion subgroup PLT/PZ, PZ and statistical correlation of categorized demographic, and laboratory parameters across the predictor variable for survival significance ($P \leq 0{\cdot}05$)

Table 3 Log-rank survival comparisons of demographic parameters

	Platelets with or without plasma transfusions ($n=72$)				Plasma only transfusions ($n=79$)		
S. no	**Dependent variable**	**Independent variable**	**Log rank (significance)**	**Censored (uncensored) events**	**Dependent variable**	**Log rank (significance)**	**Censored (uncensored) events**
1.	Sex (M:F)	Age (m)	0.316	22 (19), 20 (11)	Age (m)	0.823	20 (15), 24 (20)
2.	Sex (M:F)	Weight (g)	0.325	22 (19), 20 (11)	Weight (g)	0.454	20 (15), 24 (20)
3.	Sex (M:F)	LOS(D)	0.120	22 (19), 20 (11)	LOS (D)	0.883	20 (15), 23 (20)
4.	Age (≦ 1 m, > 1 m)	LOS(D)	0.259	20 (21), 22 (9)	LOS (D)	0.134	16 (22), 27 (13)
5.	Weight (≤ 1500 g, > 1500 g)	LOS(D)	0.109	6 (16), 36 (14)	LOS (D)	0.765	7 (8), 35 (27)
6.	Gest. (≤ 34 weeks; > 34 weeks)	LOS(D)	0.239	15 (10)	LOS (D)	0.108	11 (6), 19 (28)
7.	Preterm/ term	LOS(D)	0.131	9 (17), 33 (13)	LOS (D)	0.871	11 (12), 32 (23)
8.	LOS(F) (0–7 days; > 7 days)	Age (m)	0.002	6 (12), 35 (18)	Age (m)	0.790	6 (5), 36 (30)
9.	LOS(F) (0–7 days; > 7 days)	Weight (g)	0.001	6 (12), 35 (18)	Weight (g)	0.955	6 (5), 36 (30)
10.	LOS(D) (0–7 days; 8–14 days; ≥ 15 days)	Age (m)	0.977	8 (7), 12 (7), 23 (15)	Age (months)	0.036	10 (20), 12 (3), 21 (12)
11.	LOS(D) (0–7 days; 8–14 days; ≥ 15 days)	Weight (g)	0.807	7 (8), 12 (7), 23 (15)	Weight (g)	0.001	10 (20), 12 (3), 21 (12)
12.	Bleeding status (WHO): no bleeding, grades I to IV	LOS(D)	0.052	9 (12), 15 (4), 8 (2), 7 (6), 1 (4)	LOS (D)	0.005	10 (9), 5 (2), 13 (5), 3 (8), 1 (8)

- A regression model with regression coefficient (r^2) as a measure of significant associations between demographic, laboratory variables, and GOB with death during hospitalization as a response variable.

Results

In the present study from 2019-2022 of hospitalized Pediatric patients (≤ 24 months, $n=151$), treated with PLT/PZ ($n=72$) or PZ ($n=79$) transfusions, we observed no significant statistical differences (P>0·05) (PLT/PZ, PZ cohort) for the following demographic and laboratory variables Age(months), Weight (gm), BSA(m^2), Gestational age (weeks), LOS(D), AvHb (g/dl), AvPT/INR, aPTT with significant differences in LOS(F)(P=0·019). (Mann-Whitney test) (Table 1).

Demographic association in mortality and survival

Gender (M*:F) had higher OR of mortality (PLT/PZ) of females with no significant differences in survival across LOS(D) (Tables 2, 3).

Age ≤ 1 m had a higher OR of mortality during the hospital stay (PLT/PZ and PZ) with no significant differences in survival between age groups across LOS(D) (Tables 2, 3).

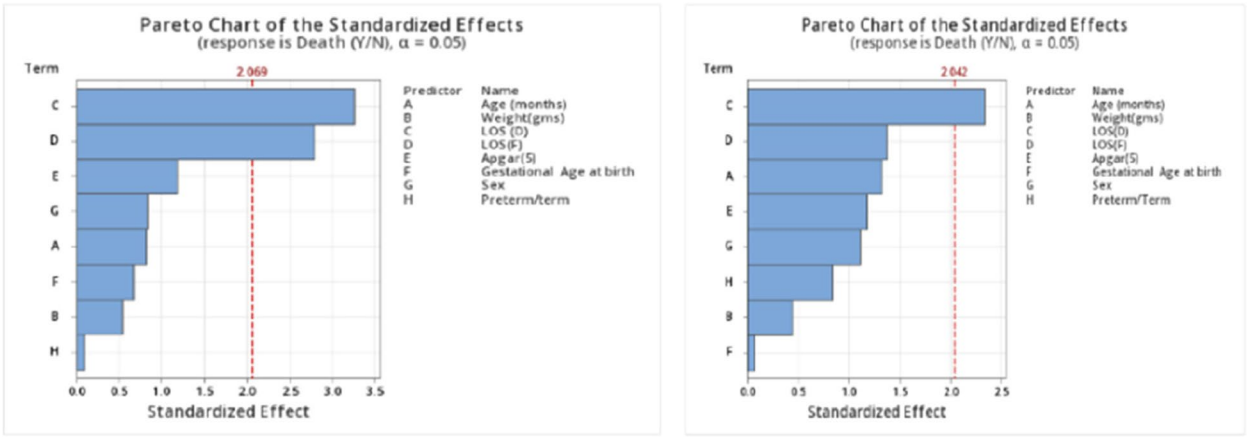
We observed weight ≤ 1500 g (PLT/PZ and PZ cohort) with higher mortality and with no significant difference in survival across LOS(D) (Tables 2, 3).

Preterm age group had higher mortality compared to term with no significant differences in survival across LOS(D) (PLT/PZ, PZ cohort) (Tables 2, 3).

Gestational age ≤ 34 weeks (PLT/PZ, PZ cohort) had higher mortality, with no significant difference in survival across LOS(D) (Tables 2, 3).

LOS(F) 0–7 days (PLT/PZ) had higher mortality. We observed a higher survival (PLT/PZ cohort) when transfused at 0–7 days compared to > 7 days across age (m) and weight (g) distribution ($P=0{\cdot}002;<0{\cdot}01$) (Table 3, Figure 1 (supplementary) i and ii). We did not observe significant survival difference (PZ cohort) whether transfused ≤ 7 days or > 7 days of hospital stay across age (months) ($P=0{\cdot}790$) and weight (g) distribution· ($P=0{\cdot}955$) (Table 3).

LOS(D) (0–7 days; ≥ 15 days*) had higher mortality at 0–7 days compared to longer duration of hospital stay in both PLT/PZ and PZ cohort. PZ showed significant differences in survival LOS(D) across age (m) and



i ii

Fig. 2 **i** Demographic predictors of death during hospitalization (PLT/PZ). **ii** Demographic predictors of death during hospitalization (PZ)

weight (g) distribution ($P=0{\cdot}036$, 0·001) with the lowest survival at 0–7-day period across the age (m) and weight (g) distribution (Tables 2, 3; Figure 2 (supplementary) — (i, ii)).

Laboratory parameters and differences in mortality and survival

We observed a higher mortality with $INR>1{\cdot}7$ and $aPTT>75$ s (PLT/PZ cohort), $INR\leq1{\cdot}7$, and $aPTT\leq75$ s (PZ cohort) across LOS(D) (Tables 2, 3). We observed a higher survival (PLT/PZ cohort) with $INR\leq1.7$ and $aPTT\leq75$ s (with coexistent thrombocytopenia) but no significant differences in survival with platelets(T) ($\leq25{,}000, >25{,}000/\mu l$) across LOS(D) ($P=0.991$) {*OR* 2.6 (0.57–11.8)} (Tables 2, 3, Figure 3 (supplementary) i, ii, iii).

We observed higher OR mortality with lower derangement of laboratory profile for PT(INR) and aPTT (PZ cohort) (Table 2). We however observed no significant difference in overall survival (PZ) *INR* ($\leq1{\cdot}7, >1{\cdot}7$) ($P=0{\cdot}699$) and aPTT ($\leq75$ s, >75 s) ($P=0{\cdot}193$) across LOS(D) (PZ cohort).

Bleeding status and mortality

In the PLT/PZ cohort, we noted significant differences in age (m), mean (SD) 3·98 (7·56), months ($P=0{\cdot}039$) with most transfusions ($n=21$) having no clinical bleeding, during the first month. We noted no significant differences in weight ($P=0{\cdot}320$), PLT(T) ($P=0{\cdot}346$), INR ($P=0{\cdot}090$), aPTT ($P=0{\cdot}347$), and LOS(D) ($P=0{\cdot}677$). Mean (SD) and Hb (g/dl) (PLT/PZ) among patients within GOB were significantly different ($P=0{\cdot}013$) (Kruskal–Wallis test) (Table 1 (supplementary)).

In the PLT/PZ cohort, GOB 4 had higher OR for mortality compared to "no bleeding"· (Table 2). We noticed, GOB 1–3, with relative lower OR of mortality compared to no bleeding ($n=21$) (Table 2). We observed a significant difference in survival (PLT/PZ cohort) within GOB across LOS(D) cohort ($n=71$) ($P=0{\cdot}052$) (Table 3, Figure 4 (supplementary) i, ii).

In the PZ cohort, most FFP transfusions (PZ cohort) were among patients without any clinical bleeding ($n=19$) mostly during the first month of birth mean (SD) 0·36 (0·52) months with significant differences in age (m) ($P=<0{\cdot}01$), weight ($P=0{\cdot}008$), Hb ($P<0{\cdot}01$), PT ($P=0{\cdot}004$), and INR ($P=0{\cdot}002$) with no bleed and GOB (1 to 4). We observed nonsignificant difference of aPTT ($P=0{\cdot}076$) across GOB. We observed higher OR of mortality in GOB 3 and 4 compared to "no bleeding" ($n=19$) (Table 2). We observed a significant difference in survival (PZ cohort) within GOB across LOS(D) ($P=0{\cdot}005$) (Table 3, Figure 4 (supplementary) ii).

Multivariable analysis on the causes of mortality

A "multivariable regression analyses" of PLT/PZ cohort, gender (*M:F), preterm/term*, age (m), weight (g), Apgar (5), LOS(D), LOS(F), and gestational age, evaluated for death during hospital stay, had $r^2=50{\cdot}36\%$ ($P=0{\cdot}021$) {R-sq. (adjusted) = 33·09%}. We observed LOS(F) ($P=0{\cdot}010$) and LOS(D) ($P=0{\cdot}003$) among significant predictors of mortality during a hospital stay (Fig. 2i). GOB PLT/PZ cohort is a significant contributor towards death in hospital $r^2=15{\cdot}42\%$ ($P=0{\cdot}030$). LI (PLT/PZ) during hospital stay, Hb (g/dl), PT, INR, aPTT, and PLT (T) together amounted to a small proportion of factors attributed to death in hospital ($r^2=10{\cdot}44\%$; $P=0{\cdot}470$).

In the PZ cohort, gender (*M:F), preterm-term*, age (months), weight (g), LOS(D), LOS(F), Apgar (5), and gestational age, on multivariable regression analysis, attributed to a nonsignificant cause of death during

hospital stay (r^2 = 33·75%, P = 0·095). LOS(D) (P = 0·026) is a significant contributor to hospital mortality (Fig. 2ii). We found GOB (PZ) (r^2 = 19·70%; P = 0·012) a significant contributor towards hospital mortality. Investigations (PZ) of Hb (g/dl), PT (s), INR, and aPTT (s) contributed towards a small proportion of factors attributing to hospital death (r^2 = 8·79%; P = 0·254).

Discussions

It is estimated that up to 73% of NICU admissions of premature infants are with very low birth weight [12, 19].

Low birth weight (< 1500 g) and preterm gestation predispose newborns to complications such as IVH, especially during procedures such as diagnostic lumbar puncture and central line placement despite hemostasis comparable to adults but physiologically lower coagulation factor levels with hyporeactive PLT [3, 8, 10].

Association for Advancement of Blood (AABB) recommends prophylactic PLT in adult patients at a PLT threshold of ≤10,000/µl [18,20]. PlaNet-2 trial recommendations include prophylactic PLT transfusions in preterm children to maintain PLT counts > 25,000/µl [18, 21]. In the present study (PLT/PZ) (n = 21), patients received prophylactic PLT transfusions, without clinical bleeding {mean PLT count 42,905 (95% *CI* 22,301–63,508)} and prophylactic PZ (n = 19) {mean (SD) *INR* 3·8 (3·6); *aPTT* 66·7 s (43·1)}.

Demographic factors attributable to PLT transfusions (Borges et al.) are low birth weight < 1000 g, *OR* 3·32 (1·8–5·5, P < 0·01); gestational age < 28 weeks, *OR* 3·6 (2·04–6·4, P < 0·01); and 5-min APGAR score < 7, *OR* 1·61 (0·87–2·9, P = 0·124) [22]. Rath et al. reported an association between immune hemolytic disease of newborns and low gestational age at birth as an independent predictor of thrombocytopenia at birth [23].

In the present study, age ≤ 1 m, weight ≤ 1500, gestational age ≤ 34 weeks, and preterm birth all corresponded towards a higher OR of mortality among patients, and no significant differences in overall survival were observed during LOS(D) (Tables 2 and 3). Preterm children (PLT/PZ) had significant difference in LOS(D) {median (IQR) 27.5 (24), 12.5 (20), P = 0.017}. The preterm (PLT/PZ) had no significant differences in INR and aPTT levels from term children (INR, P = 0.982; aPTT, P = 0.324) (Mann–Whitney *U*-test). We found (PZ cohort) PT (s) {median (IQR) 19.6 s (80), 18.0 s (16) (P = 0.048)} and INR {1.7 (7), 1.5 (1)} significantly different between preterm and term patients (P = 0.020).

Multiple determinants of clinical outcomes

Early childhood has complex transfusion requirements secondary to underlying disease conditions thrombocytopenia, deranged coagulation profile, and anemia.

Published "evidence-based guidelines" recommend different transfusion thresholds for stable non-bleeding infants and sick and/or bleeding infants [10, 12, 23].

The clinical stability of a patient is one way to monitor the efficacy of evidence-based transfusion practices. Dogra et al. observed an INR of 2·1 as a trigger of FFP transfusion for unstable patients and *INR* > 2·5 for clinically stable neonates, a finding correlating with similar observations by Stanworth et al. [13]. PLT-transfused (PLT/PZ) patients in the present study with GOB 1 to 3 bleeding had OR comparable to prophylactic PLT transfusions with no clinical bleeding. Table 2 review (Murray et al.) is suggestive that the underlying clinical illness co-existing with thrombocytopenia is an indicator of thrombocytopenia-based complications. In a study by Baer et al., severely ill patients with sepsis, necrotising enterocolitis, and prior GOB 3 or 4 IVH are more likely to receive more PLT which correlates with decreasing Apgar scores and stepwise increase in days on mechanical ventilation with each additional PLT transfused [3, 11, 24].

In the present study PLT/PZ cohort (n = 72), all patients were transfused PLT with some patients (n = 39) who were transfused both PLT and PZ units. We did not observe higher survival (PLT/PZ) with PLT(T) (≤ 25,000, > 25,000/µl*) (P = 0·109). We did however observe a significantly better survival with *INR* ≤ 1·7 and *aPTT* ≤ 75 s (P < 0·01, 0·018) (with coexistent thrombocytopenia) (Tables 2 and 3; Figure 2 (supplementary) (i, ii, iii)).

FFP as per the guidelines (HV New et al.) is recommended for newborns with significantly deranged age-related reference ranges (> 1·5 times midpoint of normal reference range) [10, 18].

PZ subjects in the present study showed higher mortality (PZ) with lower derangement of PT (≤ 50 s), INR (≤ 1.7), and aPTT (≤ 75 s). Table 2 grade-0 bleeding (n = 19) had a median PT of 19·70 s with grade-4 bleeding 16·90 s. We observed (PZ, n = 79) highest number of transfusions (n = 19) were prophylactic with no clinical bleeding. The mean (SD), age (m) 0·368 (0·524), and weight (g) 3008 (2989) are indicative of an established practice of administering prophylactic transfusions following a deranged laboratory profile to prevent complications during the infant age group. In the Present study (PZ) a higher OR mortality was observed with lower derangement of LI.

No questionnaire for quantification of infancy-specific symptoms bleeding (ISTH-BAT scale) was used for the present study [25].

This study with PLT/PZ (n = 72) is underpowered to ascertain the effect of individual bleeding grades and survival differences especially a comparison of prophylactic transfusions with higher GOB. Early transfusions can be influenced by the clinical diagnosis which could

be a potential confounding factor and were not evaluated comprehensively for the present study.

In "adults," prophylactic PLT transfusions (GOB 0 & 1) are recommended for no bleed or mild bleeding and pre-procedural and therapeutic (GOB ≥ 2) to treat anticipated bleeding [26].

Nellis et al. attributed full-day PICU admission *OR* 1·021 (1·006–1·036) ($P=0·007$) and major and minor bleeding *OR* 2·39 (1·463–3·906) ($P=0·001$) as independent variable causing hospital mortality [27]. According to Bender et al., the best predictor of LOS in the neonatal population was the VLBW neonates [28]. In underdeveloped countries (Sehiledengle et al.) apart from low gestation age and low birth weight and acquired causes such as hospital-acquired infections, sepsis are prominent causes for prolonged LOS(D) during hospital admissions [29].

This study was not powered towards a comprehensive evaluation of demographic parameters on the clinical outcome but merely to provide an association of demography and laboratory parameters with the clinical outcome of death among pediatric patients under 2 years of age.

Conclusions

Patient demographic parameters such as age (m), weight (g), gestational age, preterm birth, Apgar (5), and LOS(D) showed an association towards the patient's mortality during the hospital stay in PLT/PZ and PZ patients. PLT/PZ subjects' early therapy ≤ 7 days and LOS(F) significantly improved survival. LOS(F) and LOS(D) were both independent predictors of mortality.

Demographic parameters (PZ) were not significantly associated to mortality. LOS(D) (PZ cohort) was an independent predictor of mortality during the hospital stay.

Bleeding status is a significant independent predictor of mortality in both PLT/PZ and PZ cohorts. In PZ cohort, the association of prophylactic transfusions to clinical outcome could not be ascertained.

Laboratory investigations (PLT/PZ and PZ) parameter were not significantly associated with hospital-based mortality.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s43054-024-00302-1.

Supplementary Material 1: Supplementary figures: Figure 1. i (PLT/PZ) LOS (F) (0-7d,>7d) and weight (gms). ii (PLT/PZ) LOS (F) (0-7d,>7d) and Age (m). Figure 2. i (PLT/PZ) INR (0-1.7, >=1.8) and LOS (D). – ii (PLT/PZ) Platelet ≤ 25000,>25000) and LOS (D). iii (PLT/PZ) aPTT (0-75s, >75s) and LOS (D). Figure 3. i (PZ) LOS (D) (0-7d,8-14d,>=15d) and Age (m). ii (PZ) LOS (D) (0-7d,8-14d,>=15d) and Weight (gm). Figure 4. i (PLT/PZ) WHO Grade of Bleeding and LOS (D) Platelets with or without Plasma Transfusions. ii (PZ) WHO Grades of Bleeding and LOS (D) Plasma Transfusions. Supplementary table: Table 1. Demographic and laboratory parameters.

Acknowledgements
A special acknowledgement to my data collection team Dr. Ruchi Sharma, Dr. Dhananjay Prasad, Mr. Amit Kumar Ekka, Ms. Twinkal, and Mr. Jai Singh Thakur for their support, Department of Paediatrics for allowing access to patient data, Department of Transfusion Medicine and Blood Bank, and All India Institute of Medical Science Raipur for facilitating this study.

Authors' contributions
First author, SS: concept of the study, research and ethics approval, funding for the study, data collection, study design and statistical calculations, and main findings of the study. Second author, PP: subjective, technical support, specific details of patients, bleeding grades of the patient, and study specific specialty inputs for neonates and pediatric patients.

Funding
The first author received funding from the Chhattisgarh Council of Science and Technology (CCOST) for the present study (Grant number: 1545/CCOST/2020; dated 09/11/2020). The funding was provided for recruitment of staff and for conducting the study as per the pre-specified study objectives.

Availability of data and materials
Data for the present study is available on request.

Declarations

Ethics approval and consent to participate
Authors Dr. S. S. and Dr. P. P. would like to declare the following: all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards (project completion with ethics approval details attached as Annexure I). The present study had institute research ethics approval (IEC Proposal Number: IEC/2019/308) entitled as follows: "To analyse haemostatic parameters of the platelet and fresh-frozen Plasma transfusion among the children during first two years of life and propose best practice recommendations for the age-group." Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests, and the Egyptian Pediatric Association Gazette has the consent to publish this research.

Author details
[1]Department of Transfusion Medicine and Blood Bank, All India Institute of Medical Sciences Raipur, Raipur, Chhattisgarh, India. [2]Department of Pediatrics, All India Institute of Medical Sciences Raipur, Raipur, Chhattisgarh, India.

Received: 4 April 2024 Accepted: 31 May 2024
Published online: 30 August 2024

References

1. Andrew M, Paes B, Milner R, Johnston M, Mitchell L, Tollefsen DM, Powers P (1987) Development of the human coagulation system in the full-term infant. Blood 70(1):165–72
2. Yee ME, Josephson CD Transfusing neonates and infants. In: Practical transfusion medicine, p 417–25. https://doi.org/10.1002/9781119665885.ch35
3. Neary E, Mccallion N, Kevane B, Cotter M, Egan K, Regan I et al (2015) Coagulation indices in very preterm infants from cord blood and postnatal samples. J Thromb Haemost 13(11):2021–2030
4. Kenet G, Chan AKC, Soucie JM, Kulkarni R Bleeding disorders in neonates: bleeding disorders in neonates. 16:168–75. Available from: https://onlinelibrary.wiley.com/doi/10.1111/j.1365-2516.2010.02316.x
5. Arceci RJ, Hann IM, Smith OP (2007) Pediatric hematology: Third edition. Wiley. https://doi.org/10.1002/9780470987001

6. Maynard K (2014) Administration of blood components. In: Technical Manual, AABB, TechnicalManual15TH. p 545–59. ISBN No. 1-56395-196-7
7. Andrew M, Paes B, Milner R, Johnston M, Mitchell L, Tollefsen DM et al (1988) Development of the human coagulation system in the healthy premature infant. Blood 72(5):1651–1657
8. Arceci RJ, Hann IM, Smith OP (2006) Pediatric hematology, 3rd edn. Blackwell Publ
9. Chan AK (2013) Bleeding in neonates and children. In: Hemostasis and thrombosis: Basic principles and clinical practice, 6th edition, 6th edn. Wolters Kluwer/Lippincott Williams & Wilkins Health, Philadelphia, p 1424–33
10. New HV, Grant-Casey J, Lowe D, Kelleher A, Hennem S, Stanworth SJ (2014) Red blood cell transfusion practice in children: current status and areas for improvement? A study of the use of red blood cell transfusions in children and infants. Transfusion (Paris) 54(1):119–127
11. Roberts I, Murray NA (2003) Neonatal thrombocytopenia: causes and management. Arch Dis Child Fetal Neonatal Ed 88(5):359–364
12. Del Vecchio A, Franco C, Petrillo F, D'Amato G (2016) Neonatal transfusion practice: when do neonates need red blood cells or platelets? Am J Perinatol 33(11):1079–1084
13. Dogra K, Kaur G, Basu S, Chawla D (2020) Fresh frozen plasma and platelet transfusion practices in neonatal intensive care unit of a tertiary care hospital. Indian J Hematol Blood Transfus 36(1):141–148. https://doi.org/10.1007/s12288-019-01164-z
14. Fustolo-Gunnink SF, Fijnvandraat K, Van Klaveren D, Stanworth SJ, Curley A, Onland W et al (2019) Preterm neonates benefit from low prophylactic platelet transfusion threshold despite varying risk of bleeding or death. Blood 134(26):2354–2360
15. Carr R, Kelly AM, Williamson LM Neonatal thrombocytopenia and platelet transfusion - a UK perspective. 107(1):1–7. Available from: https://www.karger.com/Article/FullText/365163
16. Go H, Ohto H, Nollet KE, Kashiwabara N, Ogasawara K, Chishiki M et al (2020) Risk factors and treatments for disseminated intravascular coagulation in neonates. Ital J Pediatr 46(1):1–7
17. (2013) Immunology of leucocytes, platelets and plasma components. In: Mollison's blood transfusion in clinical medicine, John Wiley & Sons, Ltd., Oxford, p 583–4. Available from: https://onlinelibrary.wiley.com/doi/10.1002/9781118689943.ch13
18. Hendrickson JE, Josephson CD (2022) Platelet and plasma transfusions for infants and children. In: Jeanne E. Hendrickson1, editor. Rossi's principles of transfusion medicine. 6th ed. Wiley, p. 381–91.
19. Sharrow D, Hug Y, Liu Y (2020) Levels & trends in child mortality
20. Kaufman RM, Djulbegovic B, Gernsheimer T, Kleinman S, Tinmouth AT, Capocelli KE, et al. Platelet transfusion: a clinical practice guideline from the AABB. 162(3):205–13. Available from: https://www.acpjournals.org/doi/10.7326/M14-1589.
21. Estcourt LJ (2019) Platelet transfusion thresholds in premature neonates (PlaNeT-2 trial). Transfus Med 29(1):20–2. Available from: https://onlinelibrary.wiley.com/doi/10.1111/tme.12587. [cited 2021 Dec 15]
22. Borges JPG, Santos AMN, Cunha DHF, Mimica AFMA, Guinsburg R, Kopelman BI (2013) Restrictive guideline reduces platelet count thresholds for transfusions in very low birth weight preterm infants. Vox Sang 104:207–13
23. Rath MEA, Smits-Wintjens VEHJ, Oepkes D, van Zwet EW, van Kamp IL, Brand A et al (2012) Thrombocytopenia at birth in neonates with red cell alloimmune haemolytic disease. Vox Sang 102(3):228–233
24. Baer VL, Lambert DK, Henry E, Snow GL, Sola-Visner MC, Christensen RD Do platelet transfusions in the NICU adversely affect survival? Analysis of 1600 thrombocytopenic neonates in a multihospital healthcare system. 27(12):790–6
25. Rodeghiero F, Pabinger I, Ragni M, Abdul-Kadir R, Berntorp E, Blanchette V et al (2019) Fundamentals for a systematic approach to mild and moderate inherited bleeding disorders: an EHA Consensus Report. Hemasphere 3(5)
26. Estcourt LJ, Birchall J, Allard S, Bassey SJ, Hersey P, Kerr JP et al (2017) Guidelines for the use of platelet transfusions. Br J Haematol 176:365–94. Blackwell Publishing Ltd
27. Nellis ME, Karam O, Mauer E, Cushing MM, Davis PJ, Steiner ME et al (2018) Platelet transfusion practices in critically ill children. Crit Care Med 46(8):1309–1317
28. Bender GJ, Koestler D, Ombao H, Mccourt M, Alskinis B, Rubin LP et al (2013) Neonatal intensive care unit: predictive models for length of stay. J Perinatol 33(2):147–153
29. Sahiledengle B, Tekalegn Y, Zenbaba D, Woldeyohannes D, Teferu Z (2020) Which factors predict hospital length-of-stay for children admitted to the neonatal intensive care unit and pediatric ward? A hospital-based prospective study. Glob Pediatr Health 7:2333794X20968715

Publisher's Note