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EMERGENCY TRANSFUSION AND DAMAGE CONTROL RESUSCITATION

TRANSFUSION

Analysis of time to death for children with life-threatening hemorrhage from traumatic, surgical, and medical etiologies

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Abstract

Introduction: Life-threatening hemorrhage (LTH) is a significant cause of mortality in pediatrics. Timing of mortality in children with LTH is important for future trials.

Methods: In a secondary analysis of the prospective observational massive transfusion in children (MATIC) study, time-to-event analysis was performed to determine timing of death based on etiology of LTH and cause of death.

Results: There were 449 children with LTH; the etiologies of LTHs included trauma (46%), operative (34%), and medical (20%). The cause of death at 24 h in the trauma group was 56% from hemorrhage and 42% from central nervous system (CNS) failure; in operative group it was 94% from hemorrhage and 6% CNS failure; in medical group it was 84% hemorrhage and 3% CNS failure. The median (interquartile range [IQR]) time to death (hours) varied by cause of death (hemorrhagic: 3.3 [1.0–10.3], CNS failure: 30.4 [9.0–63.6]). For traumatic LTH, 90% of hemorrhage-related deaths occurred within 19 h and 90% of CNS failure deaths occurred within 92 h. For operative LTH, 90% of hemorrhage-related deaths occurred within 5 days and 90% of CNS failure deaths occurred within 28 days. For medical LTH, 90% of hemorrhage-related deaths occurred within 44 h and 90% of CNS failure deaths occurred within 24 days.

Conclusion: In children, timing of death differs according to etiology of LTH and by cause of death. The choice of primary outcome for trials in children with LTH should consider these differences based on the etiology of LTH being studied.

KEYWORDS
CNS injury, hemorrhage, life-threatening bleeding, mortality, pediatrics, time to death

1 | INTRODUCTION

Life-threatening hemorrhage (LTH) in children is relatively uncommon but carries a high risk of mortality. The 28- or 30-day mortality from trauma in pediatric patients is higher compared with adult patients, 36% versus 25%, respectively.[1,2] Twenty-eight day mortality is also high in children with LTH from operative and medical etiologies at 24% and 65%,[1] respectively. The cause of mortality from LTH events in children is mainly due to hemorrhage and central nervous system (CNS) failure.[1] This is different from adults where multi-organ failure is another common contributor to mortality, in addition to hemorrhage and CNS failure.[3,4]

To improve outcomes for children with LTH, damage control resuscitation (DCR) has been adapted for use in children with any etiology of bleeding, which may include trauma, medical and operative causes. DCR utilizes hemostatic resuscitation principles including balanced blood product administration, use of hemostatic adjuncts, avoidance of iatrogenic insults (hypothermia, acidosis, and dilution), and restoration of volume to prevent the myriad of adverse consequences of the shock state.[5] The appropriateness of adapting adult practice to pediatric cohorts and translating the practices of traumatic resuscitation to bleeding from other etiologies, is not known. The Massive Transfusion in Children (MATIC) prospective observational study of over 400 children from 24 institutions around the world reported associations with the use of some of the DCR principles and improved outcomes in children.[6,7] As pediatric-specific data are limited, multicenter clinical trials are being designed and conducted to inform the best practices for resuscitation of children with LTH such as the MATIC-II platform trial (NCT06070350).

An essential element of clinical trial design is choosing a primary outcome for efficacy that is clinically meaningful and relevant to the mechanism of action of the interventions studied. Identifying the timing of mortality due to different bleeding etiologies in pediatric patients is required for optimal clinical trial design. The association of patient characteristics with the timing of death can also clarify how these potential covariates might affect

TABLE 1 Demographics of children with life-threatening bleeding.

Measures	Overall population $N = 449$	Trauma $N = 207$	Operative $N = 153$	Medical $N = 89$	*p*-value
Sex					.02
Male	247 (55%)	129 (62.3%)	76 (49.7%)	42 (47.2%)	
Female	202 (45%)	78 (37.7%)	77 (50.3%)	47 (52.8%)	
Age (years)	7.3 [1.7, 14.7]	10.4 [4.7, 15.4]	2.1 [0.3, 11.8]	8.0 [1.2, 14.7]	<.01
Race					<.01
Black	109 (28.7%)	72 (41.6%)	20 (15.3%)	17 (22.4%)	
White	242 (63.7%)	98 (56.6%)	91 (69.5%)	53 (69.7%)	
Other	29 (7.6%)	3 (1.7%)	20 (15.3%)	6 (7.9%)	
Ethnicity					<.10
Hispanic/Latino	43 (11%)	16 (8.8%)	21 (15.7%)	6 (7.8%)	
Blood Group					.98
A	157 (36%)	67 (34%)	58 (38.2%)	32 (36.8%)	
B	65 (14.9%)	30 (15.2%)	22 (14.5%)	13 (14.9%)	
AB	12 (2.8%)	5 (2.5%)	5 (3.3%)	2 (2.3%)	
O	202 (46.3%)	95 (48.2%)	67 (44.1%)	40 (46.0%)	
RhD-type					.87
RhD-positive	359 (82.7%)	163 (83.2%)	123 (81.5%)	73 (83.9%)	
RhD-negative	75 (17.3%)	33 (16.8%)	28 (18.5%)	14 (16.1%)	
PRISM score	12 [6, 22]	11 [5, 23]	12 [6, 21]	18 [12, 24]	<.01
24-h mortality	99 (22.2%)	50 (24.4%)	17 (11.3%)	32 (36.0%)	<.01
28-day mortality	168 (37.8%)	74 (36.1%)	36 (23.8%)	58 (65.2%)	<.01

Note: Data presented as either *N* (%) or Median [IQR]. For full reporting of all patient variables, please see the main MATIC report by Leonard et al.[1]
Abbreviations: LTH, life-threatening hemorrhage; PRISM score, Pediatric Risk of Mortality III Score.

outcomes. Thus, the primary objective of this study was to evaluate if any differences existed in the timing of death based on the etiologies of LTH, cause of death, and patient characteristics.

2 | METHODS

2.1 | Study population and design

This is a secondary analysis of the MATIC study. In brief, the MATIC study was a multicenter prospective observational study that collected data from 24 centers internationally between 2014 and 2018. The study included children with LTH, defined as either receiving a total of 40 mL/kg or more of all blood products within 6 h or activation of a massive transfusion protocol with at least one blood product transfused.[1] In MATIC, the etiology of LTH was categorized as traumatic, intra-operative, or medical. For patients who died, the cause of death was recorded by the local research team as hemorrhage, CNS failure, airway/respiratory failure, cardiac failure, multiple organ failure, or other. All patients included in the primary MATIC study were analyzed in this report. In this analysis, we only report on the frequency of 24-hour mortality caused by hemorrhage and CNS failure since all other causes of death by 24 hours in this population occurred very infrequently.

2.2 | Statistical analysis

The main outcome of this secondary analysis of the MATIC study is 24-h mortality. We also evaluated 28-day mortality as a secondary outcome. We compared the demographics, transfusion, and outcomes between the study groups. Because the underlying cause of death may impact the timing of death, we also compared

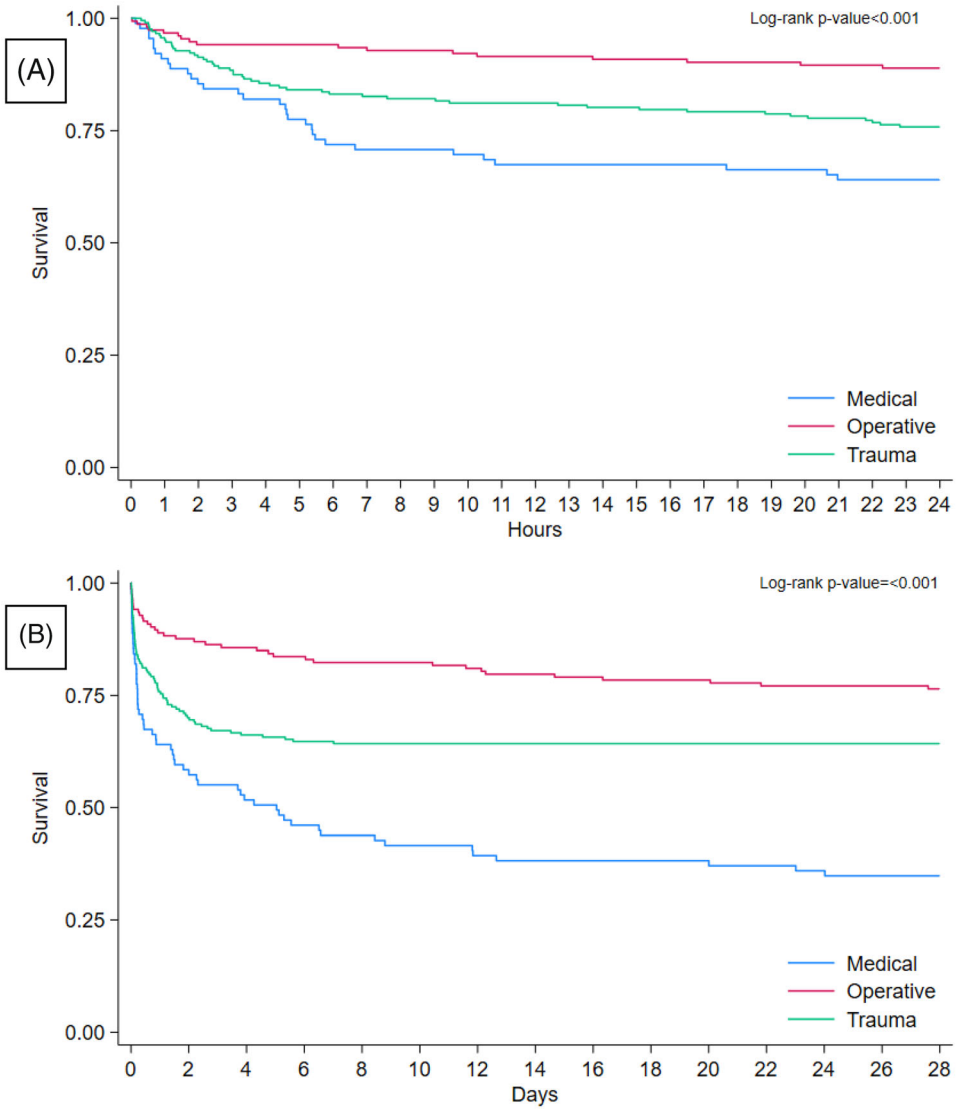

FIGURE 1 Kaplan–Meier survival curves demonstrating the survival of children with life-threatening bleeding by each etiology at two time points: (A) 24 h and (B) 28 days.

unadjusted mortality at both 24-h and 28-day timepoints between patients with hemorrhage- and CNS failure-related causes of death, stratified by LTH etiology.

We then performed time-to-event analysis using Kaplan–Meier survival curves and the Log-rank test. We compared the survival for each cause of death, stratified by etiology of LTH. We considered using Cox proportional hazards regression to perform risk-adjusted comparison of cause of death timing within LTH etiologies; however, small sample sizes and violations of the proportional hazards assumption prevented us from obtaining valid estimates from the model. Thus, we did not perform adjusted models.

Continuous data are presented as median (interquartile range [IQR]). Continuous variables were compared using

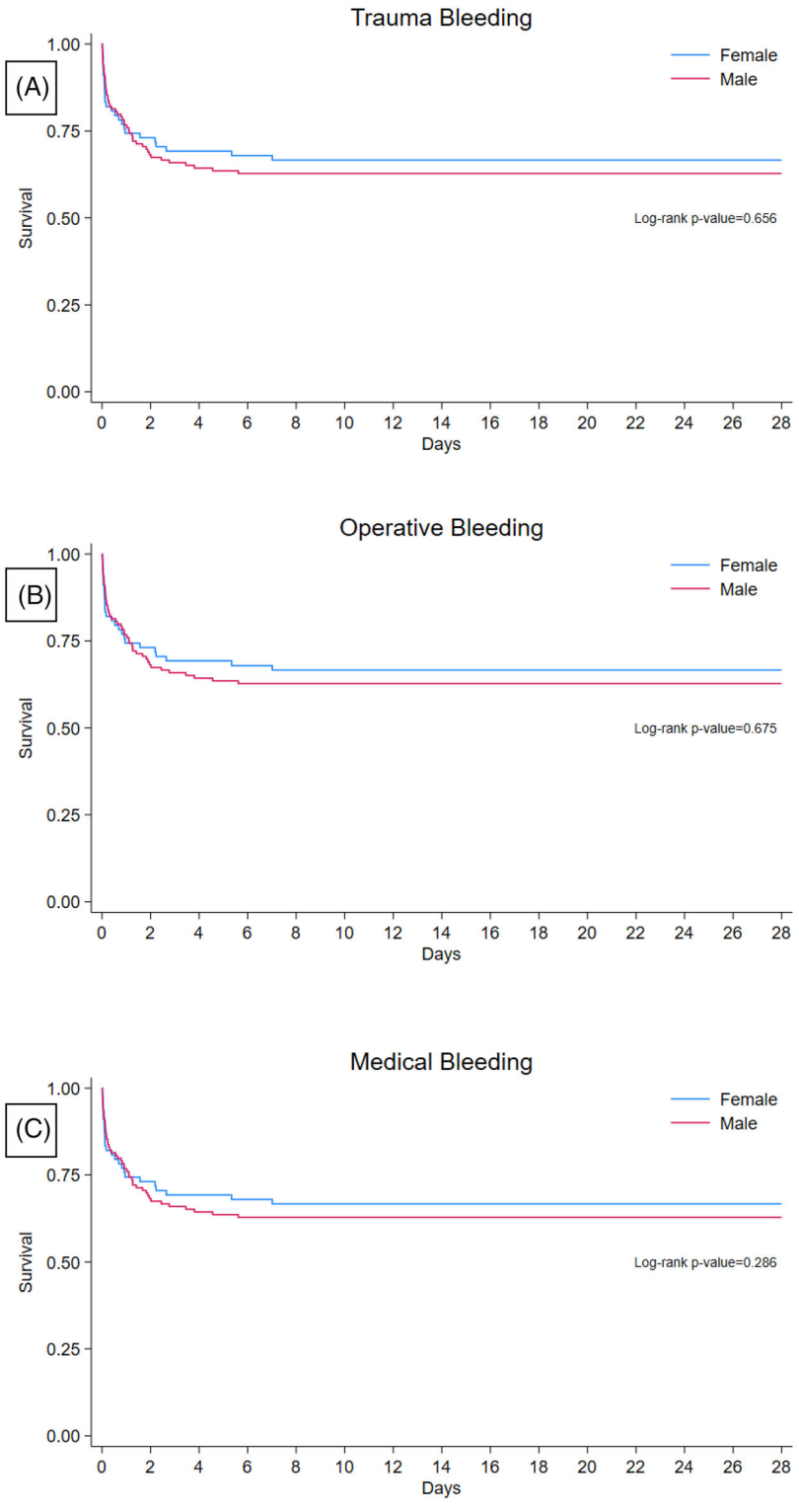

FIGURE 2 Kaplan–Meier survival curves demonstrating the survival of children (through 28 days) with life-threatening bleeding by sex within each etiology of trauma (A), operative (B), and medical (C).

Wilcoxon rank-sum tests, and categorical variables were compared using Chi-squared tests. Two-sided p-values $\leq .05$ were considered significant. Data analysis was conducted using Stata v18MP (StataCorp; College Station, TX).

The MATIC study was conducted under the waiver of informed consent granted by each participating center's institutional review board (IRB).

3 | RESULTS

A total of 449 children with LTH were analyzed. Table 1 demonstrates the demographics of the patients who were included in this analysis.

Patients in the medical etiology of LTH group had the highest rate of mortality at both timepoints, 36% at 24 h

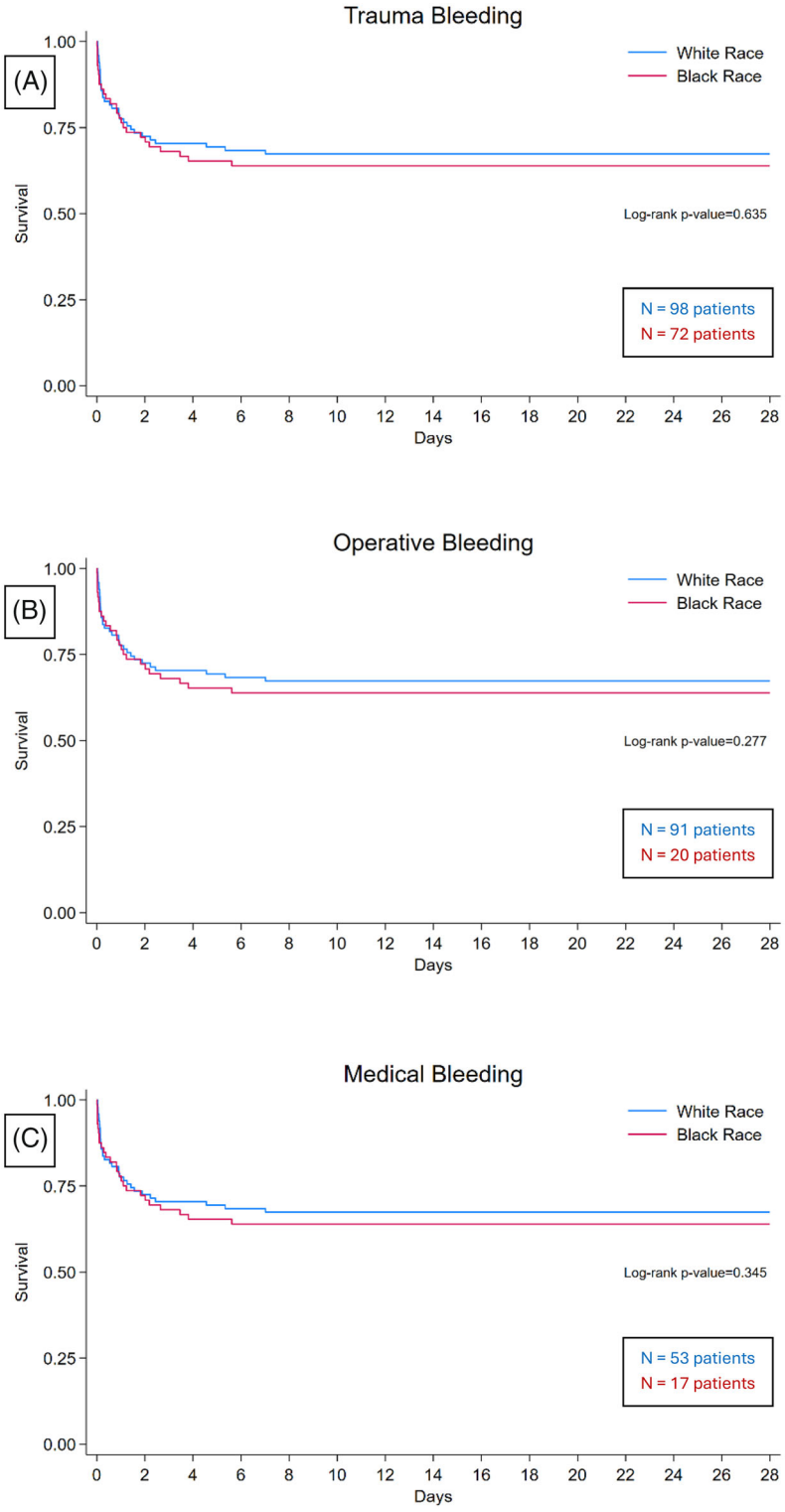

FIGURE 3 Kaplan–Meier survival curves demonstrating survival by race (through 28 days) of children with life-threatening bleeding within each etiology of trauma (A), operative (B), and medical (C).

TABLE 2 Proportion of the cause of death for each etiology of life-threatening bleeding at 24 h and 28 days.

Timing of death per etiology of LTH	Hemorrhage as cause of death	CNS failure as cause of death	Other cause of death	*p*-value
Within 24 h				<.01
Trauma ($n = 50$)	28 (56%)	21 (42%)	1 (2%)	
Operative ($n = 17$)	16 (94%)	1 (6%)	0	
Medical ($n = 32$)	27 (84%)	1 (3%)	4 (13%)	
Within 28 days				<.01
Trauma ($n = 74$)	30 (41%)	43 (58%)	1 (1%)	
Operative ($n = 36$)	19 (53%)	8 (22%)	9 (25%)	
Medical ($n = 58$)	33 (57%)	7 (12%)	18 (31%)	

Note: Data presented as *n* (%).
Abbreviations: CNS, central nervous system; LTH, life-threatening hemorrhage.

TABLE 3 Survival time (in hours) for given proportion of deaths to occur by cause of death and etiology of bleeding.

	25%	50%	75%	90%
Hemorrhage as cause of death				
Overall	1.0	3.3	10.3	36.3
Trauma	0.9	2.5	6.9	18.8
Operative	1.0	6.2	16.5	118.3
Medical	1.2	4.6	9.6	43.5
CNS failure as cause of death				
Overall	9.0	30.4	63.6	133.1
Trauma	3.8	24.6	52.5	91.4
Operative	27.3	75.0	114.2	662.3
Medical	33.2	48.1	133.1	576.5

Abbreviation: CNS, central nervous system.

and 65% at 28 days (Table 1 and Figure 1). Patient sex and race were not associated with mortality for any cause of LTH at any time point (Figures 2 and 3). In all patients, hemorrhage was the most common cause of death at 24 h and 28 days and was particularly prominent amongst those with operative and medical etiologies of LTH. However, as expected, death from CNS failure became more common at 28 days for each etiology of LTH (Table 2). The median [IQR] time to death for all subjects with hemorrhagic death was 3.3 h [1.0–10.3], and the median [IQR] time to death for all subjects with CNS failure was 30.4 h [9.0–63.6].

Table 3 displays the time at which 25%, 50%, 75%, and 90% of deaths occurred by etiology of bleeding and by cause of death. In patients with traumatic etiologies of LTH, 25% of the hemorrhagic deaths occurred within 1 h and 90% by 19 h while 25% of the CNS failure deaths occurred within 4 h and 90% by 91.5 h (4 days). In patients with operative etiologies of LTH, 25% of the hemorrhagic deaths occurred within 1 h and 90% by 118.5 h (5 days) while 25% of the CNS failure deaths occurred within 27.5 h and 90% by 662.5 h (28 days). In patients with medical etiologies of LTH, 25% of the hemorrhagic deaths occurred within 1.5 h and 90% by 43.5 h while 25% of the CNS failure deaths occurred within 33.5 h and 90% by 576.5 h (24 days). Figure 4 displays the timing of death per cause of death within 28 days.

4 | DISCUSSION

In this secondary assessment of the MATIC study, time to death varied significantly based on the etiology of LTH and by cause of death. The median time to death for subjects with hemorrhagic death occurred much earlier compared with CNS-related deaths. Hemorrhage was the most common cause of death at 24 h in all three etiologies of bleeding. At 28 days, hemorrhage was the most common cause of death in all groups except the trauma group where death from CNS failure was more prevalent than death from hemorrhage. Approximately 90% of deaths due to hemorrhage in the trauma group occurred within 24 h, while the same percentage of deaths due to hemorrhage occurred within 2 or 5 days in the medical and operative groups, respectively. These data offer insight into the timing of death in bleeding children that will facilitate the optimal selection of relevant outcomes in future clinical trials.

Most data describing the time to death after hemorrhage in children is from injured cohorts. McLaughlin et al. showed a median time to death for children (aged 1–14) of 0.99–1.15 days (23.8–27.6 h) and adolescent

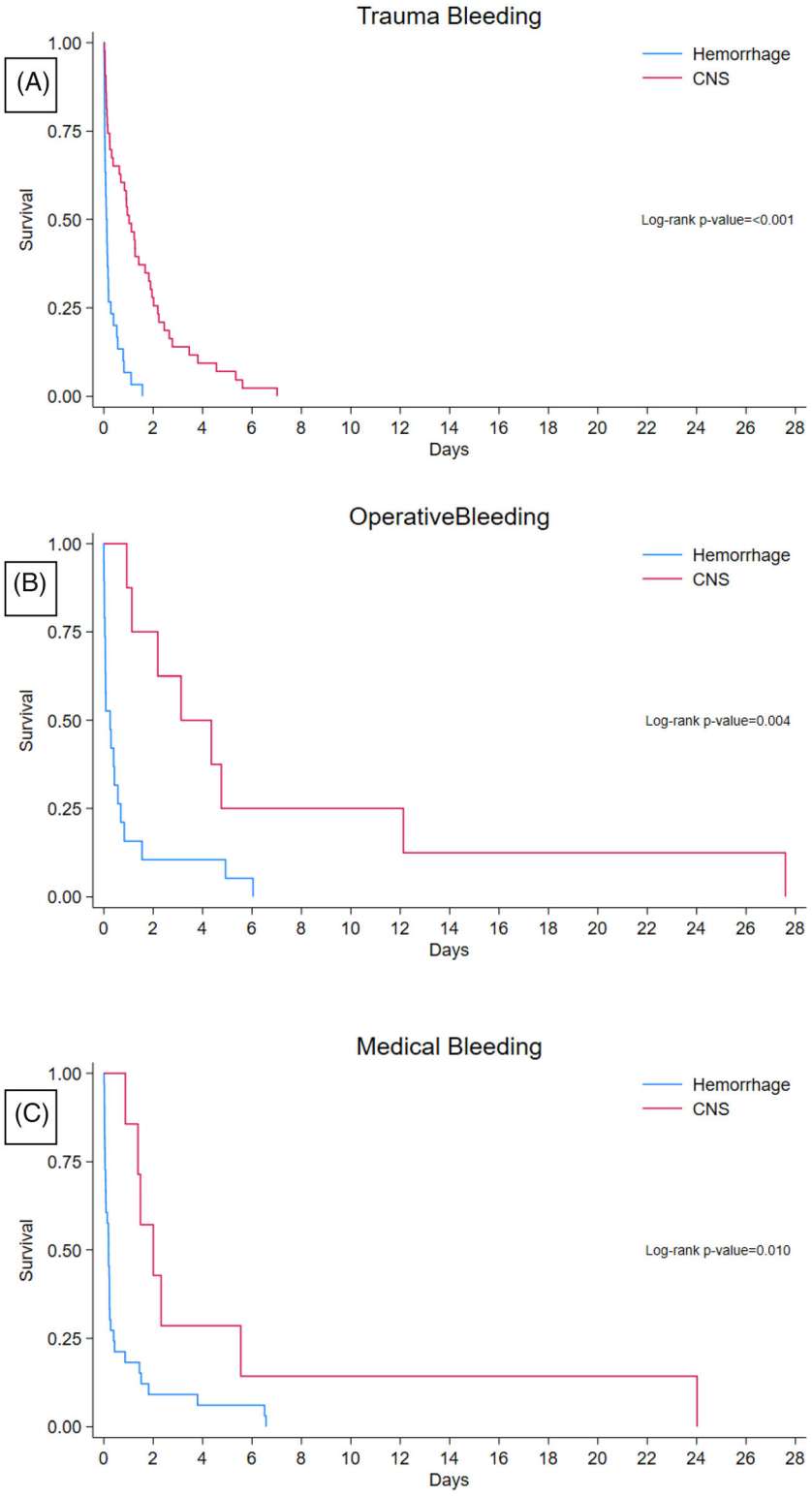

FIGURE 4 Kaplan–Meier survival curves demonstrating the time to death by cause of death of children (through 28 days) with life-threatening bleeding within each etiology of trauma (A), operative (B), and medical (C). Of note, survival curves approach zero as only children who died were included in these figures.

trauma patients (aged 15–24) of 0.78 days[8] (18.7 h). The majority (74%) of the deaths in the pediatric patients aged 0–14 years old occurred within 24 h.[8] This study did not report the patients' causes of death. Burd et al., in a multicenter cohort of trauma patients not limited to LTH, reported a 17 h median survival time of pediatric patients who went on to die from hemorrhage or hypovolemia compared with a survival time of 59 h for those who died of CNS injury.[9] The inclusion of children without LTH is likely the explanation for the differences in the time to death results with our report. Burd et al. also reported in-hospital death from CNS injury was more prevalent than

death from hemorrhage,[9] which is consistent with data in children with traumatic injury and LTH.

Recent recommendations state that for patients with traumatic LTH, the primary outcome for trials of hemostatic agents should be between 6 and 24 hours; these recommendations also state that 30 day mortality is the optimum timing to measure safety outcomes.[10,11] A large multicenter platform trial (MATIC-II) has been initiated to examine the efficacy and safety of hemostatic resuscitation principles in children with traumatic bleeding with a primary outcome of 24-h mortality (NCT06070350). Our data supports this primary outcome since 90% of the deaths from hemorrhage occurred by this timepoint for children with traumatic LTH. Conversely, children with medical and operative etiologies of LTH died from hemorrhage at later times than those with traumatic LTH. Based on this data, a potential primary outcome for trials of hemostatic products in children with LTH may be mortality at 2 days for children with medical etiologies of LTH and at 5 days for operative etiologies.

Even though ~90% of deaths due to CNS failure occurred in trauma patients with LTH within 4 days, and within 28 days for operative and medical patients with LTH, the primary outcome for interventions aimed at improving outcomes for patients with CNS injuries or who are at risk of death from intracranial bleeding or hypoperfusion and edema should be longer term outcomes that assess neurologic function, such as the extended Glasgow outcome scale (GOSE) at 6 months.[11,12]

We did not find a difference in survival in relation to patient sex or race. These findings are consistent with previous analyses of the MATIC database that did not find any difference in outcomes by sex or race for all patients.[1,13] This study further evaluated patient sex according to each etiology of LTH and did not find any differences between male and female patients. This is an area of need for future research amongst larger cohorts as it has been suggested that hemostatic changes that occur with puberty may change the pathophysiology associated with LTH.[14] Thus, a larger cohort would permit the separate analysis of prepubertal females and post-pubertal females amongst all etiologies of bleeding.

Additionally, there were no differences in survival based on race amongst each etiology of LTH. This is discordant with other data that report a higher odds ratio for mortality in African American/Black patients following bleeding events (1.24 higher odds of mortality in pediatric patients with post-operative bleeding[15] and five times higher risk of mortality in female patients with postpartum hemorrhage[16]). While these studies evaluated bleeding from operative and medical etiologies, neither quantified the volume of transfusion required or classification of LTH for inclusion. This could contribute to the discordant results; however, the difference may also be attributable to the small number of African American/Black patients in each subgroup. Larger studies are warranted to assess this relationship in LTH patients further stratified by bleeding etiology.

This study has several limitations. Notably, this is a post-hoc secondary analysis of the MATIC database. Additionally, the sample size was too small to allow for adjusted comparisons of survival curves. As a result, some of the differences noted may not be significant upon adjustment. A larger sample size would also allow for examining different subsets of bleeding etiologies. For example, the timing of death and cause of death from traumatic injury might be different for children with severe bleeding and severe traumatic brain injury compared with those without severe traumatic brain injury, or there might be mortality timing differences between patients with different medical causes of LTH.

This report provides valuable information that may assist with the choice of primary efficacy outcomes for clinical trials examining hemostatic therapies for LTH. Our data supports a primary efficacy outcome of 24 h mortality for children with traumatic LTH, 48 h mortality for children with medical LTH, and 5 day mortality for children with operative LTH.

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CONFLICT OF INTEREST STATEMENT

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