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Association of time to red blood cell transfusion on outcomes in patients with gastrointestinal bleeding

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ABSTRACT

Background: Red blood cell transfusion is frequently prescribed in the emergency department for patients with gastrointestinal bleeding (GIB), but the association of time to transfusion with patient outcome has not been thoroughly evaluated.

Methods: A retrospective cohort study analyzed adult patient data with GIB who visited the emergency department of single university-affiliated hospital between January 2016 and April 2022. The associations of time to transfusion and patient outcomes, 30-day and in-hospital mortality, were assessed.

Results: Among a total of 2,284 patients, 1,395 (61.1%) received red blood cell transfusion within 4 h of emergency department admission. Analysis of the time to transfusion showed the association between late transfusion (transfusion after 4 h) and the risk of 30-day mortality (adjusted hazard ratio, 1.65, 95% CI 1.17–2.32, $p = .004$) and in-hospital mortality (adjusted odds ratio 1.71, 95% CI 1.24–2.35, $p < .001$). Subgroup analysis revealed that the association between time to transfusion and 30-day mortality was found only in those with upper GIB, nonvariceal bleeding and a low haemoglobin level (<7.5 g/dL). Early transfusion was associated with higher 30-day transfusion demand, while no associations with length of stay and adverse transfusion reaction were noted.

Conclusions: In this study, a longer time to red blood cell transfusion was associated with an increased risk of 30-day and in-hospital mortality of patients with GIB, especially in those with upper GIB, nonvariceal bleeding and a low haemoglobin level. In the emergency department, prompt red blood cell transfusion decisions for patients with GIB may improve patient outcomes.

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Introduction

Gastrointestinal bleeding (GIB) is a frequent and critical presentation in emergency department (ED) worldwide and poses significant challenges to healthcare providers owing to its potential for severe morbidity and mortality. The mortality rate of patients hospitalized with upper GIB ranges from 4.5% to 8.2%, and that of patients with lower GIB from 3.0% to 8.8% [1].

Numerous studies have explored GIB outcomes to understand the factors affecting patient prognosis [2–7]. Research in the field has focused on variables such as age, comorbidities, hemodynamic stability, and the source of bleeding as significant determinants of GIB outcomes [2]. Other population-based studies have revealed further risk factors, such as varices and drugs [5–7].

Interventions for patients with GIB encompass a spectrum of strategies, including red blood cell (RBC) transfusion, endoscopic therapy, radiological intervention, and surgery [8,9]. Among these, RBC transfusion is one of the most common medical interventions for patients with GIB [5,10]. It serves the dual purpose of correcting anaemia arising from bleeding and restoring the intravascular volume. Research has been conducted on the criteria for determining the need for RBC transfusion in patients with GIB, and existing

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research guidelines outline the strategies and thresholds for RBC transfusion in the context of GIB management [11–13].

However, despite a substantial body of literature focusing on transfusion thresholds, limited research has addressed the timing and impact of early RBC transfusion in patients with GIB. Although established haemoglobin (Hb) thresholds for transfusion exist, there is a paucity of studies investigating the optimal timing for RBC transfusion in patients with GIB. Particularly in the ED, where physicians are provided with only limited information and management is often initiated empirically, there is a greater demand for evidence regarding the optimal timing of transfusion.

To date, the association of time to RBC transfusion with the clinical outcomes of patients visiting the ED with GIB has not been addressed. Here, we investigated patients with GIB visiting the ED of a tertiary hospital to determine whether the time to transfusion was associated with clinical outcomes.

Materials and methods

Study design and participants

This retrospective, single-centre observational study was conducted at a tertiary university hospital in Seoul, Korea, which serves approximately 90,000 visitors to the ED annually. We retrospectively examined patients who received RBC transfusions in the ED between January 2016 and April 2022.

During the ED stay, patients who received one or more units of RBC transfusion were identified, and their basic demographic details were collected. This information included the time to initial RBC transfusion, sex, age, chief complaints, systolic blood pressure, pulse rate, respiratory rate, body temperature, oxygen saturation, ED triage score, the number of RBC transfusion within 24 h and Hb level. Clinical outcomes such as 30-day mortality, in-hospital mortality, length of stay, and total number of RBC transfusions within 30 days were collected. For each patient, the presence of adverse transfusion reactions was also reviewed.

Patients <20 years of age and those with missing data were excluded. To avoid bias, patients who required massive transfusion (>8 units of RBCs within 24 h) or immediate transfusion due to overt massive bleeding (transfusion initiated within 1 h of ED admission) were also excluded. Considering the median duration of patients' stays in the ED (approximately 13.5 h), patients who received RBC transfusion more than 12 h after ED admission were also excluded. During the study period, 13,926 patients underwent RBC transfusions during their ED stay. After excluding patients <20 years of age and those with missing data, 10,490 patients were identified. Among these, we collected 2,575 patients with GIB by chief complaints. After further exclusion of patients who received massive transfusions and RBC transfusions started after 12 h or within 1 h of ED visit, 2,284 patients were finally included in the analysis.

The study was conducted in accordance with the Declaration of Helsinki and reviewed and approved by the Institutional Review Board (IRB) of the Yonsei University Health System (4-2023-0950). The IRB of Yonsei University Health System waived the need for informed consent, given the retrospective nature of this study and the use of de-identified data.

Emergency department triage score

ED triage score is designed for use from the prehospital stage through to the transport of emergency patients to the optimal hospital within an appropriate time for treatment. At the hospital level, the purpose is to assess the level of urgency based on the patient's main symptoms, guide the patient to an appropriate treatment area, and allocate effective and efficient medical human resources. Patients are classified into five stages according to severity [14], and each stage has a recommended time to start treatment: 1 (resuscitation; immediate), 2 (emergent; 15 min), 3 (urgent; 30 min), 4 (less urgent; 60 min), and 5 (non-urgent; 120 min). The validity and reliability of the ED triage score severity classification have been verified through follow-up studies.

Statistical analyses

Variables are presented as frequencies (%) or mean ± standard deviation. To balance patient characteristics between early and late transfusion groups, inverse probability of treatment weighting (IPTW) method was implemented using a propensity score. The propensity score was calculated by logistic regression using variables listed in Table 1. The weights were stabilized to reduce the variability and enhance the robustness of the analysis. The association between the time to transfusion and 30-day mortality was examined using IPTW-adjusted Kaplan–Meier analysis and Cox proportional hazard models adjusted for IPTW, and the adjusted hazard ratio (HR) was presented with a 95% confidence interval (CI). In addition, Cox proportional hazard models without IPTW was conducted. Two multivariate Cox models were used to assess the association between time to transfusion and

Table 1. Patient characteristics before and after inverse probability of treatment weighting.

	Cohort before IPTW				Cohort after IPTW		
Parameters	Total ($n=2,284$)	Early RBC transfusion, ≤4 h ($n=1,395$)	Late RBC transfusion, >4 h ($n=889$)	SMD	Early RBC transfusion, ≤4 h ($n=1,422.3$)	Late RBC transfusion, >4 h ($n=869.6$)	SMD
Sex, female (%)	1,501 (65.7)	942 (67.5)	559 (62.9)	0.098	484.5 (34.1)	289.9 (33.3)	0.015
Age, year	65.3 ± 14.5	65.4 ± 14.3	65.3 ± 14.8	0.011	65.1 ± 14.6	65.4 ± 15.2	0.018
Vital signs							
Systolic blood pressure (mmHg)	111.6 ± 24.4	107.9 ± 24.4	117.4 ± 23.1	0.397	112.2 ± 25.6	112.2 ± 23.0	0.003
Pulse rate (/min)	95.9 ± 20.2	96.2 ± 20.9	95.4 ± 19.0	0.040	96.0 ± 20.8	95.1 ± 19.1	0.047
Respiratory rate (/min)	17.7 ± 2.4	17.9 ± 2.5	17.4 ± 2.2	0.183	17.7 ± 2.5	17.7 ± 2.5	0.019
Oxygen saturation (%)	98.2 ± 2.4	98.2 ± 2.5	98.2 ± 2.1	0.014	98.2 ± 2.4	98.2 ± 2.1	0.029
ED triage score							
1	115 (5.0)	98 (7.0)	17 (1.9)	0.249	68.6 (4.8)	46.2 (5.3)	0.022
2	355 (15.5)	276 (19.8)	79 (8.9)	0.315	220.0 (15.5)	125.1 (14.4)	0.030
3	1,654 (72.4)	958 (68.7)	696 (78.3)	0.219	1025.4 (72.1)	635.3 (73.1)	0.022
4	158 (6.9)	62 (4.4)	96 (10.8)	0.241	106.6 (7.5)	62.5 (7.2)	0.012
5	2 (0.1)	1 (0.1)	1 (0.1)	0.013	1.7 (0.1)	0.5 (0.1)	0.021
Number of RBC unit transfused, >1	1,864 (81.6)	1,218 (87.2)	646 (72.7)	0.372	1142.8 (80.3)	702.6 (80.8)	0.011
Haemoglobin, g/dL	7.8 ± 2.1	7.4 ± 2.1	8.5 ± 2.1	0.545	8.0 ± 2.4	7.9 ± 2.0	0.007
Number of comorbidities							
0	195 (8.6)	113 (8.2)	82 (9.3)	0.040	125.7 (8.8)	74.0 (8.5)	0.011
1	752 (33.0)	446 (32.0)	306 (34.5)	0.052	474.3 (33.3)	282.1 (32.4)	0.020
2	694 (30.4)	421 (30.2)	273 (30.8)	0.012	427.3 (30.0)	258.9 (29.8)	0.006
≥3	643 (28.2)	415 (29.8)	228 (25.7)	0.092	395 (27.8)	254.7 (29.3)	0.033
Upper GIB	1,700 (74.4)	1,081 (77.5)	619 (69.6)	0.179	1060.4 (74.6)	644.4 (74.1)	0.010
History/presence of varix	456 (20.0)	303 (21.8)	153 (17.3)	0.114	284.9 (20.0)	167.9 (19.3)	0.018

IPTW, inverse probability of treatment weighting. RBC, red blood cell. SMD, standardized mean difference. ED, emergency department. GIB, gastrointestinal bleeding.

clinical outcomes. Model 1 included sex, age, vital signs, Hb level, the number of RBC units transfused within 24 h, and comorbidities for adjustment. Model 2 included covariates included in Model 1 and additionally included the ED triage score, the history or presence of varices. For all Cox models, the proportional hazard assumption was verified by assessing the Schoenfeld residuals test.

The association between the time to transfusion and in-hospital mortality was measured using IPTW-adjusted multivariable logistic regression models adjusted for IPTW, and the adjusted odds ratio (OR) was described with a 95% CI.

The Chi-square test and Fisher's exact test were used to compare the frequencies of transfusion reactions. All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R 4.3.2, with p-values of <.05 considered statistically significant.

Results

Patient characteristics

A total of 2,284 patients were included in the final analysis. The mean time to transfusion was 245.5 ± 137.5 min. Of the study participants, 65.7% were female (1,501/2,284). The mean age was 65.3 ± 14.5 years. Based on the time to transfusion, patients were divided into two groups. To categorize the time to transfusion, a restrictive cubic spline model was utilized (Supplementary Figure 1). According to the model, a cutoff of 4 h was applied for categorization: the early transfusion group, with time to first RBC transfusion within 4 h (61.1%; 1,395/2,284), and the late transfusion group, with time to first RBC transfusion after 4 h (38.9%; 889/2,284). Variables, including time to transfusion, sex, age, vital signs, ED triage score, number of RBC units transfused, Hb levels, comorbidities, and history of varices detailed in Table 1 were balanced after IPTW with standardized mean difference < 0.1.

Time to transfusion and mortality

The association between the time to transfusion and 30-day mortality was analyzed. The multivariate adjusted Cox model showed that every 10-minute increase of time to transfusion was associated with an increased risk of 30-day mortality (Model 2 of Supplementary Table 1, HR 1.02, 95% CI 1.00–1.03, p = .005). The multivariate Cox models were used to assess the association between time to transfusion and 30-day mortality. The model also indicated that the late transfusion group was associated with a higher 30-day mortality (Model 2 of Supplementary Table 1,

Table 2. The association of early and late red blood cell transfusion with 30-day mortality evaluated by multivariate cox proportional hazard model after adjustment by inverse probability of treatment weighting.

	30 d mortality					
	Unadjusted		Model 1[a]		Model 2[b]	
Groups	Crude HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Early (≤4 hours)	Reference		Reference		Reference	
Late (>4 hours)	1.50 (1.10–2.06)	0.011	1.60 (1.15–2.22)	0.005	1.65 (1.17–2.32)	0.004

HR, Hazard ratio. CI, confidence interval.
[a]Model 1 included variates, systolic blood pressure, pulse rate, respiratory rate, oxygen saturation, number of units transfused and emergency department triage score, which were significant in univariate analysis.
[b]Model 2 included all pre-selected variates, age, gender, number of comorbidities, haemoglobin, upper gastrointestinal bleeding and presence/history of varix, with those included in model 1.

Table 3. The association of early and late red blood cell transfusion with in-hospital mortality evaluated by multivariate logistic regression model after adjustment by inverse probability of treatment weighting.

	In-hospital mortality					
	Unadjusted		Model 1[a]		Model 2[b]	
Groups	Crude OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*	Adjusted OR (95% CI)	*P*
Early (≤4 hours)	Reference		Reference		Reference	
Late (>4 hours)	1.55 (1.14–2.11)	0.005	1.66 (1.21–2.27)	0.005	1.71 (1.24–2.35)	<0.001

OR, Odds ratio. CI, confidence interval.
[a]Model 1 included variates, systolic blood pressure, pulse rate, respiratory rate, oxygen saturation, number of units transfused and emergency department triage score, which were significant in univariate analysis.
[b]Model 2 included all pre-selected variates, age, gender, number of comorbidities, haemoglobin, upper gastrointestinal bleeding and presence/history of varix, with those included in model 1.

HR, 1.60, 95% CI 1.16–2.21, p = .005). Similar results were observed when the association between time to transfusion and in-hospital mortality was examined. Both time to transfusion (Model 2 of Supplementary Table 2, OR 1.01, 95% CI 1.00–1.03, p = .028) and late transfusion (Model 2 of Supplementary Table 2, OR, 1.56, 95% CI 1.09–2.22, p = .014) were associated with a higher in-hospital mortality.

After the balancing of cohort by IPTW, the Cox analysis also indicated that the late transfusion group was associated with a higher 30-day mortality (Model 2 of Table 2, HR 1.65, 95% CI 1.17–2.32, p = .004). Results of multivariable logistic regression were presented in Table 3, which also showed the association between late transfusion and a higher risk of in-hospital mortality (Model 2 of Table 3, OR 1.71, 95% CI 1.24–2.35, p < .001).

The IPTW-adjusted Kaplan–Meier curve also showed that the late transfusion group has a higher risk of 30-day mortality compared to the early transfusion group (Figure 1).

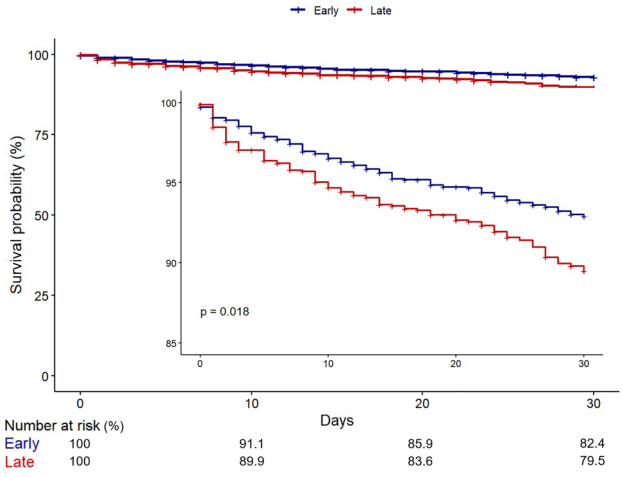

Figure 1. Inverse probability of treatment weighting-adjusted Kaplan–Meier survival curve for early vs late red blood cell transfusion for patients with gastrointestinal bleeding admitted to emergency department.

Subroup analysis

Further investigation was conducted to find whether there was a specific patient group that may benefit from early transfusion. Upon dividing the patient cohort based on the bleeding source, the association between time to transfusion and 30-day mortality was evident in the patients with upper GIB (Model 2 of Supplementary Table 3, HR 1.90, 95% CI 1.29–2.80, p = .001), while it was absent in patients with lower GIB (Model 2 of Supplementary Table 3, HR 0.94, 95% CI 0.43–2.06, p = .886) (Figure 2 and Supplementary Table 3). When the association between time to transfusion and in-hospital mortality was examined, a statistically significant association was observed only in patients with upper GIB (Model 2 of Supplementary Table 4, OR 1.86, 95% CI 1.29–2.69, p < .001), whereas no

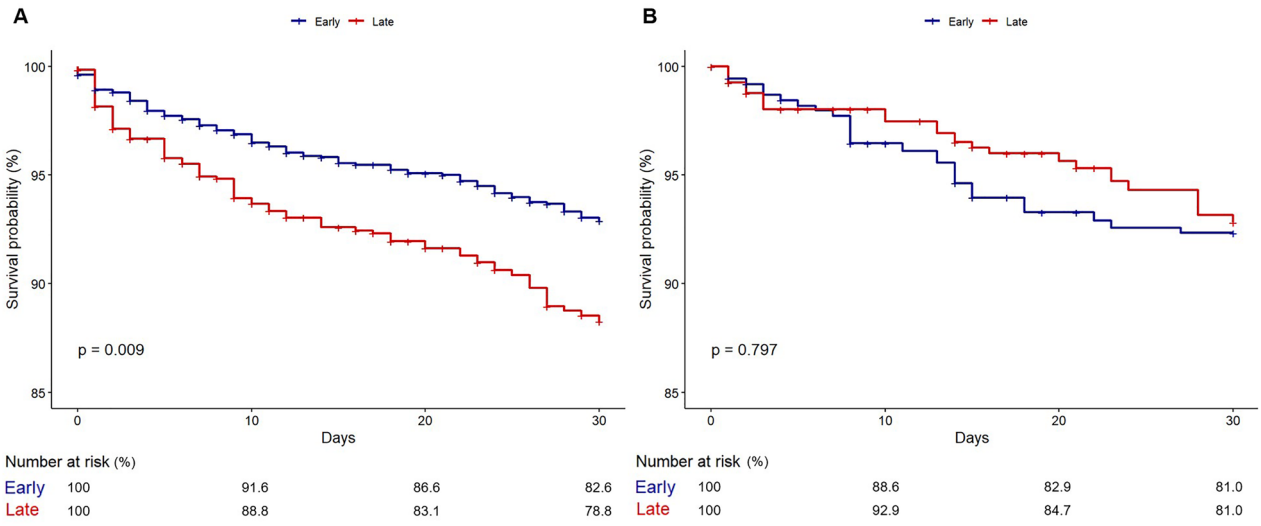

Figure 2. Inverse probability of treatment weighting-adjusted Kaplan–Meier survival curve for early vs late red blood cell transfusion for patients with (A) upper gastrointestinal bleeding (B) lower gastrointestinal bleeding admitted to emergency department.

Table 4. Length of stay, frequencies of transfusion reactions and 30-day red blood cell demand according to early and late red blood cell transfusion group.

Parameters	Early RBC transfusion, ≤4 h (n = 1,395)	Late RBC transfusion, >4 h (n = 889)	P
Length of stay, day	10.3 ± 14.4	9.8 ± 13.4	0.434
Transfusion reactions	9 (0.6)	12 (1.3)	0.135
Febrile non-haemolytic transfusion reaction	6 (0.4)	8 (0.9)	0.260
Allergic reaction	3 (0.2)	4 (0.4)	0.442
30-day RBC transfusion demand, units	4.3 ± 4.2	3.5 ± 4.3	<0.001

RBC, red blood cell.

significant association was found in patients with lower GIB (Model 2 of Supplementary Table 4, OR 1.04, 95% CI 0.53–2.03, $p = 0.913$).

Further analysis explored whether the impact of time to transfusion on patient outcomes varied by the cause of upper GIB, distinguishing between variceal and nonvariceal bleeding. A significant association was found only in patients with nonvariceal upper GIB, with late transfusion being associated with an increased risk of both 30-day mortality (Model 2 of Supplementary Table 5, HR 2.12, 95% CI 1.41–3.19, $p < 0.001$) and in-hospital mortality (Model 2 of Supplementary Table 6, OR 2.19, 95% CI 1.48–3.24, $p < 0.001$). In contrast, no significant association was observed in patients with variceal bleeding for either 30-day mortality (Model 2 of Supplementary Table 5, HR 0.58, 95% CI 0.17–2.04, $p = 0.398$) or in-hospital mortality (Model 2 of Supplementary Table 6, OR 0.46, 95% CI 0.09–1.64, $p = 0.269$).

Next, another subgroup analysis using various Hb cutoffs was conducted to identify patient groups that might benefit from early transfusion based on their Hb levels. The patients were divided into two groups according to various Hb levels and the association between time to transfusion and 30-day mortality was analyzed (Supplementary Figure 2). When a cutoff of 7 g/dL was used, late transfusion was associated with a higher risk of 30-day mortality in both groups (Hb ≥ 7 g/dL and < 7 g/dL). However, with higher Hb cutoffs (7.5, 8, and 9 g/dL), this association was observed only in patients with haemoglobin below each cutoff, which suggested that the optimal haemoglobin cut-off for the beneficial effect of early transfusion may lie between 7 and 7.5 g/dL.

Time to transfusion and other clinical outcomes

For the patients included in this study, the association of time to transfusion with other clinical outcomes other than mortality was evaluated (Table 4). There was no difference in length of stay according to time to transfusion group. The occurrence of adverse transfusion reactions according to the time of transfusion groups was also investigated. Of the 2,284 cases, we identified 21 with transfusion reactions, representing 0.9% of the total cases. The total number of transfusion reactions and the incidence of specific reactions, such as febrile non-haemolytic transfusion reactions and allergic reactions, showed no significant differences between the early and late transfusion groups. There were no cases of other severe transfusion reactions, including haemolytic transfusion reactions,

transfusion-related acute lung injury, transfusion-associated circulatory overload, or other fatal transfusion-related consequences. 30-day RBC transfusion demand was higher in early transfusion group, compared to late transfusion group.

Discussion

In this study, we investigated the association between time to transfusion and both 30-day and in-hospital mortality in patients who presented to the ED with GIB. Late transfusion was associated with a higher risk of both outcomes, with a more pronounced effect in patients with upper GIB, nonvariceal bleeding and a lower haemoglobin level.

Although it is thought that rapid evaluation and proper management should be initiated once patients with GIB arrive, current transfusion guidelines only suggest an Hb threshold for RBC transfusion [8]. Several well-established studies have revealed that a restrictive transfusion strategy (Hb threshold for RBC transfusion <7–8 g/dL) exhibited no inferior outcomes when compared with a liberal transfusion strategy (Hb threshold for RBC transfusion <9–10 g/dL) [11–13]; however, whether the time to RBC transfusion for patients with GIB is associated with the clinical outcomes has not been sufficiently assessed. In previous studies, the effect of early transfusion in patients with GIB was investigated [15,16]; however, those studies compared patients who did not receive a transfusion with those who received an early transfusion. In the present study, we focused on the timing of transfusion by comparing the effects of early versus late transfusion among patients who were transfused.

The concept that early transfusion may improve outcomes was originally assessed in patients with trauma. It has been assumed that early transfusion is beneficial [17], and some studies have demonstrated the efficacy of early transfusion. A study evaluating the value of prehospital blood transfusion for those with severe trauma reported significantly lower mortality in the prehospital blood transfusion group than in the control group, who did not receive such transfusions [18]. The advantages of prehospital early transfusion were also proven in another study that compared the mortality between those who received a prehospital transfusion and those who did not, where prehospital transfusion improved both 24-hour and 30-day mortality [19]. As well as improved survival, a further study reported that prehospital RBC transfusion was associated with a decreased risk of shock and 24-hour RBC requirement [20]. Other studies, however, did not show the efficacy of prehospital early transfusion [21,22].

In this study, the association of early RBC transfusion was evaluated in patients who presented to the ED with GIB. The results of this study demonstrated that early RBC transfusion was associated with improved outcomes in patients with GIB. Notably, the improved mortality was exclusively observed in patients with upper GIB and a low Hb level. The fact that only certain patients with GIB can benefit from early RBC transfusion is an important consideration for ED physicians when considering transfusion. These findings encourage ED physicians to promptly consider RBC transfusion for GIB patients with the factors above while also emphasizing the need for careful consideration when making RBC transfusion decisions for patients with lower GIB and a high Hb level.

The underlying mechanism of the observed benefit of early transfusion in patients with upper GIB and a low Hb level is unclear. It can be inferred from the results that those patients might be more prone to anaemia or hypovolemic status, which requires rapid recovery of that status with RBC transfusion. An earlier study regarding patients with upper GIB emphasized the potential benefit of early intervention in those patients [23], which is consistent with the result of the present study. Regarding the differences of the association of early RBC transfusion and patient outcome based on the Hb level, our result that showed the need of early initiation of RBC transfusion in patients with a lower Hb level, is aligned with previous findings supporting the appropriateness of restrictive transfusion strategy [11–13].

Among upper GIB, variceal bleeding has a distinct pathophysiology compared to nonvariceal bleeding [24]. The results of this study showed that the association between time to transfusion and patient outcomes was observed only in patients with nonvariceal bleeding, whereas this association was not seen in those with variceal bleeding. These findings align with previous understanding, which recommends minimizing unnecessary transfusions to prevent worsening variceal bleeding by increasing portal pressure [25]. Although upper GIB can indicate the need for prompt transfusion, the decision to transfusion should differ according to the cause of bleeding.

In this study, in addition to analyzing the association of time to transfusion on patient outcomes, its association with related clinical aspects was evaluated. Although further RBC transfusion requirement was significantly higher in the early transfusion group, early transfusions did not lead to prolonged length of stay, a higher rate of additional transfusion reactions, or a

higher incidence of severe transfusion-related adverse events than those of late transfusions. These results suggest that transfusions can be promptly initiated in patients who need them without increasing the length of stay or the risk of adverse transfusion reactions. This implies that the timing of transfusion, especially early intervention, can be managed more flexibly without compromising patient safety.

This study had several limitations. First, this was a retrospective study that used data from a single-centre ED. Nevertheless, it is important to highlight that despite the single-centre design, a large number of patients were included in the analysis, which enhanced the generalizability of our findings. Second, although major factors related to the outcomes were included in the analysis, other confounders may have biased the results. Third, transfusion of other blood components was not considered in this study. Specifically, there have been reports indicating an association between plasma transfusion and patient outcomes in bleeding cases, suggesting potential clinical significance. However, this aspect was not included in our study and warrants further investigation in future research endeavours [26,27]. Finally, the underlying mechanism behind the association between time to transfusion and patient outcomes could not be determined in this study. As this study only identified an association between time to transfusion and patient outcomes, further definitive studies are needed to clarify the causative role of transfusion delay in patient outcomes.

Conclusions

Our study identified an association between delayed blood transfusion and increased risks of 30-day mortality and in-hospital mortality, especially in patients with upper GIB, nonvariceal bleeding and haemoglobin levels below 7.5 g/dL. This helps emergency department physicians make decisions about who and when to perform blood transfusions, an important part of the management of patients with GIB, and contributes to the effective use of RBC, a limited resource.

Acknowledgments

SCJ, YKK, SSK, and JM conceptualized and designed this study. SJC and YKK conducted an investigation process, drafted the manuscript. SSK and JM designed the research methodology and performed data collection, analyzation, and visualization. SSK and JM reviewed & edited the manuscript. SK, HSC and IP supervised and managed the project and validated this study. All authors read and approved the final version of the manuscript.

Author contributions

CRediT: **Sol Ji Choi**: Conceptualization, Investigation, Writing – original draft; **Yu-Kyung Koo**: Conceptualization, Investigation, Writing – original draft; **Sinyoung Kim**: Funding acquisition, Supervision, Validation, Writing – review & editing; **Hyun Soo Chung**: Supervision, Validation, Writing – review & editing; **Incheol Park**: Supervision, Validation, Writing – review & editing; **Soon Sung Kwon**: Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – review & editing; **Jinwoo Myung**: Conceptualization, Data curation, Investigation, Methodology, Visualization, Writing – review & editing.

Disclosure statement

The authors declare that they have no competing interests.

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Data availability statement

De-identified patient data are available from the corresponding author upon reasonable request.

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