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ORIGINAL ARTICLE

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Effects of transfusing older red blood cells on patient outcomes in critical illness: A retrospective cohort study

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Abstract

Background and Objectives: Randomized controlled trials have demonstrated morbidity and mortality in critically ill patients are unaffected by transfusing fresh (<7 days old) packed red blood cells (pRBCs); however, there is limited evidence regarding transfusion with pRBCs nearing expiry (35–42 days). The aim of this study was to investigate the effects of transfusing pRBCs close to the end of shelf life (≥35 days) on clinical outcomes in critically ill patients.

Materials and Methods: A retrospective observational analysis of data obtained from centralized electronic medical records (2007–2013), sourced from all public and licensed private hospitals in Queensland, Australia, with intensive care units. Multivariate logistic and linear regressions were used to analyse association between

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transfusion with pRBCs nearing expiry, and in-hospital mortality, hospital length of stay (HLOS) and rate of discharge home. Comparisons are presented as odds ratios (ORs) with 95% confidence intervals (CIs).

Results: The study included 10,350 critically ill adult patients transfused ≥1 unit of non-irradiated pRBCs (64,594 pRBCs units transfused). Receiving at least 1-unit pRBCs ≥ 35 days old was associated with increased mortality (OR 1.21 [95% CI 1.06–1.38]; $p = 0.005$), decreased discharge to usual residence (OR 0.81 [95% CI 0.73–0.89]; $p < 0.0001$) and increased hospital LOS (estimate 2.55 [95% CI 1.60–3.49]; $p < 0.0001$). There was also association with increased sepsis (OR 1.27 [95% CI 1.13–1.42]; $p < 0.0001$) and delirium (OR 1.25 [95% CI 1.06–1.49]; $p = 0.01$).

Conclusion: Transfusion of ≥1-unit pRBCs ≥ 35 days old was associated with higher morbidity and mortality in critically ill patients.

Keywords

critical illness, emergency medicine, intensive care, transfusion

Highlights

- There is limited evidence in the literature on the effects of transfusing packed red blood cells (pRBCs) that are closer to the end of shelf life (35–42 days) on clinical outcomes in critically ill patients.
- We found that transfusion of at least one or more units of pRBCs close to expiry (35–42 days old) was associated with an increased risk of morbidity and mortality among critically ill patients.
- Critically ill patients are at higher risk of poorer clinical outcomes, are more likely to require blood transfusion and are likely to receive more blood products overall during their treatment. Prospective research will be required to assess the causality of the association between poorer clinical outcomes in critically ill patients receiving pRBCs between 35 and 42 days old.

INTRODUCTION

The shelf life of packed red blood cells (pRBCs) for transfusion ranges from 21 to 49 days, depending on jurisdiction [1–3]. During storage, numerous metabolic and structural changes, referred to as 'storage lesions', occur within pRBCs [1, 4]. In vitro studies have consistently demonstrated that these changes initially appear after the first 14–21 days of storage [5]. Some of these changes are reversible, such as reduced adenosine triphosphate (ATP) and 2,3-diphosphoglycerate (2,3-DPG) levels occurring from 14 days following storage [5, 6]. However, irreversible changes, including protein oxidation, aggregation and degradation, and changes to red blood cell (RBC) morphology, arise after approximately 28 days of storage [5–7]. There is limited evidence for the consequences of transfusing pRBCs older than 28 days [8–10]. Thus, the clinical significance of irreversible aspects of the pRBC storage lesion remains unclear. Furthermore, reversibility of initial storage lesions following transfusion may still be inadequate to meet the increased physiological demands of critically ill patients [5, 6].

A 2018 meta-analysis by Rygard et al. [11] identified seven randomized controlled trials (RCTs) that investigated the effect of pRBC storage duration on outcomes in critically ill adult patients [12–18]. While this meta-analysis concluded that patient morbidity and mortality were unaffected by pRBC storage duration, each of these RCTs only compared 'fresher' pRBC with either 'standard-issue pRBC', 'oldest available pRBC', or with pRBC stored for longer than 15–20 days, without specific consideration for pRBCs towards the end of their shelf life [12–18]. Thus, while these studies indicated that critically ill patients did not benefit from receiving fresher pRBCs, it remains unclear whether these patients might be harmed by receiving pRBCs nearing expiry.

Recent retrospective evidence suggests patient safety may be improved by reducing the shelf life of pRBCs to 35 days [1, 8]. However, it is difficult to compare evidence supporting this recommendation, due to heterogenous methods to categorize the age of pRBCs. Published methodology includes analysing the mean age of product received [4, 11], and including patients who exclusively received products within a defined age range [10, 19]. These methods do not consider the effect of individual units of pRBCs and are not representative of how blood products are allocated in a hospital setting. In a 2011 prospective observational study, Pettila et al. [20] grouped critically ill patients by the oldest RBCs transfused and reported increased mortality risk in critically ill patients receiving at least one unit of pRBCs nearing expiry.

We hypothesized that transfusion with any RBCs within the final week of shelf life (i.e., 35–42 days) [21] may predispose to transfusion-related mortality and morbidity. Therefore, the aim of this study was to investigate the effects of transfusing at least 1 unit of pRBCs ≥ 35 versus <35 days old on clinical outcomes in critically ill patients, and whether reducing pRBC shelf life to <35 days would improve transfusion safety.

MATERIALS AND METHODS

This was a retrospective cohort study conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational cohort studies [22] (Supplement 1). Records of all blood products transfused in public and private hospitals in the Australian state of Queensland from 2007 to 2013 were accessed from the Queensland Hospital Admitted Patient Data Collection (QHAPDC), AUSLAB (the pathology and forensic laboratory system for Queensland Health) and International Classification of Diseases (ICD) code databases (Table S8). The QHAPDC database provides information about a patient's 'mode of separation' from hospital, their length of stay and major diagnostic category (MDC). Data were linked to individual patient admissions, with one entry per blood product transfused; thus, the unit of analysis was an admission event. These data were condensed to summarize all products that patients were transfused within a given admission.

The age of pRBC units was calculated as the difference between the date of blood donation and the date on which the product was released from the laboratory, as recorded on AUSLAB. Where the AUSLAB date was missing ($n = 36{,}433$; 5.0%), the date the transfusion was marked as administered by the ward was used instead.

A total of 167,303 patients were present in the QHAPDC dataset. Patients who did not receive pRBC transfusion were excluded, as were those who received ≥1-unit irradiated pRBCs, as irradiated pRBCs expire at 28 days (Figure 1).

Standardized paediatric terminology in healthcare defines children as ≤12 years old [23] hence, only adults were included, defined as patients ≥13 years old. Critically ill patients were defined as those who received ≥1 transfusion of either pRBCs, plasma, platelets or cryoprecipitate while admitted in intensive care unit (ICU). Patients who received pRBC > 42 days old were excluded, as these are considered expired units. The Age of Blood Evaluation (ABLE) and the Standard Issue Transfusion versus Fresher Red-Cell Use in Intensive Care (TRANSFUSE) RCTs both investigated patients to 180-day follow-up [12, 13]; we extended this to patients who had a hospital length of stay (HLOS) up to 1 year, excluding patients who were admitted >365 days. These patients were identified by an admission episode identification number. Readmissions were considered as a new patient entry.

Patients' admission events were separated into two groups: those who received ≥1-unit pRBCs that were ≥35 days old ($n = 2521$ admission events) those who received exclusively pRBCs < 35 days old ($n = 7829$ admission events).

In-hospital mortality was a key outcome investigated, determined by the mode of separation. The QHAPDC database did not link patients who were transferred between hospitals or to other care facilities, which could lead to under-reporting of mortality. Thus, the rate of discharge home was also investigated as a marker of a positive patient outcome, as was HLOS. Comorbid outcomes of sepsis, thrombotic events, cardiac ischaemia and delirium were investigated. These comorbidities were included based on evidence that storage lesions in transfused pRBCs can predispose to increased infection, hypercoagulability and impaired tissue oxygenation [6]. Comorbidity data were sourced from the ICD code database and linked to patient identifiers on the QHAPDC database. Categorization of ICD codes is listed in Supplement 2. A summary of the ABO-blood group frequencies is presented in Table S9.

Statistical analyses

For each outcome, univariate analysis was conducted. Independent variables included in univariate analysis were exclusively pRBCs < 35 days old, age, sex, year of transfusion, HLOS, number of pRBCs transfused, number of plasma products transfused, number of platelet products transfused, number of cryoprecipitate units transfused, sepsis, thrombotic events, cardiac ischaemia and delirium. In-hospital mortality and rate of discharge home were also included as independent variables for HLOS.

All variables that were included in univariate analysis were also included in multivariate analysis, irrespective of whether these variables displayed statistical significance and Bonferroni correction was performed for multiple comparisons. Logistic regression models were used for all outcomes, with the exception of HLOS, for which a linear regression model was used.

Statistical analysis was conducted using STATA SE 17.0. Results were reported using odds ratios (ORs) or regression coefficients with 95% confidence intervals (CIs). Statistical significance was defined with an alpha level of 0.05.

Ethics statement

Access to confidential health information for the period 1 January 2007 to 31 June 2013 was approved by the Queensland Health Central Office Human Research Ethics Committee (HREC/15/QPCH/31). In accordance with the requirements of the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research 2007, sections 2.3.6–2.3.8, the HREC waived the requirement for consent for the collection, use and/or disclosure of personal information in medical research or personal health information for the research project listed.

RESULTS

Between January 2007 and December 2013, 149,635 patients were transfused a total of 494,090 pRBC units. A total of 10,350 patients'

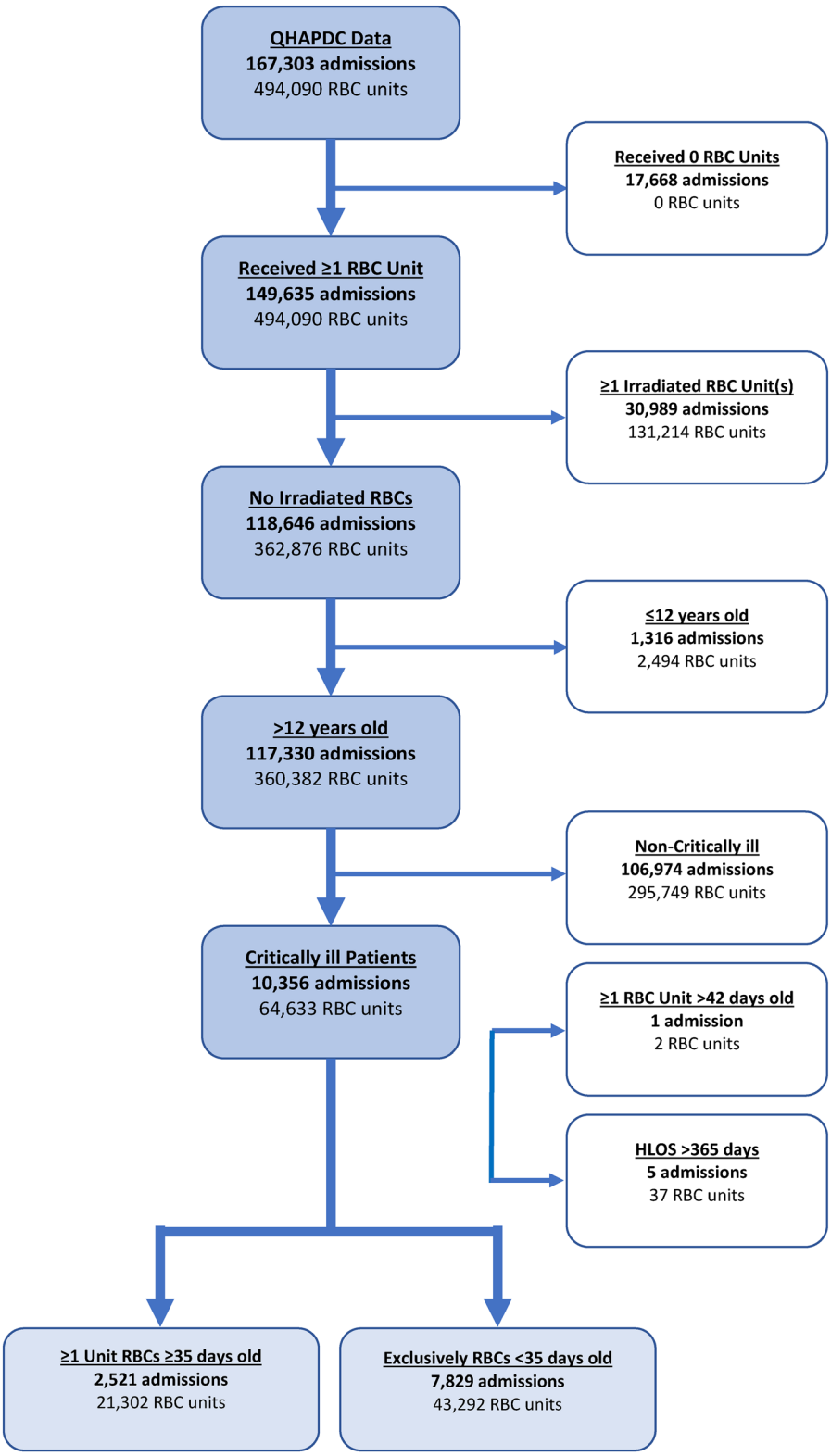

FIGURE 1 Flow diagram representing the exclusion of the admission events from the initial Queensland Hospital Admitted Patient Data Collection (QHAPDC) database, and the methods of categorizing critically ill patient admission events for analyses. HLOS, hospital length of stay; RBC, red blood cell.

admission events were included in our analysis, receiving a total of 64,594 units of pRBCs. These patient admission events were separated for analysis into those who received ≥1 unit of pRBC that was ≥35 days old ($n = 2521$ admission events), and those who were transfused pRBCs exclusively <35 days old ($n = 7829$ admission events) (as shown in Figure 1).

TABLE 1 Baseline characteristics, transfusions and outcomes of critically ill patients transfused packed red blood cells exclusively <35 days old, compared to critically ill patients who received ≥1 unit of packed red blood cell that was ≥35 days old.

Characteristics	≥1-unit pRBC ≥ 35 days old ($n = 2521$ patient admission events)	Exclusively pRBCs < 35 days old ($n = 7829$ patient admission events)	p-value[d]
Age (years)[a]	63 (49–74)	64 (50–75)	**0.03**
Female sex[b]	998 (39.6)	3206 (40.9)	0.23
No. of pRBC units transfused per patient[c]	6.5 ± 7.2	3.3 ± 2.8	**<0.0001**
Cost of total pRBCs (AUD, 2013)[a]	1826 (953.9–3471.6)	1199.8 (694.3–2192.0)	**<0.0001**
HLOS (days)[a,e]	22 (11–40)	16 (9–28)	**<0.0001**
In-hospital mortality[b]	461 (18.3)	1252 (16.0)	**0.008**
Discharged home to usual residence[b]	1120 (44.4)	4198 (53.6)	**<0.0001**
Morbid outcomes[b]			
Sepsis	650 (25.8)	1419 (18.1)	**<0.0001**
Thrombotic	275 (10.9)	631 (8.1)	**<0.0001**
Cardiac ischaemia	314 (12.4)	908 (11.6)	0.26
Delirium	228 (9.0)	485 (6.2)	**<0.0001**

Note: Satistical significance was defined as an alpha level of <0.05 (in bold).
Abbreviations: HLOS, hospital length of stay; IQR, inter-quartile range; pRBCs, packed red blood cells.
[a]Median (IQR); statistical analysis using Mann–Whitney non-parametric test.
[b]*n* (%); statistical analysis using Fisher's exact test.
[c]Mean (SD); statistical analysis using Student's *t* test.
[d]Comparison of patients who received exclusively pRBCs < 35 days old with patients who received ≥1-unit pRBC ≥ 35 days old.
[e]Excludes patients who died in hospital.

Baseline characteristics for these two groups were compared (Table 1).

Frequency distribution of pRBC ages between groups was significantly different ($p < 0.05$), as illustrated in Figure 2.

Patients were comparable in age (64 vs. 63 years; $p = 0.03$) and were as likely to be male as female ($p = 0.23$). Patients who received ≥1 unit of pRBCs that was ≥35 days old received more pRBC units compared with patients exclusively transfused with pRBCs < 35 days old (6 vs. 4 units; $p < 0.0001$). This was associated with a higher median pRBC transfusion cost per patient ($1826 vs. $1200; $p < 0.0001$).

In univariate modelling, receiving ≥1 unit of pRBC that was ≥35 days old was a predictor of increased mortality (OR 1.17 [95% CI 1.04–1.32]; $p = 0.007$), decreased likelihood of discharge to patient's usual residence (OR 0.69 [95% CI 0.63–0.76]; $p < 0.0001$) and increased HLOS (estimate 6.87 [95% CI 5.81–7.93]; $p < 0.0001$). Patients who received ≥1 unit of pRBC that was ≥35 days old were also more likely to experience comorbid sepsis (OR 1.56 [95% CI 1.41–1.74]; $p < 0.0001$), thrombosis (OR 1.39 [95% CI 1.20–1.62]; $p < 0.0001$) or delirium (OR 1.50 [95% CI 1.28–1.77]; $p < 0.0001$).

In a multivariate model containing all patients (Table 2), patients receiving ≥1 unit of pRBC that was ≥35 days old experienced increased mortality (OR 1.21 [95% CI 1.06–1.38]; $p = 0.005$).

Receiving ≥1 unit of pRBC that was ≥35 days old was associated with decreased discharge to a patient's usual residence (OR 0.81 [95% CI 0.73–0.89]; $p < 0.0001$) and increased HLOS (estimate 2.55 [95% CI 1.60–3.49]; $p < 0.0001$). Multivariate analysis of comorbid outcomes found increased rates of sepsis (OR 1.27 [95% CI 1.13–1.42]; $p < 0.0001$) and delirium (OR 1.25 [95% CI 1.06–1.49]; $p = 0.01$) in patients transfused ≥1 unit of pRBC that was ≥35 days old. A summary of the univariate and multivariate analysis is shown in Supplement 3. Figure 3 shows the cumulative hazard of adverse events occurring. The total time at risk is 238,740 patient-days with an incident rate of 0.02 adverse events. The median time to adverse event is 39 h (inter-quartile range [IQR] 22–64 h) per transfusion event that is associated with an adverse event occurrence.

DISCUSSION

There is limited evidence for the effect of transfusing critically ill patients with pRBCs close to the end of shelf life. This study represents the largest retrospective analysis of the effect of transfusing these older pRBCs in critical care patients. Using a robust database analysis, this study demonstrated transfusion of pRBCs nearing expiry (≥35 days) could be associated with more comorbidities and less favourable patient outcomes in critical illness.

The ABLE trial [12] defined 'fresh blood' as exclusively ≤7 days old, and subsequent retrospective analyses only included patients who received pRBCs entirely from within set thresholds (e.g., ≥28 days old) [8, 10, 19]. Such exclusive age brackets are not representative of the manner in which blood products are allocated in hospital settings and thus, results from such sub-group analysis do not entirely reflect patient outcomes in a clinical setting. Our study addressed this issue by comparing patients who received pRBCs exclusively <35 days old to those transfused at least 1 unit of pRBCs ≥ 35 days old. These results indicated patients receiving pRBCs nearing expiry experienced increased rates of in-hospital mortality and lengths of hospital stay, were less frequently discharged to their usual residence and experienced increased

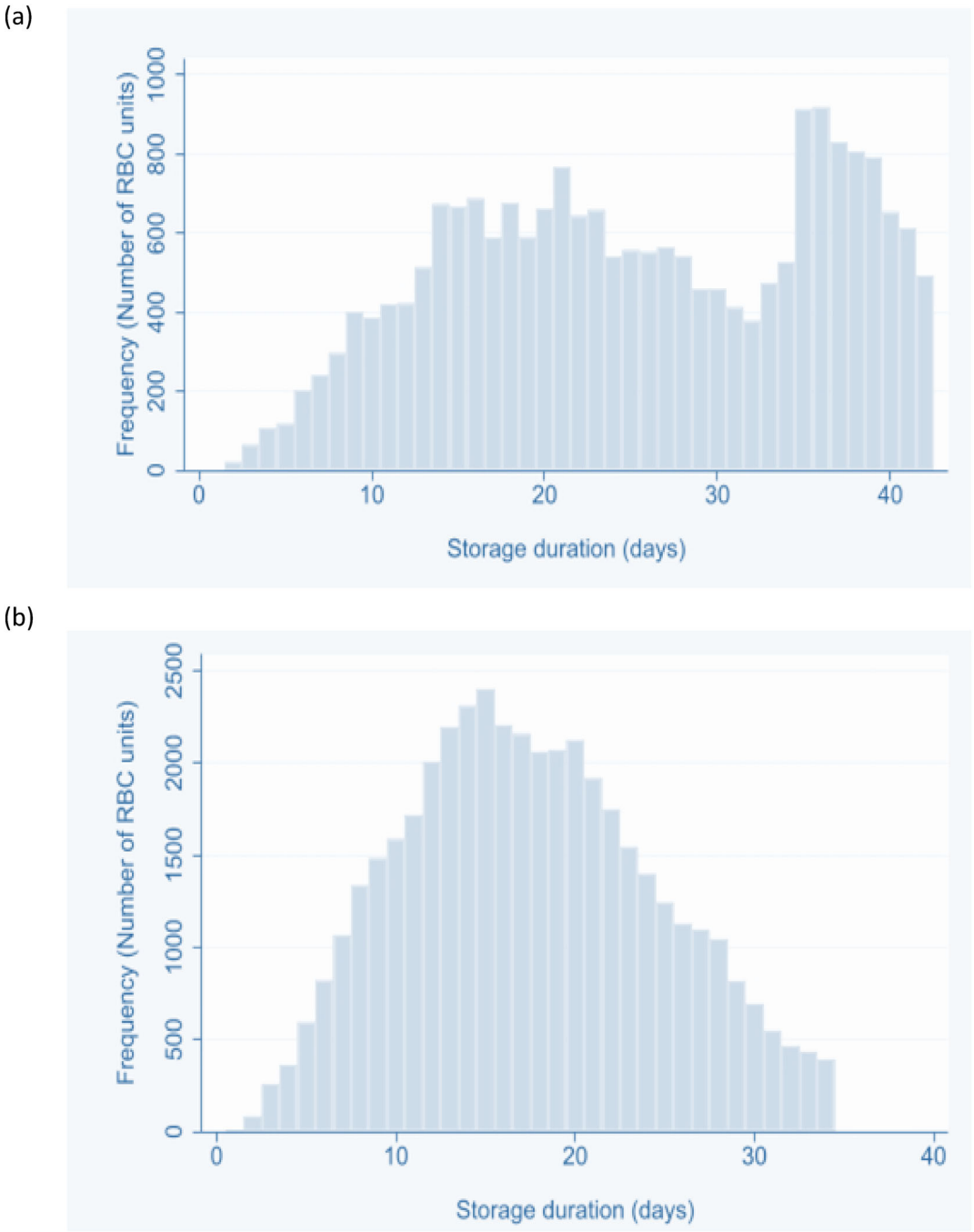

FIGURE 2 Frequency distribution of packed red blood cell (pRBC) age for (a) patients who received ≥1-unit pRBC ≥ 35 days old ($n = 2521$; median 38 days, inter-quartile range [IQR] 36.0–39.4); and (b) patients who exclusively received pRBCs < 35 days old ($n = 7829$; median 20 days, IQR 14.8–25.1). The difference between the groups is significant at $p < 0.05$.

rates of comorbid outcomes. This suggests that the outcomes of critically ill patients could be improved if the expiry date of pRBCs was reduced to 35 days for this cohort. A confounding issue in these results was the fact that patients who received at least 1 unit of pRBCs ≥ 35 days received more units of pRBC per patient. This could indicate that poorer patient outcomes were due to the severity of illness, the absolute number of pRBCs transfused, or more transfusions, rather than as a consequence of the age of the pRBCs. However, exclusively receiving pRBCs < 35 days old was still found to be an independent predictor of reduced mortality and morbidity even when multivariate analysis adjusted for the number of pRBCs units transfused.

It is possible that these results are the clinical manifestation of irreversible storage lesions seen in vitro in pRBCs at the end of their shelf life, which are likely exacerbated in a critically ill patient cohort where physiological demand is increased. The protein degradation and metabolite depletion observed in pRBCs beyond 28 days of

TABLE 2 Odds ratios of critically ill patients who received ≥1 unit of packed red blood cell that was ≥35 days old, compared to critically ill patients transfused packed red blood cells exclusively <35 days old, as a predictor of morbidity and mortality.

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*p*-value	Odds ratio	95% CI	*p*-value
In-hospital mortality[a]	1.17	1.04–1.32	**0.007**	1.21	1.06–1.38	**0.005**
Discharged home to usual residence[a]	0.69	0.63–0.76	**<0.0001**	0.81	0.73–0.89	**<0.0001**
HLOS[b]	6.87	5.81–7.93	**<0.0001**	2.55	1.60–3.49	**<0.0001**
Morbid outcomes[a]						
Sepsis	1.56	1.41–1.74	**<0.0001**	1.27	1.13–1.42	**<0.0001**
Thrombotic	1.39	1.20–1.62	**<0.0001**	1.12	0.95–1.31	0.17
Cardiac ischaemia	1.08	0.95–1.24	0.25	1.01	0.88–1.16	0.91
Delirium	1.51	1.28–1.77	**<0.0001**	1.25	1.06–1.49	**0.01**

Note: *p* value <0.05 considered as significant. Satistical significance was defined as an alpha level of <0.05 (in bold).
Abbreviations: CI, confidence interval; HLOS, hospital length of stay.
[a]Logistic regression used for dependent variables with binary outcomes.
[b]Linear regression used for hospital length of stay as a continuous variable, coefficients reported in the columns for odds ratio and 95% CI.

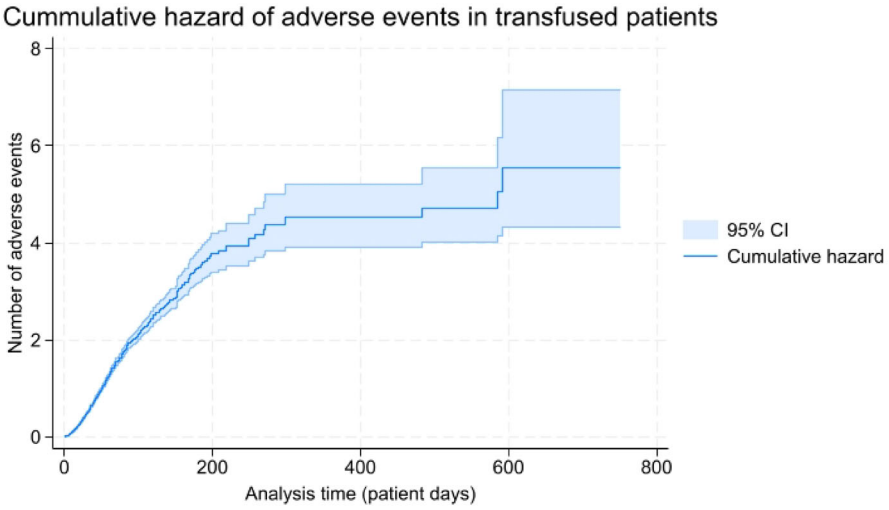

FIGURE 3 Cumulative hazard of adverse events occurring. The total time at risk is 238,740 patient-days with an incident rate of 0.02 adverse events and a median time to adverse event of 39 h (interquartile range 22–64 h). CI, confidence interval.

storage can potentially cause endovascular haemolysis, insufficient nitrous oxide bioavailability (INOBA) and, hence, vasoconstriction [5, 6, 24]. Decreased oxygen transport and impaired perfusion would have multi-system effects, such as increased likelihood of delirium secondary to impaired brain perfusion, as was observed in our results. A further consequence of endovascular haemolysis due to transfusion of pRBCs with irreversible storage lesions is iron overload, which is associated with reduced tolerance to infection and subsequently predisposes to increased likelihood of sepsis [6, 25]. This is consistent with the results of this study, in which there was an association between receiving ≥1 unit of pRBC that was ≥35 days old and increased rates of sepsis.

RCTs have demonstrated critically ill patients do not benefit from receiving the freshest available blood [12, 13, 17, 26], and ensuing retrospective analyses have investigated whether patients are harmed by receiving the oldest pRBCs at the end of their shelf life (≥35 days old). Goel et al. compared patients exclusively receiving blood ≤21 days old to those who only transfused blood ≥28 days old and ≥35 days old [8]. Their results demonstrated that patients exclusively receiving blood ≥35 days old had increased morbidity as compared to patients only given blood ≤21 days old, and that mortality was also increased in a sub-group of critically ill patients. Our results furthered those of Goel et al., demonstrating that increased morbidity and mortality were not just associated with receiving entirely pRBCs ≥ 35 days old, but also with transfusion of as little as one older pRBC unit. This is much more pragmatic in clinical settings, where patients receive pRBCs dispensed from blood banks based on a first-in first-out basis to prevent wastage of blood products without necessarily separating the products into discrete groups.

Similarly, a pooled patient data analysis by Ng et al. in 2018 examined over 14,000 patients and found an association between

pRBCs > 30 days old and greater in-hospital mortality risk [1]. Contrary to our results, no association was observed between older pRBCs and increased HLOS or increased morbidity, which could be due to two reasons. First, the 2018 study included all patients receiving transfusions and was not specific to critically ill patients. It is possible that the harmful clinical consequences of older pRBCs could be exaggerated in critical illness given limited compensatory reserve. Second, the 2018 study compared the mean age of pRBCs and did not consider the potential harmful effects of receiving a single unit of older pRBCs. Our comparison of patients who received at least 1 unit of pRBCs ≥ 35 days old, regardless of other products received, allowed a more accurate representation of the effect of receiving pRBC units nearing expiry, and could explain the additional association seen between older pRBCs and increased morbidity.

The limitations of this study included the retrospective design, which limited our ability to define a clear cause and effect between older pRBCs and poorer patient outcomes. A lack of longitudinal follow-up of patients and no sequential information about the timing of comorbid events during the course of admission further restrict our results to recognizing association only. The database identified patients with codes unique to a single admission only, preventing us from identifying patients who required additional transfusion in future admissions; hence, readmissions were considered as a new patient entry and as such some patients included in the <35-day old group may have received a pRBC transfusion nearing expiry in a previous admission, thereby diluting the observed harm. Additional information to define the extent of critical illness, such as a patient's Acute Physiology And Chronic Health Evaluation II (APACHE II) score, was also not recorded in the database, meaning that disease severity may have confounded comparison. While the standard practice is to store blood for up to 42 days, we acknowledge that the comparison of transfused blood <35 days old versus blood ≥35 days old does not represent common categories and can be confounded by the number of transfusions, especially in cases where patients require multiple transfusions and are more likely to receive blood ≥35 days. This limitation is consistent with findings reported by Edgren et al. [27].

In conclusion, this retrospective analysis showed an association between the transfusion of pRBCs close to the end of shelf life with adverse clinical outcomes in critically ill patients. This association was present regardless of whether the patient received exclusively older pRBCs or only a single unit of older pRBCs. Therefore, critically ill patients may have better clinical outcomes if transfusions are restricted to pRBC units <35 days old. Prospective clinical studies could further explore this association and elucidate its implications on clinical outcomes.

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N.G.O., D.P.S., M.T., L.E.S.H., G.L.B., J.P.F., J.-P.T., J.Y.S. and J.F.F. conceived and designed the study. N.G.O., D.P.S., M.T. and B.S. collected the data, and N.G.O., D.P.S., N.W. and L.E.S.H. analysed them. N.G.O., D.P.S., N.W., L.E.S.H., G.L.B., J.P.F., J.-P.T., J.Y.S. and J.F.F. interpreted the data. N.G.O. and D.P.S. prepared the figures and tables. N.G.O. and D.P.S. drafted the original manuscript, while N.G.O., D.P.S., N.W., M.T., B.S., R.H.R., L.E.S.H., G.L.B., J.P.F., J.-P.T., J.Y.S. and J.F.F. reviewed, edited and interpreted it. N.G.O., D.P.S., N.W., M.T., B.S., R.H.R., L.E.S.H., G.L.B., J.P.F., J.-P.T., J.Y.S. and J.F.F. gave final approval for submission. Open access publishing facilitated by The University of Queensland, as part of the Wiley - The University of Queensland agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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