

Lower hemoglobin transfusion trigger is associated with higher mortality in patients hospitalized with pneumonia

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Abstract

Patients hospitalized with pneumonia may require packed red blood cell (RBC) transfusion during their hospital stay. Patient survival may be associated with the transfusion trigger. These patients may need a higher hemoglobin (Hb) trigger than that suggested by the AABB guidelines (7 g/dL).

The objective of this study was to evaluate the association between the initial transfusion Hb trigger and in-hospital mortality.

A historical cohort study of all patients hospitalized in an internal medicine ward between 2009 and 2014 with pneumonia, who received at least 1 unit of RBC, was evaluated. The primary outcome was all-cause in-hospital mortality.

One hundred males and 77 females with a median age of 80 (interquartile range 71–87) years were included. The median Hb trigger was 8.10 g/dL. Mortality rate was 56% in patients with Hb trigger ≤ 7 g/dL, 43.8% in Hb trigger 7 to 8 g/dL, and 29.5% in Hb trigger > 8 g/dL ($P = .045$). Patients in the 3 Hb trigger categories did not differ in age, sex, comorbidities, albumin, creatinine, C-reactive protein, white blood cells, and platelet counts. The result of a multivariate analysis showed that only lower Hb trigger (odds ratio [OR] _{≤ 7 vs. > 8} = 5.24, OR _{$7-8$ vs. > 8} = 2.13, $P = .035$) and higher neutrophil count ($P = .012$) were associated with increased in-hospital mortality.

In conclusion, a lower transfusion trigger is associated with increased risk for in-hospital mortality in patients hospitalized with pneumonia requiring RBC transfusion.

Abbreviations: CAP = community-acquired pneumonia, CI = confidence interval, CRP = C-reactive protein, Hb = hemoglobin, IQR = interquartile range, OR = odds ratio, RBC = red blood cells, SD = standard deviation.

Keywords: blood transfusion, mortality, pneumonia

1. Introduction

Pneumonia is a significant cause of morbidity and mortality worldwide.^[1] Pneumonia and influenza rank as a leading cause of death in the United States in 2014 with 55,000 deaths.^[2] Patients with pneumonia requiring hospitalization are generally older, experience comorbidities, and are more ailing than the general population.^[3] Older patients tend to receive more red blood cell (RBC) transfusions in the hospital setting.^[4] The decision when to transfuse is based both on the hemoglobin (Hb) level and the

clinical presentation. Hebert et al,^[5] in the TRICC trial, conducted a randomized controlled clinical trial to determine whether a restrictive approach to RBC transfusion that maintains Hb concentrations between 7.0 and 9.0 g/dL is equivalent to a more liberal strategy of maintaining Hb concentrations between 10.0 and 12.0 g/dL in critically ill patients. They found that the lower range was at least as effective as the higher one. RBC practice guidelines from 2012 state that the Hb trigger for transfusion is 7 to 8 g/dL for hospitalized stable patients and 8 g/dL for symptomatic patients.^[6] In 2016 these guidelines have been updated, reducing the trigger to 7 g/dL for hospitalized hemodynamically stable adult patients, including critically ill patients. A transfusion trigger of 7 g/dL may be appropriate, but there are not enough randomized clinical trials to support this.^[7] As the hospitalized population in Internal Medicine departments is not homogenous, it is important to evaluate the influence of the Hb trigger on patients' outcome in subpopulations. This study aims to evaluate the association between the Hb trigger at transfusion of the first RBC unit and all-cause in-hospital mortality in hospitalized patients with pneumonia.

2. Material and methods

2.1. Study design

This is a historical cohort study.

2.2. Setting

Internal medicine department "A" at Assaf Harofeh Medical Center, which is an 850-bed university hospital in central Israel,

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treats an urban and rural population of approximately 1 million people. Data were collected between January 2009 and December 2014.

Ethical approval for this study (Protocol number 91/13) was provided by the Assaf Harofeh Medical Center Institutional Review Board on June 20, 2013.

2.3. Participants

All patients older than 18 years were admitted with a diagnosis of pneumonia and received a transfusion of at least 1 unit of packed RBC. Only the first hospitalization of each patient was included.

2.4. Variables

Age, sex, comorbidities, laboratory tests, and survival status at discharge, were recorded.

The comorbidities included in the study were chronic obstructive pulmonary disease, hypertension, ischemic heart disease, congestive heart failure, atrial fibrillation, cerebrovascular disease, diabetes mellitus (including insulin-dependent diabetes mellitus and non-insulin-dependent diabetes mellitus), hypothyroidism, dyslipidemia, chronic renal failure, hematologic malignancies, solid tumor malignancies, and cognitive disorders. Complete blood count, creatinine level, C-reactive protein (CRP), and albumin were included.

All-cause in-hospital mortality was used as the primary outcome of the study.

2.5. Data source

Data source are the hospital electronic health records.

2.6. Measurements

The closest complete blood count, creatinine level, and CRP in the 24 hours before the first RBC transfusion were included. Albumin was recorded as a marker for patient status on admission.

Hb level before transfusion was defined as the transfusion trigger. The Hb transfusion trigger was divided into 3 categories using a threshold value of 7 and 8 g/dL.

2.7. Study size

To identify a mortality difference between the triggers, we assumed a medium effect size (effect size, $w=0.3$) and used a significant level of 0.05 and a power of 80%. A total of at least 108 patients are needed to meet these criteria.

2.8. Statistical methods

Categorical variables were described as frequency and percentage. Continuous variables were evaluated for the normal distributions using histograms and Q-Q plots. Normally distributed continuous variables were reported by their mean and standard deviation (SD), and non-normally distributed continuous variables were reported by their median and interquartile range (IQR). Categorical variables were compared between Hb trigger categories and mortality using either a chi-squared test or Fischer exact test. Continuous variables were compared using analysis of variance, independent sample *t* test, Kruskal-Wallis test, or Mann-Whitney test,

as appropriate. Age, sex, and variables that were associated in the univariate analysis with mortality at a significant level of $P<.1$ were included in the multivariate analysis. When 2 variables considered for inclusion in the multivariate analysis were highly correlated, the most significant was included. Logistic regression was used for the multivariate analysis. Odds ratio (OR) and 95% confidence interval (CI) were reported. The regression model was evaluated using Hosmer and Lemeshow goodness-of-fit test; $P<.05$ was considered as statistically significant. All statistical tests were 2-tailed. SPSS (IBM Corp., Released 2016, IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY) was used for all statistical analyses.

3. Results

3.1. Participants

One hundred seventy-seven patients were included in the study, of them 100 (56.5%) were males and the median age was 80 (IQR 71–87) years. Eighty-three (46.9%) patients received a single unit of RBC, 54 (30.5%) received 2 units of RBC, and 21 (11.9%) patients received 3 units of RBC. Patients' characteristics including demographics, RBC transfused, comorbidities, and blood tests are described in Table 1.

Ten patients (0.6%) had mild febrile transfusion reactions and none of them had hemolysis. There were no severe transfusion reactions in the study cohort.

Sixty-six (37.3%) patients died during the hospitalization. Ninety-five patients (53.7%) were transfused at Hb >8 g/dL, 64 (36.1%) at 7 to 8 g/dL, and 18 (10.2%) at Hb ≤ 7 g/dL. Patients in the lower Hb trigger group ($P=.003$) and in the mid trigger group ($P=.011$) had more RBC transfused compared to the higher trigger group. However, there was no significant difference between the mid and lower trigger groups ($P=.329$). Age, sex, complete blood count parameters, creatinine, CRP, albumin, and comorbidities did not statistically differ in the 3 Hb transfusion trigger groups ($P>.05$ for all, Table 1).

The characteristics of the patients who died and those who survived are presented in Table 2. Fifty-five percent of the patients with a history of Cerebro-vascular Accident (CVA) died, compared to 34% without a history of CVA ($p=0.033$). Elevated white blood cell and neutrophil counts were associated with increased mortality ($p=0.015$, $p=0.004$, respectively, Table 2).

Lower albumin and Hb levels before transfusion were also associated with a higher mortality ($p=0.038$, $p=0.015$, respectively). Fifty six percent of the patients who received RBC transfusion at a Hb trigger ≤ 7 g/dL died as compared to 43.8% at a trigger of 7 to 8 g/dL, and 29.5% at a trigger of >8 g/dL ($P=.045$, Fig. 1).

Multivariate analysis demonstrated that only higher neutrophil counts (adjusted odds ratio [OR]=1.12, 95% confidence interval [CI] 1.03–1.22, $P=.012$) and lower Hb trigger ($P=.035$, Table 3, Fig. 2) were significantly associated with increased mortality. The lower Hb trigger category (≤ 7 g/dL) was significantly associated with higher mortality (adjusted OR=5.24, 95% CI 1.33–20.61, $P=.018$), and the intermediate category (Hb 7–8 g/dL) tends to be at higher risk for mortality (adjusted OR=2.13, 95% CI 0.92–4.94, $P=.079$), when comparing these categories to the higher trigger (Hb >8 g/dL). When comparing patients using 8 g/dL as a single cutoff value, patients with Hb <8 g/dL had significantly higher risk for mortality (adjusted OR=2.54, 95% CI 1.14–5.66, $P=.022$).

Table 1
Patients' characteristics and comparison between hemoglobin trigger categories.

	Study Population N=177	Hemoglobin before transfusion g/dL			P
		≤7.00 (N=18)	7.01–8.00 (N=64)	≥8.01 (N=95)	
Male, n (%)	100 (56.5)	10 (55.6)	35 (54.7)	55 (57.9)	.920
Age, y, median (IQR)	80 (71–87)	81 (75–83)	79 (68–85)	80 (72–88)	.577
Packed red blood cell units, median (IQR)	2 (1–2)	2 (2–3)	2 (1–3)	1 (1–2)	.003
Comorbidity, n (%)					
Chronic obstructive pulmonary disease	6 (3.4)	2 (11.1)	3 (4.7)	1 (1.1)	.053
Hypertension	129 (72.9)	13 (72.2)	47 (73.4)	69 (72.6)	.992
Ischemic heart disease	67 (37.9)	5 (27.8)	20 (31.3)	42 (44.2)	.166
Congestive heart failure	39 (22)	2 (11.1)	14 (21.9)	23 (24.2)	.469
Atrial fibrillation	35 (19.8)	3 (16.7)	12 (18.8)	20 (21.1)	.883
Cerebro vascular disease	27 (15.3)	1 (5.6)	11 (17.2)	15 (15.8)	.469
Diabetes mellitus	77 (43.5)	7 (38.9)	32 (50.0)	38 (40.0)	.421
Non-insulin-dependent diabetes mellitus	70 (39.5)	5 (27.8)	29 (45.3)	36 (37.9)	.360
Insulin-dependent diabetes mellitus	7 (4)	2 (11.1)	3 (4.7)	2 (2.1)	.125
Hypothyroidism	22 (12.4)	1 (5.6)	7 (10.9)	14 (14.7)	.502
Hyperlipidemia + hypercholesterolemia	63 (35.6)	7 (38.9)	23 (35.9)	33 (34.7)	.942
Chronic renal failure	60 (33.9)	8 (44.4)	24 (37.5)	28 (29.5)	.351
Hemato-oncology	19 (10.7)	1 (5.6)	6 (9.4)	12 (12.6)	.611
Solid tumor	16 (9.0)	2 (11.1)	6 (9.4)	8 (8.4)	.929
Cognitive disorders	31 (17.5)	2 (11.1)	12 (18.8)	17 (17.9)	.745
Complete blood count before first blood transfusion, median (IQR)					
White blood cell (10 ³ cells/μL)	10.10 (7.05–13.80)	9.2 (6.4–14.8)	10.5 (6.7–12.6)	10.1 (7.3–13.9)	.841
Absolute neutrophil (10 ³ cells/μL)	8.0 (5.43–11.48)	7.3 (5.1–11.4)	8.5 (5.1–10.7)	7.7 (5.7–11.7)	.809
Absolute lymphocyte (10 ³ cells/μL)	1.0 (0.7–1.5)	1.1 (0.6–1.8)	0.9 (0.7–1.5)	7.7 (5.7–11.7)	.610
Absolute monocyte (10 ³ cells/μL)	0.6 (0.4–0.8)	0.5 (0.3–0.8)	0.6 (0.4–0.8)	0.6 (0.4–0.7)	.806
Absolute eosinophil (10 ³ cells/μL)	0.1 (0–0.2)	0.2 (0.1–0.4)	0.1 (0–0.1)	0.1 (0–0.2)	.156
Absolute basophil (10 ³ cells/μL)	0 (0–0)	0 (0–0.1)	0 (0–0)	0 (0–0)	.326
Hemoglobin, g/dL	8.1 (7.7–8.6)	6.5 (6.2–6.7)	7.7 (7.5–7.9)	8.6 (8.4–9.0)	
Hematocrit (%)	24.5 (22.8–25.9)	20.2 (19.8–20.9)	23.2 (22.5–23.9)	25.8 (24.9–27.1)	
Platelet count (10 ³ cells/μL)	204 (144–277)	184 (151–283)	190 (146–285)	212 (141–278)	.850
Biochemistry before first blood transfusion, median (IQR)					
Creatinine, mg/dL	1.38 (0.85–2.60)	1.62 (1.13–3.91)	1.39 (0.91–2.47)	1.3 (0.82–2.56)	.583
C-reactive protein, mg/L	96.9 (50.6–157.0)	107.3 (36.5–181.1)	76.9 (54.7–137.9)	120.3 (31.4–158.2)	.886
Biochemistry at admission, mean (SD)					
Albumin, g/dL	3.01 (0.58)	2.88 (0.49)	2.94 (0.63)	3.09 (0.55)	.256

IQR=interquartile range, SD=standard deviation.

4. Discussion

This study included 177 patients hospitalized with pneumonia, who received at least 1 unit of RBC with an in-hospital mortality rate of 37.3%. In our study, a significant difference in in-hospital mortality was demonstrated for different Hb transfusion trigger categories (Hb ≤7 g/dL: 56%, Hb 7 to 8 g/dL: 43.8%, Hb >8 g/dL: 29.5%, $P=.045$). Lower Hb trigger and higher neutrophil counts were independent predictors for in-hospital mortality.

Lower respiratory infections are among the leading causes of death worldwide,^[8] with community-acquired pneumonia (CAP) being one of the most frequent causes of hospitalization.^[9] Anemia has been cited as a contributor to length of stay in these patients.^[10] To the best of our knowledge, no study has investigated the association between Hb transfusion trigger and in-hospital mortality in patients hospitalized with pneumonia receiving RBC transfusions. Ding et al^[11] reported 20.6% 30-day in-hospital mortality in 890 CAP patients aged 65 years or older; anemia was not looked at in their study. Vicco et al^[12] looked at in-hospital mortality risk factors in patients with CAP and found that white blood cell count was associated with significantly higher rates of mortality; we found a

similar association. Several studies have examined the prevalence of anemia in pneumonia and its association with mortality in patients hospitalized with CAP.^[13] Reade et al^[14] studied the prevalence of anemia and its association with 90 day mortality in patients hospitalized with CAP and reported that anemia is associated with higher 90-day mortality in this patient population; however, they did not find an association with transfusion. Waterer et al^[15] found that anemia with a hematocrit <35% had an OR of 1.61 (95% CI 1.03–2.52, $P<.035$) for mortality within 2 to 3 years of discharge after CAP. Raz et al^[16] found that anemia with a Hb <8 g/dL was associated with an increased 1-year mortality in patients hospitalized with pneumonia. Hsu et al^[17] conducted a retrospective study examining 1-year outcomes of CAP in the Veteran Affairs Healthcare System, and found 1-year, including after discharge, mortality to be as high as 41%. Fine et al^[18] found that 21.5% of the patients deceased within 30 days of hospitalization for CAP had a hematocrit <25%. Fine et al^[19] collected and analyzed data to devise a prediction rule identifying low-risk patients with CAP. Hematocrit <30% was included as a predictor for mortality in their model. Barbarova et al^[20] conducted a retrospective cohort analysis of 209 consecutive patients suffering from myocardial injury, with

Table 2

Univariate analysis of the association between patients' characteristics and in-hospital mortality.

	In-hospital mortality		P
	No (N=111)	Yes (N=66)	
Male, n (%)	65 (58.6)	35 (53)	.473
Age, y, median (IQR)	78 (68–87)	80 (76–87)	.229
Packed red blood cell units, median (IQR)	1 (1–2)	2 (1–3)	.038
Comorbidity, n (%)			
Chronic obstructive pulmonary disease	3 (2.7)	3 (4.5)	.672
Hypertension	82 (73.9)	47 (71.2)	.700
Ischemic heart disease	43 (38.7)	24 (36.4)	.753
Congestive heart failure	26 (23.4)	13 (19.7)	.563
Atrial fibrillation	20 (18)	15 (22.7)	.447
Cerebro vascular disease	12 (10.8)	15 (22.7)	.033
Diabetes mellitus	47 (42.3)	30 (45.5)	.686
Non-insulin-dependent diabetes mellitus	44 (39.6)	26 (39.4)	.974
Insulin-dependent diabetes mellitus	3 (2.7)	4 (6.1)	.427
Hypothyroidism	17 (15.3)	5 (7.6)	.131
Hyperlipidemia + hypercholesterolemia	46 (41.4)	17 (25.8)	.035
Chronic renal failure	33 (29.7)	27 (40.9)	.129
Hemato-oncology	14 (12.6)	5 (7.6)	.295
Solid tumor	10 (9.0)	6 (9.1)	.985
Cognitive disorders	16 (14.4)	15 (22.7)	.159
Complete blood count before first blood transfusion, median (IQR)			
White blood cell (10 ³ cells/μL)	9.3 (6.8–12.6)	11.6 (7.5–16.0)	.015
Absolute neutrophil (10 ³ cells/μL)	7.4 (5.1–10.1)	9.6 (6.1–12.8)	.004
Absolute lymphocyte (10 ³ cells/μL)	1.0 (0.7–1.5)	0.9 (0.6–1.6)	.981
Absolute monocyte (10 ³ cells/μL)	0.6 (0.5–0.8)	0.5 (0.3–0.7)	.035
Absolute eosinophil (10 ³ cells/μL)	0.1 (0–0.2)	0.1 (0–0.2)	.820
Absolute basophil (10 ³ cells/μL)	0 (0–0)	0 (0–0)	.950
Hemoglobin, g/dL	8.3 (7.8–8.8)	8.0 (7.4–8.5)	.015
≤7.00	8 (7.2)	10 (15.2)	.045
7.01–8.00	36 (32.4)	28 (42.4)	
≥8.01	67 (60.4)	28 (42.4)	
Hematocrit (%)	24.8 (23.2–26.2)	24.1 (22.4–25.3)	.039
Platelet count (10 ³ cells/μL)	206 (145–285)	196 (143–276)	.629
Biochemistry before first blood transfusion, median (IQR)			
Creatinine, mg/dL	1.34 (0.84–2.56)	1.45 (0.88–2.80)	.866
C-reactive protein, mg/L	113.6 (51.8–157.5)	85.1 (41.0–122.3)	.374
Biochemistry at admission, mean (SD)			
Albumin, g/dL	3.08 (0.61)	2.92 (0.54)	.038

IQR = interquartile range, SD = standard deviation.

concomitant anemia. In their study, Hb <8 g/dL was found to be an independent risk factor reducing survival in patients not receiving RBC transfusions when compared to transfused patients, whereas no significant difference was observed in patients with Hb ≥8 g/dL

between the 2 groups. A meta-analysis examining the impact of more restrictive blood transfusion strategies on clinical outcomes in patients with critical illnesses concluded that in-hospital mortality was reduced with a Hb transfusion trigger of ≤7 g/dL.^{12,11}

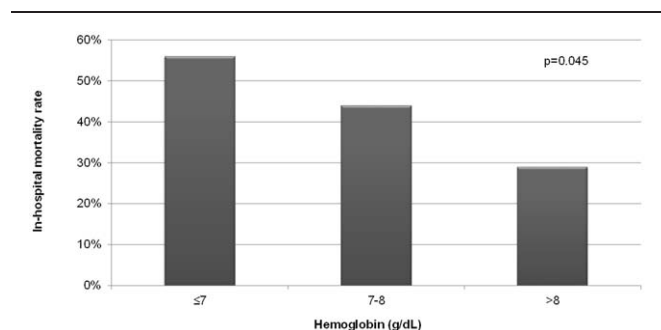


Figure 1. Hospital mortality rate in percentage in the 3 categories: hemoglobin transfusion trigger ≤7 g/dL, between 7 and 8 g/dL, and >8 g/dL.

Table 3

Multivariate analysis of the association between hemoglobin trigger and in-hospital mortality.

Variable	OR (95% CI)	P
Age	1.02 (0.99–1.05)	.227
Male	0.95 (0.43–2.09)	.898
Cerebro vascular disease	1.82 (0.67–4.93)	.242
Hyperlipidema	0.59 (0.25–1.41)	.237
Albumin at admission	0.98 (0.91–1.05)	.543
Absolute neutrophil count at admission	1.12 (1.03–1.22)	.012
Hemoglobin before transfusion, g/dL		
>8	1	.035
7–8	2.13 (0.92–4.94)	
≤7	5.24 (1.33–20.61)	

CI = confidence interval, OR = odds ratio.

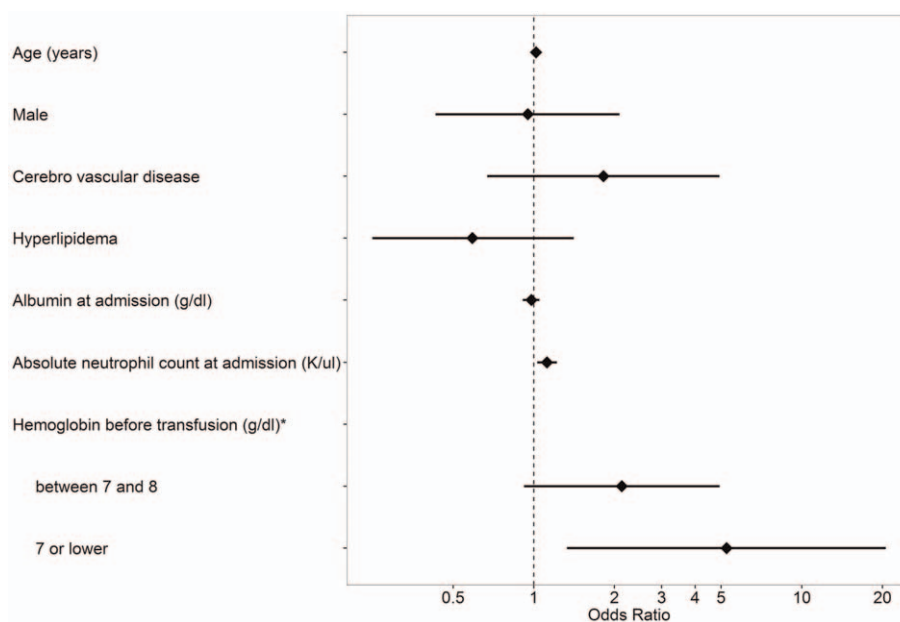


Figure 2. A forest plot for in-hospital mortality demonstrating the odds ratio and 95% confidence interval for the variables that were included in the multivariate analysis.

Transfusion reactions are the most frequent adverse effect associated with the administration of blood components, occurring in up to 1 in 100 transfusions, febrile nonhemolytic transfusion reactions being the most common among them.^[22] There were 0.6% febrile nonhemolytic and no severe transfusion-associated reactions in the study population. In this study, lower Hb trigger was associated with higher number of RBC transfused and therefore may be associated with higher risk for transfusion associated reactions.

Many studies have been published looking for risk factors predicting mortality in CAP, and anemia has been found to be associated with mortality. However, we did not find studies examining the effect of Hb transfusion trigger in patients hospitalized with CAP. After previous studies have identified anemia as an independent risk factor for mortality in these patients, our study aimed to evaluate the effect of RBC transfusion at different Hb levels that were suggested in studies and guidelines for hospitalized patients.

Patients in the 3 trigger groups had similar comorbidities. Thus, the decision to transfuse was based on patients' clinical presentation and the Hb on admission. This study demonstrated that a lower Hb trigger level is associated with increased risk of mortality. Therefore, it can be assumed that earlier admission and more liberal transfusion practice may have reduced in-hospital mortality.

Our study has several limitations. Owing to the historical cohort study, we were unable to collect important data on the contribution of patients' symptoms to the decision to transfuse them with RBCs. However, the common practice in our setting is to transfuse only symptomatic patients or those with a very low Hb level. Moreover, we collected data on a large number of comorbidities and blood tests on admission and before transfusion in our study cohort and did not find a difference between the 3 transfusion trigger categories. CAP scoring such as the pneumonia severity index (PSI) and CURB-65 could help to standardize the results and compare the groups. However, it is difficult to apply these scores in historical studies based on an

internal medicine department population, as some of the parameters required for the scoring are not performed or documented routinely in these patients' files. To handle this limitation, as stated above, we used biomarkers (white blood cell, neutrophil and lymphocyte counts, CRP, creatinine, and albumin) to compare between the groups.

We only studied in-hospital mortality, which limited our ability to draw conclusions on the impact of transfusion trigger on longer survival. However, a high rate of in-hospital mortality was reported in our study and we believe that the major impact of the blood transfusion is during the hospital stay. Critical care in patients hospitalized with CAP includes transfusion of RBC. Usually postdischarge mortality is investigated as the primary outcome in patients with CAP. However, in this study, we used in-hospital mortality as the primary outcome, as RBC transfusions are part of critical care and are mostly a predictor for in-hospital mortality rather than post-discharge mortality. Prospective/randomized studies are needed to confirm our results. However, in a prospective study, randomization may be very difficult to implement as physicians might be reluctant to implement a liberal strategy in overall younger patients with stable condition at admission or a restrictive strategy in elderly patients with unstable condition at admission.

In conclusion, our findings demonstrate a statistically significant association between lower Hb trigger and increased in-hospital mortality in patients hospitalized with pneumonia, which supports transfusing at a Hb trigger >8 g/dL in these patients. The data suggest that practice flexibility toward liberal transfusion is needed in defined patient populations.

Author contributions

Conceptualization: N. Rahimi-Levene, A. Golik, T. Ziv-Baran.

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Writing – original draft: N. Rahimi-Levene, M. Koren-Michowitz, T. Ziv-Baran.

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