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Letter to the Editor

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Mortality in Critically III Patients Does Not Differ according to Transfusion Strategy

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Dear Editor,

We read with great interest the meta-analysis by Zhang et al. [1] comparing the effects of two transfusion strategies in critically ill patients. The authors conclude that the restrictive transfusion strategy potentially reduced in-hospital mortality in critically ill adults as compared with a more liberal strategy. Unfortunately, we have several concerns in regard to this study and its results. First of all, as per the inclusion criteria stated by the authors, the meta-analysis focused on trials reporting mortality in critically ill adults receiving restrictive or liberal red-cell transfusion. The authors decided to include only critically ill patients with hemoglobin concentrations of 90 g/L or less on admission. Considering such criteria, we note that they missed the study by Mazza et al. [2] conducted in septic shock patients; conversely, they included the study by Mazer et al. [3] where the authors included patients with baseline values of hemoglobin over 130 g/L. Nonetheless, mild errors in inclusion of studies may happen [4], and our colleagues did a very hard work when screening studies from a huge literature search. Importantly, by strictly limiting the inclusion of studies according to the hemoglobin levels on admission, at least five important trials conducted in a cardiac surgery population [5-7] and in patients with traumatic brain injury [8, 9] were excluded by the meta-analysis. A second consideration that warrants further caution when interpreting the results of the meta-analysis [1] is the authors' choice to perform a meta-analysis with a fixed-

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This is an Open Access article licensed under the Creative Commons Attribution-NonCommercial-4.0 International License (CC BY-NC) (http://www.karger.com/Services/OpenAccessLicense), applicable to the online version of the article only. Usage and distribution for commercial purposes requires written permission. effects model, which assumes that the "true effect" is the same across studies. However, it is unlikely that all included studies have an identical or similar "true effect" due to the clinical heterogeneity of the included populations, ranging from all the critically ill patients admitted to intensive care to a more specific population (septic shock or patients undergoing cardiac surgery). More importantly, the fixed-effects model should not be used when there is statistical heterogeneity (I^2) as in most of the forest plots of the meta-analysis by Zhang et al. [1]. In such cases, it is strongly advisable to use a random-effects model, which better balances the weights of the included studies [10].

A third concern regards the authors' decision to separate the analyses on the outcome of mortality into several endpoints. This resulted in 7 forest plots on the same outcome (mortality), but most of them included a very low number of studies (1–3 studies). For instance, the conclusion on a reduction of in-hospital mortality with a restrictive strategy seems rather hazardous as it is based on 2 studies only. With such a low number of included studies, it is difficult to interpret also the robustness of the results, considering that a trial sequential analysis has not been carried out [11].

In order to correct for all the above-mentioned concerns, we provide a forest plot including the 6 missed studies with an analysis performed according to the random-effects model. We used the longest follow-up mortality provided by the studies, rather than dispersing the

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	Restrictive trans	sfusion l	_iberal trans	fusion		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.1.1 General ICU							
Hebert 1995	13	33	11	36	2.8%	1.29 [0.67, 2.47]	
Hebert 1999	95	418	111	420	12.5%	0.86 [0.68, 1.09]	
Nalsh 2013	19	51	27	49	5.6%	0.68 (0.44, 1.05)	
Subtotal (95% CI)		502		505	20.9%	0.85 [0.66, 1.10]	•
otal events	127		149				
Heterogeneity: Tau ² =	0.01; Chi ² = 2.65,	df = 2 (P = 1	0.27); I ² = 25	%			
est for overall effect:	Z = 1.21 (P = 0.23))					
I.1.2 Sepsis and/or s	eptic shock						
Bergamin 2017	106	151	88	149	17.0%	1.19 [1.00, 1.41]	
Holst 2014	216	502	223	496	19.2%	0.96 [0.83, 1.10]	+
azza 2015	11	22	13	24	3.7%	0.92 (0.53, 1.61)	
Subtotal (95% CI)		675		669	39.9%	1.05 [0.88, 1.25]	
otal events	333		324				[
Heterogeneity: Tau ² =	0.01; Chi ² = 4.07.	df = 2 (P = 1	0.13); I ² = 51	%			
est for overall effect:	Z = 0.50 (P = 0.62))					
I.1.3 Surgical ICU							
le Ameida 2015	99	151	84	149	16.0%	1.16 [0.97, 1.40]	+ - -
Subtotal (95% CI)		151		149	16.0%	1.16 [0.97, 1.40]	◆
otal events	99		84				
Heterogeneity: Not ap	plicable						
Test for overall effect:	Z = 1.62 (P = 0.10))					
1.1.4 Cardiac Surger	y ICU						
Bracey 1999	3	215	6	222	0.7%	0.52 [0.13, 2.04]	
Hajjar 2010	15	249	11	253	2.1%	1.39 [0.65, 2.96]	
Mazer 2017	141	2291	149	2318	13.4%	0.96 [0.77, 1.20]	-
Murphy 2015	26	1000	19	1003	3.4%	1.37 [0.76, 2.46]	
Shehata 2012	4	25	1	25	0.3%	4.00 (0.48, 33, 33]	
Subtotal (95% CI)		3780		3821	20.0%	1.06 [0.82, 1.37]	◆
otal events	189		186				
Heterogeneity: Tau ² =	0.01: Chi ² = 4.47.	df = 4 (P = 1	0.35); $ ^2 = 10^{\circ}$	%			
Fest for overall effect:	Z = 0.44 (P = 0.66))	,				
.1.5 Traumatic brair	n injury						
3obatto 2019	7	23	1	21	0.3%	6.39 [0.86, 47.70]	
Robertson 2014	14	98	17	101	2.8%	0.85 [0.44, 1.63]	
Subtotal (95% CI)		121		122	3.2%	1.87 [0.26, 13.49]	
Fotal events	21		18				
Heterogeneity: Tau ² =	1.56; Chi ² = 3.69.	df = 1 (P = 1	0.05); I ² = 73	%			
est for overall effect:	Z = 0.62 (P = 0.54))					
fotal (95% CI)		5229		5266	100.0%	1.02 [0.91, 1.15]	
otal events	769		761				
Heterogeneity: Tau ² =	0.01; Chi ² = 20.07	, df = 13 (P	= 0.09); l ² = 3	35%			
act for overall effect:	Z = 0.37 (P = 0.71))					0.1 0.2 0.5 1 2 5 10
estion overall ellect.		/					

Fig. 1. Forest plot analysis on mortality at longest follow-up in critically ill patients randomized to a restrictive or liberal transfusion strategy. Analysis performed with random-effects model and Mantel-Haenszel (M-H). CI, confidence interval.

mortality outcome in multiple time points. Furthermore, we separated studies into subgroups according to the clinical setting. As shown in Figure 1, there were no differences in mortality according to the transfusion strategy: risk ratio 1.02 (95% confidence interval 0.91–1.15; p = 0.71) with mild heterogeneity ($I^2 = 35\%$) and no subgroup differences (p = 0.40). Of note, our results remain unchanged if the analyses are limited to the studies strictly adhering to the original criteria (admission hemoglobin of 90 g/L or less).

In light of the corrected approach with new studies included and with the use of the recommended effects model, our pooled results suggest that there is currently no difference in mortality in critically ill adult patients according to the transfusion strategy.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All authors read and discussed the meta-analysis in a journal club. F.S., L.L.V., and P.M. conducted a search to find other relevant articles that were missed. F.S., L.L.V., and M.A. performed the meta-analysis. F.S. and L.L.V. wrote the draft of the manuscript. P.M. and M.A. revised the draft. All authors approved the final version.

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