LETTER   **Open Access**

Benefits of red blood cell transfusion in patients with traumatic brain injury

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To the editor,

Anemia is a common clinical condition in patients suffering from traumatic brain injury (TBI). As low hemoglobin level may increase the risk of poor brain oxygen delivery and secondary ischemic injury in TBI, red blood cell (RBC) transfusion is often applied in postoperative intensive care. However, the benefits remain debated. Dozens of cohort studies were performed to investigate the association between RBC transfusion and clinical outcomes, such as mortality and long-term neurological function. However, the conclusions were conflicting which is largely due to the great heterogeneity. For instance, the hemoglobin targets vary greatly, from 6 to 12 g/dl, using one hemoglobin value to represent the whole hemoglobin level; there is no specific RBC transfusion protocol and unadjusted confounding factors. Of course, aiming to address these limitations, randomized controlled trials (RCT) were also conducted. Aiming to provide a systematic review, we conducted a literature search on PubMed and Embase, without limitations. Only three RCTs were identified investigating the RBC transfusion efficacy in patients with TBI, and several limitations should be noticed. First is the mortality rate. All the three RCTs reported the mortality rate, and McIntyre et al. [1] and Robertson et al. [2] found no significant difference in overall mortality, while in Gobatto et al.'s [3] study, 44 TBI patients were included and a significant reduction of mortality was found (7/23 vs. 1/21, $p = 0.048$). In the meta-analysis, the pooled outcome also showed a non-significant conclusion, with significant heterogeneity. Noteworthy, we noticed all the death in Gobatto et al.'s study occurred during ICU stay. However, in clinical practice, a significant proportion of TBI patients may die shortly after admission because of severe brain damage which may also explain the fact that in the other two RCTs, 60% [1] of death occurred during ICU stay and more than 60% of death [2] occurred within 13 days after admission (Fig. 3 in Robertson et al.'s [2] study). Furthermore, despite 7 g/L and 9 g/L were defined as the restrictive and liberal transfusion targets, the hemoglobin levels are almost the same within the first 4 days in Gobatto et al.'s study (Fig. 2). Thus, the timing of death of these patients should be presented as the inclusion of these patients may lead to a biased conclusion. Second, the GOS was commonly used as an index for long-term neurological outcome (Fig. 1). In our meta-analysis, no significant improvement was found both in subgroups including and excluding death. Based on the current evidence, the debate of RBC transfusion remains unsettled. Well-designed multicenter investigations are needed to reach a stable conclusion.

Authors' response
Red blood cells' transfusions and mortality in traumatic brain-injured patients
André L. N. Gobatto, Milena A. Link, Davi J. F. Solla and Luiz M. S. Malbouisson

To the editor,

The letter from Dr. Zhang et al. is very interesting and gives us the opportunity to explore some details regarding the relationship between transfusion and mortality in patients with traumatic brain injury (TBI).

To date, only three randomized clinical trials (RCTs) have evaluated blood transfusion strategies in patients with TBI, with different results. The trials by McIntyre et al. [1] and Robertson et al. [2] found no significant

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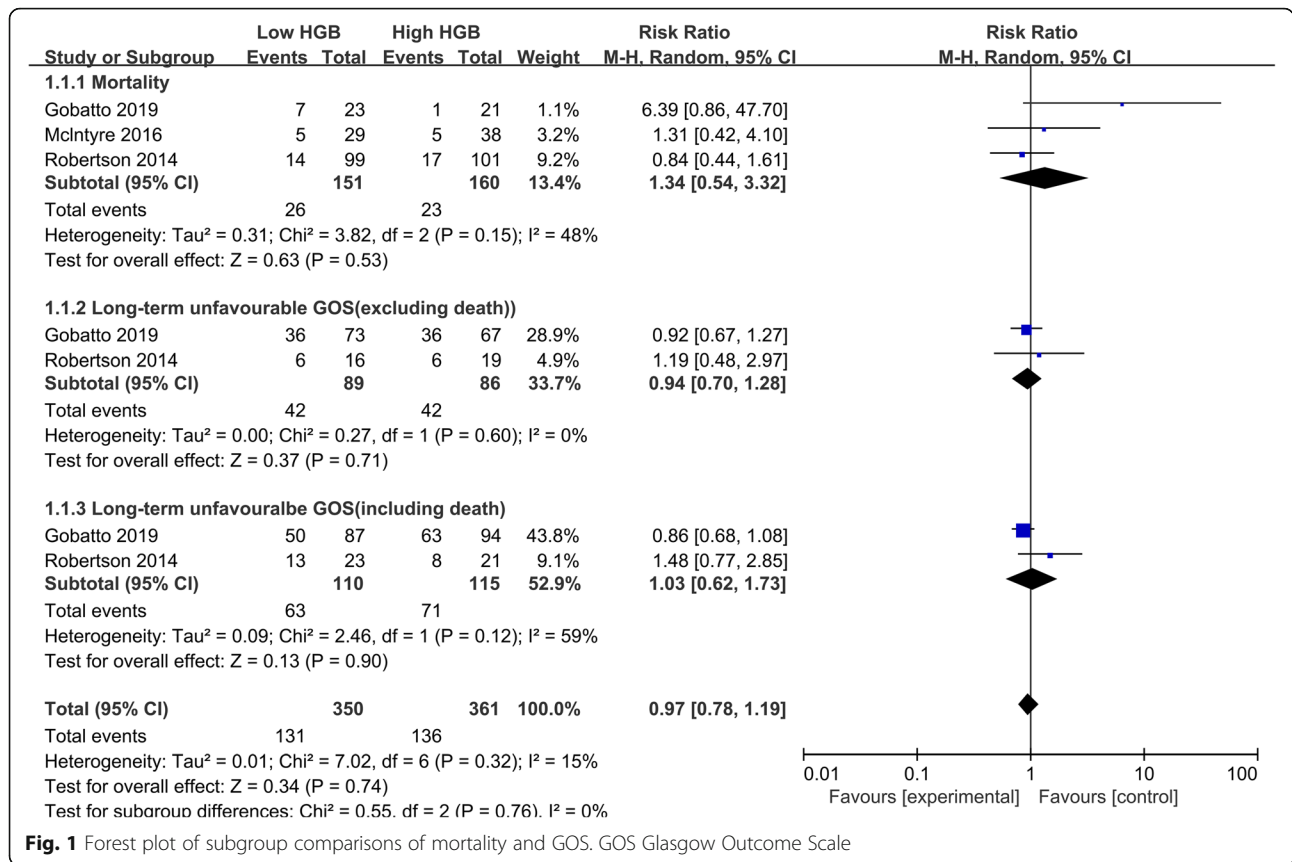
Study or Subgroup	Low HGB Events	Total	High HGB Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.1.1 Mortality							
Gobatto 2019	7	23	1	21	1.1%	6.39 [0.86, 47.70]	
McIntyre 2016	5	29	5	38	3.2%	1.31 [0.42, 4.10]	
Robertson 2014	14	99	17	101	9.2%	0.84 [0.44, 1.61]	
Subtotal (95% CI)		151		160	13.4%	1.34 [0.54, 3.32]	
Total events	26		23				

Heterogeneity: Tau² = 0.31; Chi² = 3.82, df = 2 (P = 0.15); I² = 48%
Test for overall effect: Z = 0.63 (P = 0.53)

1.1.2 Long-term unfavourable GOS(excluding death))							
Gobatto 2019	36	73	36	67	28.9%	0.92 [0.67, 1.27]	
Robertson 2014	6	16	6	19	4.9%	1.19 [0.48, 2.97]	
Subtotal (95% CI)		89		86	33.7%	0.94 [0.70, 1.28]	
Total events	42		42				

Heterogeneity: Tau² = 0.00; Chi² = 0.27, df = 1 (P = 0.60); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)

1.1.3 Long-term unfavouralbe GOS(including death)							
Gobatto 2019	50	87	63	94	43.8%	0.86 [0.68, 1.08]	
Robertson 2014	13	23	8	21	9.1%	1.48 [0.77, 2.85]	
Subtotal (95% CI)		110		115	52.9%	1.03 [0.62, 1.73]	
Total events	63		71				

Heterogeneity: Tau² = 0.09; Chi² = 2.46, df = 1 (P = 0.12); I² = 59%
Test for overall effect: Z = 0.13 (P = 0.90)

Total (95% CI)		350		361	100.0%	0.97 [0.78, 1.19]	
Total events	131		136				

Heterogeneity: Tau² = 0.01; Chi² = 7.02, df = 6 (P = 0.32); I² = 15%
Test for overall effect: Z = 0.34 (P = 0.74)
Test for subgroup differences: Chi² = 0.55, df = 2 (P = 0.76), I² = 0%

0.01   0.1   1   10   100
Favours [experimental]   Favours [control]

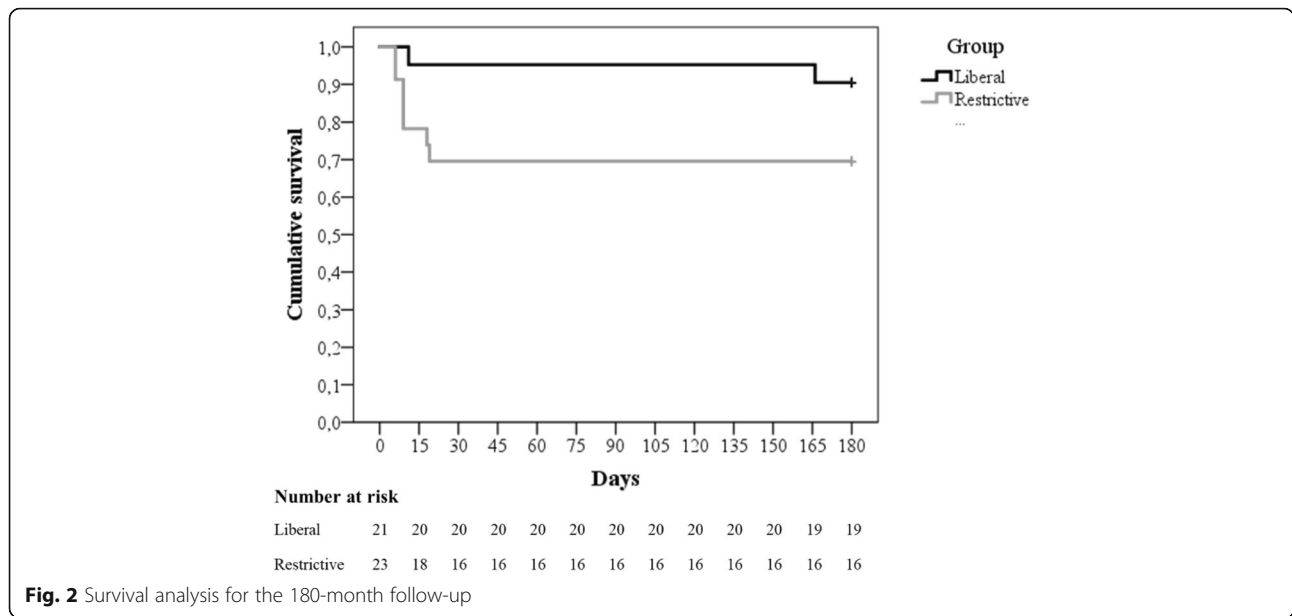**Fig. 1** Forest plot of subgroup comparisons of mortality and GOS. GOS Glasgow Outcome Scale

difference in overall mortality, while in our study [3] a significant reduction of mortality was found (7/23 vs. 1/21, $p = 0.048$). Part of these results might be explained by different design, inclusion criteria, and patient populations. The trial by McIntyre et al. [1] is actually a sub analysis of the TRICC trial, evaluating 67 TBI patients from the main 838 patients cohort, randomized to a liberal (Hb > 7.0 g/dL) or conservative (Hb > 10 g/dL) transfusion strategy. The trial included stable, resuscitated patients in the intensive care unit (ICU) and was not designed to study TBI patients. Moreover, in the trial by Robertson et al. [2], anemia was not an inclusion criterion and the patients in both groups had average hemoglobin concentrations (Hb) greater than 9 g/dL at all reported time points (e.g., Hb 9.7 vs. 11.4 g/dL at day 9, in restrictive and liberal groups, respectively), which may have precluded adequate assessment of the effects of the restrictive transfusion strategy.

By contrast, in TRAHT, by including only TBI patients with a hemoglobin concentration under 9 g/dL, we created a difference between the groups, using a real restrictive transfusion strategy in the control group. Most TBI patients are not severely anemic at ICU admission and develop anemia during ICU stay. In our trial, the mean hemoglobin concentration during the first 14 days after hospital admission was 9.3 ± 1.3 g/dL in the liberal group and 8.4 ± 1.0 g/dL in the restrictive group ($p < 0.01$),

giving a mean difference of 0.9 ± 0.2 g/dL. This difference gradually increased after the fourth day, to a peak on the tenth day, when the difference was 1.8 ± 0.4 g/dL (CI 95% 1.0–2.6, $p < 0.01$). The mean Hb at ICU admission was 10.2 ± 1.4, similar between groups, as well as during the first 3 days. The median time from ICU admission to randomization was 3 [2–4] days, which is compatible with the difference in Hb levels between groups being clearer from the 4th day on.

In our trial, most deaths occurred during ICU stay (7/23 vs. 1/21, $p = 0.048$). At 6-month follow-up, one patient from the liberal group died (7/23 vs. 2/21). In a post hoc analysis, the hospital deaths occurred at a median of 9 [7.5–14.5] days, a similar time point as compared to the Robertson's study. At the 6-month follow-up, the restrictive group mean survival was 117.7 ± 18.7 vs. 169.2 ± 9.6 days for the liberal group (log-rank test, $\chi^2 = 3.223$, $p = 0.073$) (Fig. 2).

TRAHT was a pilot trial, aimed at evaluating the feasibility of a randomized clinical trial comparing liberal and restrictive blood transfusion strategies in patients with moderate and severe TBI. Although its secondary analysis in favor of the liberal transfusion strategy were noteworthy, we agree the study results should be interpreted cautiously and well-designed multicenter RCT are still necessary.

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Fig. 2 Survival analysis for the 180-month follow-up

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References
1. McIntyre LA, Fergusson DA, Hutchison JS, Pagliarello G, Marshall JC, Yetisir E, Hare GM, Hebert PC. Effect of a liberal versus restrictive transfusion strategy on mortality in patients with moderate to severe head injury. Neurocrit Care. 2006;5:4–9.
2. Robertson CS, Hannay HJ, Yamal JM, Gopinath S, Goodman JC, Tilley BC, Epo Severe TBITI, Baldwin A, Rivera Lara L, Saucedo-Crespo H, Ahmed O, Sadasivan S, Ponce L, Cruz-Navarro J, Shahin H, Aisiku IP, Doshi P, Valadka A, Neipert L, Waguspack JM, Rubin ML, Benoit JS, Swank P. Effect of erythropoietin and transfusion threshold on neurological recovery after traumatic brain injury: a randomized clinical trial. JAMA. 2014;312:36–47.
3. Gobatto ALN, Link MA, Solla DJ, Bassi E, Tierno PF, Paiva W, Taccone FS, Malbouisson LM. Transfusion requirements after head trauma: a randomized feasibility controlled trial. Crit Care. 2019;23:89.