A Different Perspective on Transfusion Requirements in Surgical Oncology Patients

To the Editor:

We read with interest the recent article "Transfusion Requirements in Surgical Oncology Patients," by Pinheiro de Almeida *et al.*[1] Much attention has been drawn to this study as exemplified by an accompanying editorial[2] and an illustration,[3] which highlight its results. We would suggest that some caution be applied when interpreting the results of this study.

Recently, there have been numerous randomized trials of restrictive *versus* liberal transfusion thresholds in a variety of different patient populations.[4–6] With the exception of a small pilot study in patients experiencing acute cardiac events,[7] all have demonstrated that patients in the restrictive groups have not experienced worse outcomes than patients in the liberal groups.[5,8] So the question arises as to why the work of Pinheiro de Almeida *et al.*[1] showed the opposite effect. Have they identified a novel patient population that might benefit from a higher hemoglobin concentration? Perhaps, but the results of this study are not straightforward.

The patients in this study were randomized to a restrictive or liberal transfusion strategy when they were admitted to the intensive care unit (ICU) following their abdominal cancer surgery. The transfusion thresholds, less than 7 g/dl or less than 9 g/dl, for the restrictive and liberal groups, respectively, only applied when the patients were in the ICU—a median of 4 days for patients in both groups. During their time in the ICU, only 21 of 101 patients (21%) in the restrictive group and 41 of 97 patients (42%) in the liberal group actually received even a single transfusion. Furthermore, among the small number of patients in both groups who were actually transfused in the ICU, the median number of erythrocyte units administered to the patients who were actually transfused was not significantly different! (Median, 1 unit in the restrictive group; median, 2 units in the liberal group; $P = 0.17$.) Thus, although the authors randomly allocated patients to two different transfusion threshold groups, this randomization did not actually produce two different patient populations to study as both groups received statistically the same number of erythrocyte units in the ICU. In other words, although there was a plan to administer erythrocytes based on a liberal or a restrictive transfusion threshold, thereby creating highly and not highly transfused groups, the end result was that there was not a meaningful separation of the two groups in terms of the number of units transfused per patient. Thus, any outcome differences between these two groups cannot be explained by differences in the amount of erythrocytes transfused to patients in these groups.

The absence of a difference in the number of erythrocyte units transfused to those patients who actually received one continued once the patients arrived on a regular ward. Outside the ICU, the transfusion threshold strategy, determined by randomization, no longer applied; the decision to transfuse was left to the discretion of the treating physicians who appeared to use a relatively restrictive transfusion threshold as the mean pretransfusion hemoglobin concentration in both groups of patients in the wards was identical at 7.5 g/dl. Only 33 of 101 patients (33%) in the restrictive group and 47 of 97 patients (48%)in the liberal group actually received a transfusion by the end of their hospitalization. As the total number of erythrocyte units transfused during their hospitalization to patients in the restrictive and liberal groups was 88 and 134, respectively, the average number of erythrocyte units that were administered to the patients who were actually transfused was 2.67 and 2.85 units, respectively. This difference is not clinically meaningful. So neither at the end of the ICU admission nor at the end of the hospitalization did patients in the liberal group receive more erythrocyte units per patient than those in the restrictive group. Thus, the differences in patient outcomes observed in this study cannot be ascribed to one group having received more (or fewer) erythrocyte units than the other.

It is interesting to note that statistical *P* values were not presented in tables 1 and 2 to accompany the presentation of the patient demographic information. Although patients in the two groups appear similar, subtle differences might also have influenced some of the outcomes. One of the adverse events included in the primary outcome measure was major cardiovascular complications, itself a composite outcome. There were no differences between the patients in the two groups in terms of peripheral arterial disease, cerebrovascular disease, congestive heart failure, and arterial coronary disease when compared individually. However, when the patients within each group with these four comorbidities are added together, and this composite metric of cardiovascular disease is compared between the two groups, there is certainly a trend ($P = 0.0636$) toward a higher incidence of cardiovascular disease among the patients in the restrictive group. This trend toward having a higher incidence of cardiovascular disease among patients in the restrictive group could certainly explain at least in part the overall higher incidence of cardiovascular complications observed in these patients.

Overall, the fact that there was no difference in the number of erythrocytes administered to the small number of patients who received a transfusion in both groups indicates that the lower mortality in the liberal group cannot be explained by the quantity of erythrocytes transfused to the patients who actually received them. Confounders like the higher incidence of abdominal sepsis and more patients

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with lower gastrointestinal tumors in the restrictive group can better explain the differences in outcomes between the groups than the quantity of transfused erythrocytes per patient. These data do not support preoperative erythrocyte transfusion for anemic patients undergoing cancer surgery; if a higher preoperative hemoglobin concentration is desired, then consider iron therapy.

Competing Interests

The authors declare no competing interests.

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References

1. Pinheiro de Almeida J, Vincent JL, Barbosa Gomes Galas FR, Pinto Marinho de Almeida E, Fukushima JT, Osawa EA, Bergamin F, Lee Park C, Nakamura RE, Fonseca SM, Cutait G, Inacio Alves J, Bazan M, Vieira S, Vieira Sandrini AC, Palomba H, Ribeiro U Jr, Crippa A, Dalloglio M, Del Pilar Estevez Diz M, Kalil Filho R, Costa Auler JO Jr, Rhodes A, Hajjar LA: Transfusion requirements in surgical oncology patients: A prospective, randomized controlled trial. ANESTHESIOLOGY 2015; 122:29–38
2. Cata JP: Perioperative anemia and blood transfusions in patients with cancer. ANESTHESIOLOGY 2015; 122:3–4
3. Wanderer JP, Rathmell JP, Johnson A: Perioperative transfusion: A complicated story. ANESTHESIOLOGY 2015; 122:xxiii
4. Carson JL, Terrin ML, Noveck H, Sanders DW, Chaitman BR, Rhoads GG, Nemo G, Dragert K, Beaupre L, Hildebrand K, Macaulay W, Lewis C, Cook DR, Dobbin G, Zakriya KJ, Apple FS, Horney RA, Magaziner J; FOCUS Investigators: Liberal or restrictive transfusion in high-risk patients after hip surgery. N Engl J Med 2011; 365:2453–62
5. Holst LB, Haase N, Wetterslev J, Wernerman J, Guttormsen AB, Karlsson S, Johansson PI, Aneman A, Vang ML, Winding R, Nebrich L, Nibro HL, Rasmussen BS, Lauridsen JR, Nielsen JS, Oldner A, Pettilä V, Cronhjort MB, Andersen LH, Pedersen UG, Reiter N, Wiis J, White JO, Russell L, Thornberg KJ, Hjortrup PB, Müller RG, Møller MH, Steensen M, Tjäder I, Kilsand K, Odeberg-Wernerman S, Sjøbø B, Bundgaard H, Thyø MA, Lodahl D, Mærkedahl R, Albeck C, Illum D, Kruse M, Winkel P, Perner A; TRISS Trial Group; Scandinavian Critical Care Trials Group: Lower *versus* higher hemoglobin threshold for transfusion in septic shock. N Engl J Med 2014; 371:1381–91
6. Villanueva C, Colomo A, Bosch A, Concepción M, Hernandez-Gea V, Aracil C, Graupera I, Poca M, Alvarez-Urturi C, Gordillo J, Guarner-Argente C, Santaló M, Muñiz E, Guarner C: Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013; 368:11–21
7. Carson JL, Brooks MM, Abbott JD, Chaitman B, Kelsey SF, Triulzi DJ, Srinivas V, Menegus MA, Marroquin OC, Rao SV, Noveck H, Passano E, Hardison RM, Smitherman T, Vagaonescu T, Wimmer NJ, Williams DO: Liberal *versus* restrictive transfusion thresholds for patients with symptomatic coronary artery disease. Am Heart J 2013; 165:964–971.e1
8. Yazer MH, Triulzi DJ: Things aren't always as they seem: What the randomized trials of red blood cell transfusion tell us about adverse outcomes. Transfusion 2014; 54:3243–6; quiz 3242

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Association of Postoperative Transfusion Strategy with Short-term Outcomes in Surgical Oncology Patients

To the Editor:

In a controlled, randomized clinical trial assessing the effect of postoperative transfusion strategy on the short-term outcomes in the intensive care unit (ICU) high-risk patients undergoing abdominal oncological surgery, Pinheiro de Almeida *et al.*[1] showed that a liberal transfusion strategy with a hemoglobin trigger of 9 g/dl was associated with fewer major postoperative complications and decreased short-term mortality compared with a restrictive strategy with a hemoglobin threshold of 7.0 g/dl. Their results are different from the findings of the recent two large controlled, randomized clinical trials by Carson *et al.*,[2,3] in which reduced severe complications and short- or long-term mortality after hip fracture surgery in a high-risk group of elderly patients with cardiovascular disease or risk factors are not demonstrated when comparing a postoperative liberal transfusion strategy with a restrictive transfusion strategy. Other than slightly higher transfusion triggers (liberal strategy with a hemoglobin of 10 g/dl and restrictive strategy with a hemoglobin of 8 g/dl) used in the studies by Carson *et al.*,[2,3] several important issues of the study by Pinheiro de Almeida *et al.*[1] should be clarified and discussed before adoption of their results into routine practice.

First, comparing preoperative albumin levels between groups is barely meaningful. Preoperative hypoalbuminemia is a common problem in cancer patients and has been independently associated with the postoperative complications and mortality.[4,5]

Second, we were not provided with detail of anesthesia and intraoperative managements. It has been shown that intraoperative hypoxemia, hypotension, tachycardia, and hypertension are independently associated with morbidity and mortality after noncardiac surgery.[6–8] Furthermore, the authors did not provide intraoperative blood loss and transfusion hemoglobin triggers although they are important for postoperative short-term outcomes. Among elderly patients undergoing major noncardiac surgery, intraoperative blood transfusion has been associated with decreased mortality risk in patients with preoperative hematocrit levels of less than 24% or in patients with mild to no preoperative anemia (hematocrit of 30% or greater) when there is substantial blood loss (500 to 999 ml). However, intraoperative transfusion is not helpful for patients with hematocrit levels of 24% or greater when the estimated blood loss is less than 500 ml, and it may be harmful if their preoperative hematocrit levels are between 30 and 35.9%.[9]

Third, most patients included in this study were classified as American Society of Anesthesiologists physical status 2 or 3 and had a good performance status and localized disease. The mean hemoglobin levels at ICU admission were 11.0 to 11.2 g/dl. However, the mean hemoglobin levels before transfusion in ICU decreased to 6.8 to 7.9 g/dl, and most transfusions were given after the third day of the ICU stay.

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