nonsignificant) excess of patients with diabetes, chronic obstructive pulmonary disease, and congestive heart failure in the restrictive group. Adequate blinding is challenging for this patient group, and treating physicians were not blinded to the randomization. It is therefore possible that the rest of the care delivered was different between the groups. These confounding factors may have contributed toward the worse outcomes in the patients in the restrictive transfusion group.

The implications of this study could be substantial, and although the numbers of patients are small compared with other similar studies, the outcomes are apparently significant. However, the evidence that true differences in hemoglobin between the two groups was achieved is lacking, and furthermore, less than half of the patients even in the liberal group required transfusion and less than a third of patients in the study received any blood. This makes it difficult to assign differences in outcomes between the groups to transfusion.

Given the unexpected findings of this study, we would advise caution in interpreting the results. We feel differences in outcome cannot be attributed to the transfusion strategy alone. Further randomized studies are needed prior to alterations in clinical practice.

Competing Interests

The authors declare no competing interests.

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Liberal Transfusion Practice or Perioperative Treatment of Anemia to Avoid Transfusion?

To the Editor:

With great interest we read the article by Pinheiro de Almeida *et al.*[1] on "Transfusion Requirements in Surgical Oncology Patients" that addresses a clinical problem of utmost importance and ongoing debate. However, there remain some concerns with the interpretation of data and conclusions that can be drawn from these results.

1. Patients were included in this study if their hemoglobin level was more than or equal to 9 g/dl before admission to the intensive care unit (ICU). A hemoglobin level of 9 to 10 g/dl represents a state of severe anemia that occurred in a certain number of patients despite transfusion before randomization (fig. 3). Unfortunately, the incidence and severity of anemia according to the World Health Organization definition in the study groups is not reported. Regarding the further comorbidity profile of patients included, the number of patients with emergency operations (n = 13 *vs.* 9), congestive heart failure (n = 6 *vs.* 3), chronic obstructive pulmonary disease (n = 9 *vs.* 5), diabetes mellitus (n = 26 *vs.* 20), metastatic cancer disease (n = 39 *vs.* 32), and cerebrovascular disease (n = 8 *vs.* 2) were, at least numerically, higher in the restrictive group. It would be interesting whether the composite of these comorbidities was equally distributed between groups to better understand the interaction of anemia and preoperative

comorbidities. This would be of great importance for the reader as it has been reported by Musallam *et al.*[2] that the composite postoperative morbidity at 30 days was also higher in patients with anemia than in those without anemia (adjusted odds ratio, 1.35; 95% CI, 1.30 to 1.40). Taken these points together, one may speculate that a higher proportion of sicker patients were randomized into the restrictive group, which could have benefitted from treatment of preoperative anemia to improve their condition before surgery.

2. Another important limitation that needs to be discussed is that randomization was performed on admission to the ICU. However, during surgery, a mean of 27.8% of patients in the liberal group and 24.8% in the restrictive group have been transfused with one or more units of erythrocytes, resulting in a mean hemoglobin level of 11.0 g/dl in the liberal group and 11.2 g/dl in the restrictive group when being randomized into this study. In this setting, the situation may have occurred that patients were transfused during surgery and being randomized into the restrictive group while patients who were not transfused during surgery could have been randomized to the liberal group having a higher chance of transfusion in the ICU. Both patients may have received the same number of erythrocyte units during surgery and ICU treatment although being in different study groups, which may question the conclusion that a liberal transfusion trigger improves outcome.
3. The transfusion protocol was followed until discharge from the ICU; however, after discharge from the ICU, transfusion of erythrocytes was left to the discretion of the attending physician until discharge from hospital. The pretransfusion hemoglobin trigger after discharge from the ICU was neither different (mean, 7.5 g/dl in both groups) nor restrictive. This may give rise to the assumption that not a restrictive transfusion practice impaired outcome, but that tolerance of severe anemia with a hemoglobin level between 7 and 9 g/dl during ICU treatment burdens oncologic patients with cardiac, cerebrovascular, and pulmonary comorbidities with a substantial risk of complications (higher incidence of cardiovascular complications with 13.9 *vs.* 5.2%, $P = 0.038$, reoperations with 16.8 *vs.* 10.3%, and abdominal infections with 14.9 *vs.* 5.2%) and mortality. Preoperative anemia treatment may have prevented hemoglobin levels to decrease until serious adverse effects of anemia become apparent. In addition, the mean ICU stay was 4 days in both groups and survival started to differ between groups after day 12 (fig. 2). This supports the view that severe perioperative anemia may exhibit a delayed negative impact on outcome. In conjunction with the issue of intraoperative transfusions that was described above, this does not necessarily mean that a restrictive transfusion practice impairs complication rate and mortality, but could be attributed to the adverse effects of severe perioperative anemia in oncologic patients.
4. The pathophysiological explanation for the effect of a more liberal transfusion practice is unclear. The authors speculate that anemia and reduced oxygen delivery may have played a role for impaired tissue oxygenation or microvascular flow. With regard to blood cell transfusion, basic physiology indicates that an increase of hemoglobin enhances oxygen delivery, even though there is still a debate that enhanced oxygen delivery maintains organ function by increasing cellular oxygen uptake and consumption[3,4] on a cellular level. In contrast to the results of the presented study, several analyses have shown that the transfusion of erythrocytes has been associated with adverse outcomes, for example, higher infection rates. Furthermore, a large prospective randomized trial in septic shock patients did not describe a higher survival and lower infection rate for a liberal transfusion trigger less than 9 g/dl compared with a more restrictive transfusion at a hemoglobin level less than 7 g/dl.[5]

In conclusion, to our understanding, it is still controversial whether the restrictive transfusion strategy or the effect of sustained perioperative anemia caused the significant increase in mortality in this group of patients. A prospective trial on the efficacy of a preoperative anemia treatment protocol in patients with cardiac, cerebrovascular, and pulmonary comorbidities undergoing oncologic surgery may answer this question.

Competing Interests

Dr. von Heymann has received honoraria for consultancy work and lectures from Vifor Pharma GmbH, Germany, and Janssen-Cilag GmbH, Germany, within the last 36 months. The other authors declare no competing interests.

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In Reply:

We do not believe that randomized controlled trials (RCTs) have shown similar outcomes with a restrictive transfusion strategy compared to a liberal one—this is true only at first sight.[1–3] Indeed, a deeper analysis of these trials indicates that the reality might not be so straightforward. Just to take the latest study on blood transfusions after cardiac surgery,[3] in which the conclusion based on the primary outcome was that a restrictive transfusion threshold was not superior to a liberal threshold, there were actually more deaths in the restrictive than in the liberal threshold group (4.2 *vs.* 2.6%; hazard ratio, 1.64; 95% CI, 1.00 to 2.67; $P = 0.045$).

Importantly, in these large RCTs, it is more than likely that there were patients in each arm who experienced benefit and others who were harmed. In other words, there will have been some patients who received a transfusion simply because they were randomized to the high threshold group, although in normal practice a transfusion would not have been considered; similarly, some patients at higher risk who would normally have been transfused will have received no transfusion because they were randomized to the low threshold group. This concept was highlighted by an analysis of the data from the landmark Canadian Transfusion Requirements in Critical Care study by Deans *et al.*,[4] showing that 30-day mortality rates were different and opposite in the liberal compared with the restrictive arm depending on the presence (21 *vs.* 26%) or absence (25 *vs.* 16%) of ischemic heart disease ($P = 0.03$).

The need for erythrocyte transfusion and the benefit/risk ratio vary according to individual patient characteristics, including age and comorbidities, so large-scale RCTs in heterogeneous groups of patients may not be the most appropriate tool to investigate these issues; smaller RCTs in carefully defined patient groups may provide more useful information.[5] Observational studies including a sufficient number of covariates have also indicated that blood transfusions can be associated with better outcomes in critically ill patients.[6–8]

Our results[9] clearly show that a liberal strategy of erythrocyte transfusion, in comparison with a restrictive one, reduced mortality and major complications in our population of surgical cancer patients. We focused on cancer patients undergoing major abdominal surgery during their ICU stay because there is good evidence that transfusions are most beneficial in the sickest patients,[4,10] and the majority of postoperative complications happen in the ICU setting.[1–3] Our RCT included well-balanced groups in terms of baseline demographic data and preoperative characteristics. As Dr. Waters and colleagues will know, calculations of *P* values should not be used to compare baseline data[11] and are avoided in the leading journals.[3] The intervention was clearly different in the two groups. The proportion of patients who received a transfusion was about 50% lower in the restrictive group than in the liberal one, both during the ICU stay and during the hospital stay. The restrictive group received a total of 88 erythrocyte units and the liberal group 134 units. The average hemoglobin concentration was higher in the liberal strategy group than in the restrictive strategy group before transfusion (7.9 ± 0.5 *vs.* 6.8 ± 0.5 g/dl; $P < 0.001$) and during the ICU stay. As a result, the restrictive group was exposed to more postoperative severe anemia than the liberal group, which may explain their higher rates of complications.

Drs. Sharifpour, Hall, and von Heymann comment that our results were different from those of the Transfusion Requirements in Septic Shock trial.[2] However, there are some clear differences between our study and the Transfusion Requirements in Septic Shock trial, in which patients were already in septic shock with marked organ failure (median Sequential Organ Failure Assessment score of 10 in both groups). This was not the case in our study. At that stage of septic shock, few interventions have been shown to improve outcome.

We agree with Dr. Xue *et al.* that low serum albumin concentration is a common finding in patients with cancer and has been associated with poor outcome in surgical patients in previous studies. We reported the serum albumin concentration of patients, along with other laboratory and clinical data, to describe our population. We do not believe that intraoperative adverse events and different reasons for admission could have influenced our results. As mentioned above, prerandomization characteristics were well balanced between groups, including intraoperative factors, such as type of anesthesia, duration of surgery, and rates of erythrocyte transfusion. We agree with Dr. Xue *et al.* that in clinical practice we also consider clinical variables to guide our transfusion decisions, but this potential limitation was