In a single center, randomized, controlled trial entitled “Liberal Versus Restrictive Transfusion Strategy in Critically Ill Oncologic Patients: The Transfusion Requirements in Critically Ill Oncologic Patients Randomized Controlled Trial”, the authors conclude that a liberal strategy for blood transfusions (hemoglobin threshold <9 g/dL) may be more favorable in adult cancer patients with septic shock, compared to a restrictive strategy which utilized a hemoglobin threshold of <7 g/dL (1). The transfusions included only leukodepleted units, and hematologic malignancy patients were excluded due to high inherent transfusion requirements.

The study conclusion appears to be discordant with the Surviving Sepsis Campaign (SSC) guidelines for the management of anemia in sepsis and septic shock. From 2004 to 2012, the SSC guidelines recommended a restrictive approach to blood transfusions “once tissue hypoperfusion has resolved and in the absence of extenuating circumstances, such as significant coronary artery disease, acute hemorrhage, or lactic acidosis” (2-4). Interestingly, in the 2016 SSC guidelines the caveat of “once tissue hypoperfusion has resolved” was omitted and the recommendations emphasized only the “extenuating circumstances” and a hemoglobin threshold of <7 g/dL (5). The rationale for the recommendations in the 2016 guidelines was based on two studies, namely the transfusion requirements in septic shock (TRISS) and the protocol-based care for early septic shock (ProCESS) trials (6,7). Both trials showed similar mortality rates for the two treatments groups with respect to transfusions; however, it is notable that the patients in the ProCESS trial had already received resuscitation at the time of enrollment and thus potentially had less tissue hypoperfusion. Neither of the studies included a significant enough percentage of oncology patients for the results to be valid in that particular population.

Prior studies reviewing the use of blood transfusions in critically ill patients, not limited to sepsis or cancer, showed increased mortality rates for those patients who received transfusions or a liberal transfusion strategy (8,9). In contrast, the 2006 observational SOAP study (10) concluded that blood transfusion was not associated with an increased risk of death when controlled for organ dysfunction scores, such as SAPSII and SOFA. Interestingly, another study incorporating a leukoreduction program demonstrated a decreased mortality in critically ill surgical patients who received blood transfusions (11).

Unfortunately, studies specifically addressing blood transfusions in critically ill cancer patients with sepsis are severely limited, and the current SSC guidelines do not adequately address the question in this particular population. Of the limited data available in cancer patients,
A number of studies have shown that blood transfusions for anemia are associated with increased risk of mortality, and of venous and arterial thrombosis (12).

It is also worthwhile to mention that the adverse effects of blood transfusions may not only be related primarily to leukocytes but rather to the impact of the high amounts of free hemoglobin especially in older blood due to its properties to inactivate NO that may severely impair nutritive blood flow (13,14). This may be especially harmful in sepsis patients (15). A number of studies that evaluated the impact on NO inactivation in septic shock by NO inhibitors demonstrated harmful effects and worse outcomes (16,17). Phase II studies evaluating the safety and efficacy of free hemoglobin solutions were stopped prematurely for safety reasons. What the above studies collectively illustrated is that a liberal transfusion strategy is not superior to a restrictive one.

The study authors agree that their results have limited external generalizability due to the selected cohort of patients studied, i.e., solid tumor cancer patients at a single tertiary care institution which specializes in cancer care. Another potential limitation is the small sample size of the study population, consisting of 300 patients. We would stress this as a major limitation, because it is well-known that small-sized sepsis studies again and again have produced results that could not be confirmed in larger multiple-center trials (18-20).

Based on our review and assessment, this study does not provide conclusive enough evidence that a liberal strategy for blood transfusion should be utilized in cancer patients with sepsis. However, this important clinical question clearly requires further investigation with a larger multiple-center study to help clarify the area of uncertainty.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References
