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Wayne State University School of Medicine
Detroit, Mich

BLOOD TRANSFUSION

To the Editor:

I enjoyed the recent article “Perioperative Blood Transfusion as a Dose-Dependent Relationship With Disease Recurrence and Survival in Patients With Non–Small Cell Lung Cancer” by Latif and colleagues¹ in the June 2019 issue of *The Journal of Thoracic and Cardiovascular Surgery*. Latif and colleagues¹ are to be congratulated for their low 1-unit blood transfusion rate (4%) and low rate of transfusion of 2 or more units of packed red blood cells (6%) during the 16-year study including 4847 operations.

When a patient received 1 unit of blood during an operation, the Monday morning quarterbacks usually concluded that the patient may not have required that single unit. Did the group who received 1 unit of blood have an epidural catheter for pain relief and concomitant increase in fluid requirements? Were they operated on while taking clopidogrel or other antiplatelet drugs? Could they have been exposed to checkpoint inhibitors, which may result in more prominent lymph nodes and greater intraoperative blood loss, or might they have a postoperative systemic inflammatory response syndrome reaction resulting in a greater fluid requirement and transfusion?

In addition, the length of the hospital stay is not mentioned, and this may have been a factor in how many units of blood the patient received. A longer hospitalization with intravenous fluids, epidural, and daily blood draws may have affected the number of units of blood transfused.

If the data for the patients receiving 2 or more units of blood were available, one would suspect that culprits such as intraoperative vascular injury, coagulopathy, or low systemic vascular resistance would affect overall survival and recurrence statistics.

Frank A. Baciewicz, Jr, MD

Division of Cardiothoracic Surgery

Michael and Marian Ilitch Department of Surgery

The Editor welcomes submissions for possible publication in the Letters to the Editor section that consist of commentary on an article published in the Journal or other relevant issues. Authors should: • Include no more than 500 words of text, three authors, and five references. • Type with double-spacing. • See <http://jtcvs.ctsnetjournals.org/misc/fora.shtml> for detailed submission instructions. • Submit the letter electronically via jtcvs.editorialmanager.com. Letters commenting on an article published in the JTCVS will be considered if they are received within 6 weeks of the time the article was published. Authors of the article being commented on will be given an opportunity to offer a timely response (2 weeks) to the letter. Authors of letters will be notified that the letter has been received. Unpublished letters cannot be returned.

Reference

1. Latif MJ, Tan KS, Molena D, Huang J, Bott MJ, Park BJ, et al. Perioperative blood transfusion has a dose-dependent relationship with disease recurrence and survival in patients with non–small cell lung cancer. *J Thorac Cardiovasc Surg*. 2019;157:2469-77.

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REPLY: PERIOPERATIVE TRANSFUSION: IMMUNOLOGICAL BEAST OR SCAPEGOAT Reply to the Editor:

I enjoyed reading the letter to the Editor by Dr Baciewicz, who asks several relevant questions about the article, “Perioperative blood transfusion has a dose-dependent relationship with disease recurrence and survival in patients with non–small cell lung cancer” by Dr Latif and colleagues. First, Dr Baciewicz congratulated the Memorial Sloan Kettering Thoracic Surgery group for the low rate of transfusion. This low rate with a high number of cases enables Latif and colleagues to examine the effects of blood transfusions on patient outcomes without excessive complications or marginal technique that helps eliminate compounding variables.

However, Dr Baciewicz does note that other potential compound variables were not addressed in the article. He asks about epidural use, increases in the dose of epidural infusions, length of stay, and clopidogrel or other antiplatelet agents. He also mentions that checkpoint inhibitors is another variable, yet neoadjuvant chemotherapy before and after the matching-weights analysis was not statistically significant. Although not stated, I suspect most patients with neoadjuvant therapy had cytotoxic agents rather than immunotherapy and checkpoints are not an unadjusted, compounding variable. Other clinical variable often called the “eyeball test” are physician judgements or clinical decisions that are made daily in our practices, but are rarely quantifiable. For example, does the patient appear fatigued or pale? Is the patient not ambulating as well as expected? These judgements are part of normal clinical variation that we do not incorporate well in studies. Other than the checkpoint inhibitors, I agree with Dr Baciewicz that these variables could bias the results slightly.

Regardless of these limitations, Dr Latif and colleagues performed a well designed, large study with rigorous statistical analysis. Their data suggest that 1 unit is not particularly consequential in patient outcomes. One unit of blood contains approximately 250 mL with a substantial

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number of antigens that should easily activate the immune system even with appropriate donor matching. I think their article shows us that the immune system is invoked as the culprit of poor patient outcomes too often.

*R. Taylor Ripley, MD
Division of General Thoracic Surgery
The Michael E. DeBakey Department of Surgery
Baylor College of Medicine
Houston, Tex.*

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REPLY: RESPONSE TO LETTER “BLOOD TRANSFUSION”

Reply to the Editor:

In their recently published article in the *Journal*, Latif and colleagues¹ retrospectively demonstrated that patients undergoing resection of non–small cell lung cancer are at higher risk for recurrence and decreased longevity if they receive 2 or more units of blood in the perioperative period. In his correspondence addressing this article, Dr Baciewicz highlights several factors potentially associated both with increasing transfusion requirements and with detriments in overall and recurrence-free survival that are potentially confounding. Whereas the authors of the original article may address the relevance of these individual factors to their findings, this letter should inspire our readers to maintain critical appraisal of our published literature. In our field, causality between an intervention and an outcome is less commonly supported by randomized, prospective data than by assimilation of layers of evidence from retrospective and prospective cohort

studies. For example, the majority of recommendations of the National Comprehensive Cancer Network are based on “lower-level” evidence, with uniform National Comprehensive Cancer Network expert panel consensus that the intervention is appropriate (category 2A). Although there may be no prospective, randomized data showing that allogeneic blood products negatively influence survival or recurrence after resection of human malignancies, there is an overwhelming and accumulating body of retrospective studies, systematic reviews, and meta-analyses demonstrating that perioperative blood transfusion is independently associated with decreased overall or recurrence-free survival after resection of upper and lower gastrointestinal, pancreatic, hepatobiliary, and urologic malignancies. The study of Latif and colleagues¹ addresses a knowledge gap in the surgical treatment of non–small cell lung cancer and is bolstered by a robust sample and rigorous design. I am also interested in the response to Dr Baciewicz by Latif and colleagues¹ and await additional confirmation of their findings in non–small cell lung cancer, while transfusing my patients as infrequently as possible.

*Bryan M. Burt, MD
Division of General Thoracic Surgery
Department of Surgery
Baylor College of Medicine
Houston, Tex*

Reference

1. Latif MJ, Tan KS, Molena D, Huang J, Bott MJ, Park BJ, et al. Perioperative blood transfusion has a dose-dependent relationship with disease recurrence and survival in patients with non–small cell lung cancer. *J Thorac Cardiovasc Surg*. 2019;157: 2469-77.

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