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EDITORIAL COMMENT

More Alike Than Not? Predicting Mortality in the Cardiac and Medical Intensive Care Units*

Jeffrey Wang, MD, Marc D. Thames, MD

The modern cardiac intensive care unit (CICU) has changed significantly since the advent of the coronary care unit in the 1960s.[1] It has been transformed from the initial coronary care unit, which was dedicated to caring for patients presenting with acute coronary syndromes, into the current CICU in which a multidisciplinary team cares for circulatory failure due to various pathologies in complex patients.[2] While the leading admission diagnosis for the CICU remains acute coronary syndromes (29.4%), this is now followed by heart failure (15.7%) and valvular heart disease (7.8%).[3] In a recent retrospective study of 2 large tertiary centers, CICU patients were reported to have multiple comorbidities, with 11% of patients having 3 or more.[4] While clinical investigations into the medical intensive care unit population have been established for several decades with many randomized clinical trials completed and more ongoing,[5] the CICU is a relative newcomer in this regard and could be a site for important future studies.

One area of interest is in creating models using readily available data to better predict the risk of mortality in patients admitted specifically to the CICU.[6] In the critical care literature, leukocytosis, a commonly detected laboratory abnormality, was previously considered to be associated mainly with sepsis. There is evidence to suggest that a higher degree of leukocytosis is associated with an increased risk of mortality.[7,8] Less commonly, sepsis can also present with leukopenia, which is considered an ominous sign.[9] Interest in using the leukocyte count exists in the cardiology literature as well, which observed that leukocytosis after myocardial infarction or percutaneous coronary intervention predicted increased risk of mortality.[10,11] In patients with cardiogenic shock, leukocytosis also predicted a higher risk of mortality.[12] What has been missing is determining if these findings still hold true in a large modern CICU database in whom sepsis would be less prevalent.

In this issue of *JACC: Advances*, Smith et al[13] utilize the Mayo CICU database (final analytic cohort: n = 10,195), which has been previously characterized and is well published.[14] The authors categorized the cohort based on admission leukocyte count using generally accepted cutoffs (low <4, normal 4-11, high 11-22, very high >22 10^9 cells/L). They first demonstrated (Figure 1 of Smith et al[13]) that there is a "J-shaped" association between in-hospital mortality with leukocyte count. Mortality is lowest in the normal leukocyte count (4-11), higher in the low leukocyte and high leukocyte groups, and highest in the very high leukocyte group. This relationship persisted after using multivariate modeling. To confirm the findings using a machine learning approach, they used random forest modeling, which is a decision tree-based algorithm that maximizes prediction of mortality. Evaluation of the random forest model using a feature importance plot (Figure 4 of Smith et al[13]) demonstrated continued importance of the leukocyte count in predicting mortality, thus confirming their findings.

The authors should be commended for putting together a thorough and thoughtful analysis utilizing a readily available laboratory value while

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From the Division of Cardiology, Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA.
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incorporating novel techniques of machine learning. The strengths of this analysis are: 1) their use of a large representative data set in a novel CICU population; 2) their selection of mortality as the primary outcome rather than other less clinically relevant end points; and 3) their use of leukocyte count as the predictor, which is a readily available laboratory value. These types of foundational investigations are hypothesis generating and serve as the basis for future prospective clinical studies in the CICU. There are several important limitations that should be noted.

The Mayo CICU cohort is a heterogenous group (as CICU populations are) and the authors appropriately demonstrate that this cohort includes patients with various cardiac and noncardiac pathologies—including sepsis. The methods employed by this investigation do not stratify by type of shock or admission diagnosis, which may make it difficult to detect important effects in subpopulations. A strength of this patient cohort is that only 6.5% of patients had an admission diagnosis of sepsis or septic shock (Table 1 of Smith et al[13]), and most patients had various forms of cardiac pathologies leading to circulatory failure. Secondly, the methods employed in the investigation are for predicting mortality in the CICU based on the initial leukocyte count—not that leukocytosis or leukopenia is necessarily a mechanism contributing to increased risk of mortality. We advise caution in interpreting this investigation as supporting targeting inflammation or leukocyte count as a therapy. Further support for this precaution is that their approach to variable selection during multivariate analysis used 4 methods: Akaike Information Criterion, Bayes Information Criterion, Least Absolute Shrinkage and Selection Operator, and Elastic Net. These approaches, while valid, seek to maximize the ability of leukocyte count to predict mortality. Based on the data and methods, we should interpret admission leukocyte count as another marker (or predictor) clinicians can use to assess a patient's severity of illness and thus risk for mortality. This is akin to postintubation PaO_2:FiO_2 ratio in predicting mortality in patients with acute respiratory distress syndrome.

In Smith et al,[13] the investigators have selected a routinely measured laboratory value (leukocyte count) and have demonstrated that it does have clinical predictive ability in a heterogenous, and critically ill patient cohort admitted to the CICU—most of whom were not septic. They found that there is a J-shaped relationship between leukocyte count and risk of mortality, with both low and high leukocyte counts predicting increased risk of mortality. These patterns resemble the findings from the literature in sepsis and septic shock where leukopenia and leukocytosis were also associated with increased mortality.[7,9] The work performed by Smith et al[13] is important and suggests further investigations are needed to advance our ability to identify early risk predictors for patients admitted to the CICU. By doing these types of investigations, we reveal that while intensive care units have become increasingly stratified by subspecialty, the underlying human physiology and pathophysiology are still the lingua franca of critical care medicine and applicable no matter the unit in which one practices.

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ADDRESS FOR CORRESPONDENCE: Dr Jeffrey Wang, Emory University School of Medicine, 1750 Haygood Drive NE, Atlanta, Georgia 30322, USA. E-mail: jwang37@emory.edu.

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