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EDITORIAL

The EAS(E)IX of predicting sepsis after allogeneic hematopoietic cell transplantation

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Various scoring systems have been developed and validated to predict overall outcomes after allogeneic hematopoietic cell transplantation (allo-HCT) by considering a patient's comorbidities, disease-specific characteristics, and donor-specific elements [1, 2]. The Endothelial Activation Stress Index (EASIX) is an easy scoring system first described in 2017 aimed at predicting overall mortality and mortality after the development of acute graft-versus-host disease (GVHD) in patients post-allo-HCT [3]. The score is derived from three common laboratory parameters that are associated with endothelial dysfunction from the diagnostic criteria of transplantation-associated thrombotic microangiopathy (TA-TMA), that is lactate dehydrogenase (U/L) × creatinine (mg/dL)/platelet count (10^9/L), and can be collected at various time points of an allo-HCT patient's clinical course. Endothelial dysfunction is a key feature of other important complications of allo-HCT that may require admission to the intensive care unit (ICU) including GVHD, sinusoidal obstruction syndrome (SOS/VOD),® idiopathic pneumonia syndrome, and sepsis [4]. Therefore, EASIX may help clinicians to longitudinally assess the potential risks of complications during the post-allo-HCT course [5].

Since its inception, EASIX has been applied to various settings and patient populations such as ICU admission in patients affected by coronavirus disease 2019 (COVID-19), the development of cytokine release syndrome or neurotoxicity in chimeric antigen receptor T-cell (CAR-T) recipients, and the survival of patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) [6–8]. In many cases, the score (or a permutation) has been identified as a negative outcome predictor, with patients situated in a higher range at significant risk of deterioration. Arguments for the biological plausibility of the EASIX, which is usually more capable than the sum of its parts in predicting hazard, rely on the central theme of endothelial injury mediating and perpetuating the disease processes; in circumstances where endothelial dysfunction does not underlie toxicity as obviously as it does in TA-TMA (such as neurotoxicity in CAR-T recipients), these arguments rely on preclinical models [9].

In 2022, the Heidelberg group sought to examine EASIX as a predictor of sepsis in their allo-HCT cohort (when the score was calculated prior to transplant, or *EASIX-pre*), finding a roughly 16-fold hazard ratio for the development of sepsis in patients who surpassed an EASIX threshold of 2.32 [10]. In this issue of Intensive Care Medicine, Korell et al., in their follow-up letter, examine the use of the EASIX score for the prediction of sepsis using a large, new, American validation cohort of patients undergoing allo-HCT [11]. This is the second publication to highlight the use of *EASIX-pre* in the context of sepsis and it replicated the efficacy of the previously reported cutoff in discriminating high from low sepsis risk in the allo-HCT population. Furthermore, the authors generated a similar hazard ratio in the Cox regression model employed, despite other differences between United States and German cohorts, as elaborated on in their supplemental material. This is likely to shape further investigation into how this score could be

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used to influence clinical practice in high-risk patients undergoing allo-HCT.

Future research directions involving EASIX are manifold. Dynamic models assessing the score longitudinally rather than at a fixed pre- or post-transplant point in time could provide further improvement in the prediction of non-relapse mortality among allo-HCT patients [5]. Similarly, Korell et al. have reported in their supplementary data on EASIX range disparities across time by presence or absence of sepsis, with uncertain significance. Additionally, considering the quite extensive use made of EASIX in assessing non-allo-HCT patient outcomes (such as those in DLBCL), Korell et al.'s findings now invite trialing sepsis prediction in these cohorts. A more granular understanding of the specific microbial causes and patterns of sepsis in patients with high *EASIX-pre* is warranted. While predictive scores can be helpful in cross-trial comparisons and potentially in counseling patients about risks, their true utility is questionable unless the scores can be used clinically to guide treatment decisions such as choice of conditioning regimen, GVHD prophylaxis, anti-microbial prophylaxis, and other decisions that ultimately optimize the efficacy, tolerability, and safety of allo-HCT. As partners in the care of this patient population, ICU clinicians should be aware of the ease, utility and limitations of EASIX. We should reserve judgement as to how it could be used for ICU triage or other decision-making once an allo-HCT patient requires ICU level of care.

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