Dear Editor,

Endothelial complications are important causes of mortality after allogeneic stem cell transplantation (alloSCT) and can be predicted by endothelial activation and stress index (EASIX) [1–3]. EASIX integrates basic laboratory parameters (LDH, creatinine, and platelets) characterizing transplant-associated thrombotic microangiopathy and is prognostic for outcome in a variety of clinical settings, including coronavirus disease 2019 (COVID-19) and chimeric antigen receptor T (CAR-T) cell therapy [4, 5].

Sepsis is a dysfunctional endothelial response to harmful microorganisms. We hypothesized that EASIX may predict hazard of sepsis.

In this retrospective evaluation, 1290 adult patients allografted at our institution between 2004 and 2018 were assessed for presence of sepsis, neutropenic fever, and infectious pathogens within 50 days after transplantation. Neutropenic fever was graded according to the 2010 Infectious Diseases Society of America (IDSA) guidelines, while sepsis and septic shock were defined according to the modified Sepsis-3 guidelines by the Intensive Care Working Party (iCHOP) of the German Society of Hematology and Medical Oncology (DGHO) for neutropenic cancer patients (see supplements). Established pre-transplant scores and additional serum markers [Ferritin, interferon-gamma (IFNγ), CXCL9, interleukin (IL)-18, suppressor of tumorigenicity 2 (ST-2)], and soluble thrombomodulin (sCD141) were assessed longitudinally before and after transplantation (supplements) and correlated with outcome. EASIX was calculated as \( \text{LDH(U/L)} \times \text{creatinine(mg/dl)} / \text{platelets (per nl)} \). For risk factor evaluation, patients were randomly allocated 1:1 to a training and a validation cohort, respectively.

Neutropenic fever occurred in 77%, while infectious pathogens could be identified in 31% of patients. Sepsis was diagnosed in 7.2% of patients (Suppl. Tables 1, 2). Patients who developed sepsis had higher median EASIX values before conditioning (EASIX-pre) and at any later time point until day +28 irrespective of pathogen detection (Fig. 1A).

In the training cohort, EASIX-pre was the only marker significantly associated with hazard of sepsis in multivariable cause-specific Cox regression analyses (HR 2.3 for a two-fold change, \( p < 0.001 \), Suppl. Table 3). When EASIX-pre was replaced by its three single parameters in a separate multivariable analysis, LDH and platelets but not creatinine were significantly associated with sepsis risk (suppl. Table 4).

Based on Gray’s maximally selected rank statistics performed in the training cohort, EASIX was dichotomized into a “low-risk” group (EASIX < 2.32) and a “high-risk” group (EASIX > 2.32). Using this cut-off for multivariable Cox regression analysis in the validation cohort, we observed a cause-specific HR of 16.1 (7.0–36.9) for EASIX > 2.32 with respect to time to sepsis, corresponding to 7/462 sepsis events (1.5%) in the low-risk group vs 40/172 (23%) in the high-risk group (Suppl. Table 5). Prediction errors measured via time-dependent Brier score were smaller for the model including EASIX (Fig. 1B).

Sepsis risk was also significantly associated with post-, but not with pre-transplant levels of the endothelial vulnerability markers ST-2 and IL-18, but not with IFNγ;
Fig. 1 (See legend on next page.)
CXCL9, and sCD141 (Suppl. Figure 2). EASIX was superior to other established transplantation risk scores for predicting sepsis and 6-month non-relapse mortality (Fig. 1C–E).

Limitations of the study are its retrospective design and the single-center analysis.

In conclusion, EASIX-pre is a powerful prognostic marker of sepsis after alloSCT and might be used for guiding risk-adapted prevention strategies.

**Supplementary Information**
The online version contains supplementary material available at https://doi.org/10.1007/s00134-022-06676-3.

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