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LETTER

Validation of pre-conditioning EASIX for prediction of sepsis after allogeneic stem cell transplantation

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Dear Editor,

Sepsis represents a life-threatening emergency after allogeneic stem cell transplantation (alloSCT) associated with endothelial cell dysfunction [1], which is also linked to other complications after alloSCT such as transplant-associated microangiopathy (TAM) or sinusoidal obstruction syndrome (SOS) [2]. We hypothesized that endothelial activation and stress index (EASIX) might be a prognostic marker to predict risk of sepsis already pre-conditioning therapy (EASIX-pre), and we previously published results on EASIX-pre in sepsis from a single-center experience [3].

We validate the effect of EASIX-pre from the initial Heidelberg cohort including 1290 patients divided into training and testing cohorts (645 patients each) while balancing the number of sepsis events. The validation cohort consisted of 353 patients receiving alloSCT at the Massachusetts General Hospital Cancer Center (2017–2020). Patients were assessed for presence and grading of sepsis, neutropenic fever, and infectious pathogens within 50 days after transplantation. The modified Sepsis-3 guidelines for neutropenic cancer patients by the Intensive Care Working Party of the German Society of Hematology and Medical Oncology for sepsis and septic shock definitions were used [4]. EASIX was calculated with the formula lactate dehydrogenase (U/L) × creatinine (mg/dL) / platelets (10^9 cells/L) [5] at different timepoints, starting prior to application of conditioning chemotherapy, and for visualization until day + 28 after alloSCT. The predictive potential of EASIX-pre within multivariate (cause-specific) Cox regression was investigated by comparing time-dependent Brier score curves.

Sepsis was found in similar proportion in the validation cohort ($n = 27$ (7.7%)) as within the two initial cohorts (training $n = 46$ (7.1%), testing $n = 47$ (7.3%)) (see electronic supplementary material, ESM). Patients who developed sepsis until day + 50 had higher median EASIX-pre values before conditioning therapy, and higher EASIX values at any later time point until day + 28, compared with patients without sepsis (validation cohort, Fig. 1A). The coincidence of high EASIX-pre with sepsis was observed irrespective of pathogen detection or sepsis severity (ESM).

Our study validated an EASIX-pre cut-off (estimated at 2.32 in the training cohort) for distinguishing patients with a low risk of sepsis from a high-risk cohort: EASIX-pre above 2.32 measured prior to conditioning therapy confers a hazard ratio (HR) of 15.0 ($p < 0.001$) compared to lower EASIX-pre levels in the independent validation cohort, confirming results from the testing cohort (HR 17.9, $p < 0.001$). EASIX-pre > 2.32 also associated with increased hazards of 6-month non-relapse mortality (NRM) in both the testing and validation cohorts (ESM). The multivariable models of the testing cohort for the effects of EASIX-pre (continuous and dichotomized) were validated in the independent cohort for risk of sepsis and risk of 6-month NRM (Fig. 1B, C). EASIX-pre

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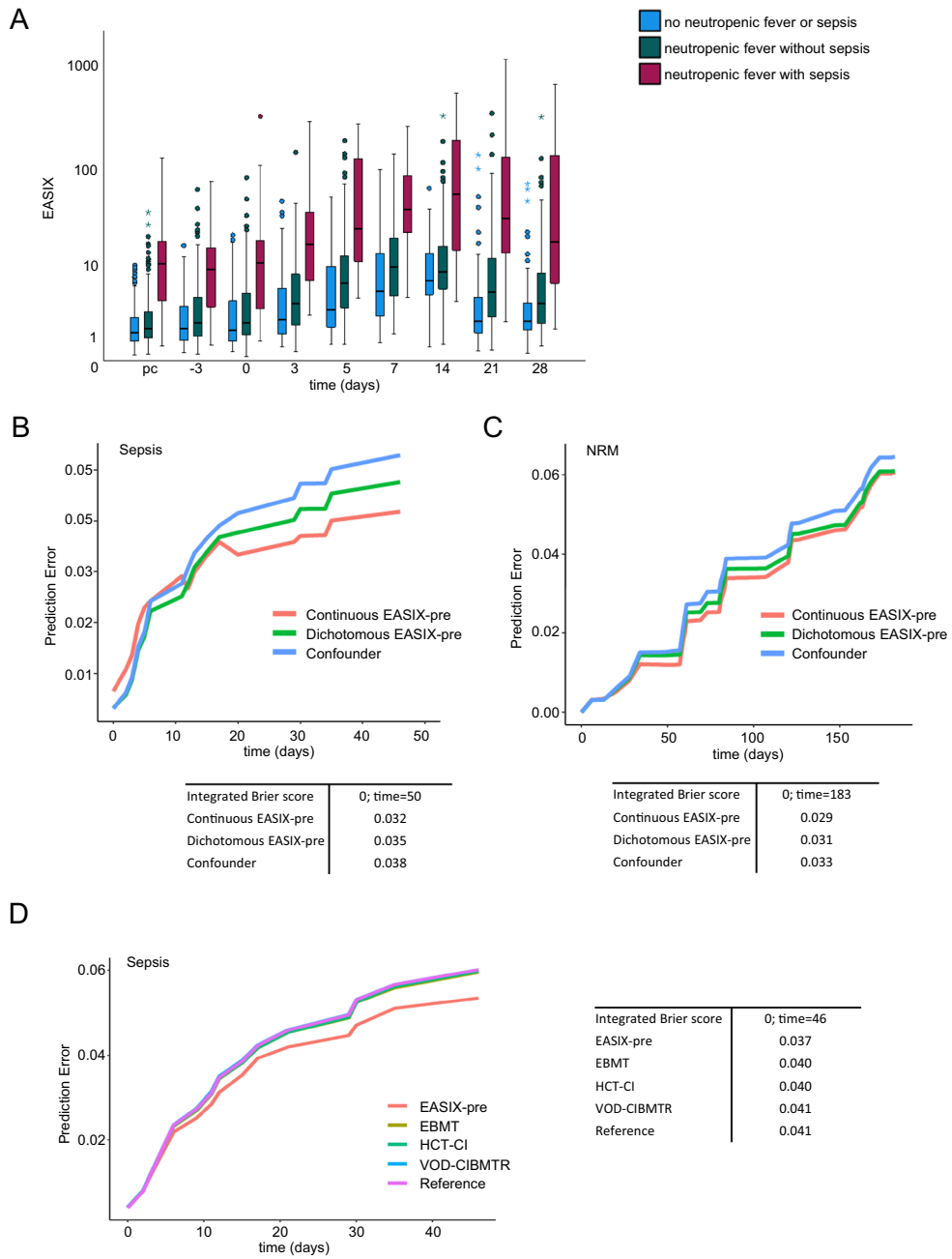

Fig. 1 (See legend on previous page.)

was also a superior predictor of sepsis compared to three other validated pre-transplantation scores (Fig. 1D).

The limitation of our study is the retrospective design. However, inclusion of an external independent validation cohort and the overall large patient number for a two-center study should offset this. As numbers of patients with sepsis were still small, these results warrant

(See figure on next page.)

Fig. 1 **A** Descriptive comparison of EASIX measured before and at the indicated time points after alloSCT in patients of the validation cohort who did ($n=27$) or did not ($n=326$) develop sepsis within 50 days after transplantation. Sepsis patients were subgrouped by no neutropenic fever or sepsis, and neutropenic fever without and with sepsis. * represent outliers. Patient numbers for EASIX calculation are listed in following order (no neutropenic fever or sepsis / neutropenic fever without sepsis/neutropenic fever with sepsis) for the different timepoints: prior conditioning $n=125/200/27$, day-3 $n=85/159/23$, day 0 $n=84/159/23$, day 3 $n=86/157/23$, day 5 $n=87/153/22$, day 7 $n=89/157/22$, day 14 $n=108/161/20$, day 21 $n=119/185/21$, day 28 $n=120/194/17$. One patient could not be classified regarding neutropenic fever (also see suppl. Table 2). **B** and **C** Prediction Error curves (Brier score) for multivariable cause-specific Cox regression validated in the external cohort ($n=353$), with integrated Brier score calculation. All multivariable models were established in the testing cohort ($n=609$) and included EASIX-pre (continuous EASIX-pre) or EASIX-pre cutoff 2.32 (dichotomous EASIX-pre) contrasted with multivariable models without EASIX-pre (Confounders). Endpoints (**B**) sepsis until d + 50, (**C**) NRM within 6 months. **D** Prediction Error curves (Brier score) for univariable cause-specific Cox regression validated in the validation cohort ($n=254$), with integrated Brier score calculation and sepsis within 50 days as endpoint. All univariable models were established in the testing cohort ($n=540$). EASIX-pre = dichotomous with cut 2.32. EASIX-pre = endothelial activation and stress index measured prior to conditioning therapy, alloSCT = allogeneic stem cell transplantation. *pc* prior conditioning, *NRM* non-relapse mortality, *EBMT* European Society for Blood and Marrow Transplantation, *HCT-CI* hematopoietic cell transplantation-specific comorbidity index, *CIBMTR-VOD* center for international blood and marrow transplant research-veno-occlusive disease

confirmation in larger multicenter trials with more sepsis patients.

In conclusion, EASIX-pre is a validated prognostic marker of early sepsis and 6-month NRM after alloSCT.

Supplementary Information
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