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Endothelial Activation and Stress Index (EASIX) to predict mortality after allogeneic stem cell transplantation: a prospective study

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ABSTRACT

Background We previously reported that the "Endothelial Activation and Stress Index" (EASIX; ((creatinine×lactate dehydrogenase)÷thrombocytes)) measured before start of conditioning predicts mortality after allogeneic hematopoietic stem cell transplantation (alloSCT) when used as continuous score. For broad clinical implementation, a prospectively validated EASIX-pre cut-off is needed that defines a high-risk cohort and is easy to use.

Method In the current study, we first performed a retrospective cohort analysis in n=2022 alloSCT recipients and identified an optimal cut-off for predicting non-relapse mortality (NRM) as EASIX-pre=3. For cut-off validation, we conducted a multicenter prospective study with inclusion of n=317 first alloSCTs from peripheral blood stem cell in adult patients with acute leukemia, lymphoma or myelodysplastic syndrome/myeloproliferative neoplasms in the European Society for Blood and Marrow Transplantation network.

Results Twenty-three % (n=74) of alloSCT recipients had EASIX-pre ≥3 taken before conditioning. NRM at 2 years was 31.1% in the high EASIX group versus 11.5% in the low EASIX group (p<0.001). Patients with high EASIX-pre also had worse 2 years overall survival (51.6% vs 70.9%; p=0.002). We were able to validate the cut-off and found that EASIX ≥3 was associated with more than twofold increased risk for NRM in multivariate analysis (HR=2.18, 95% CI 1.2 to 3.94; p=0.01). No statistically significant difference could be observed for the incidence of relapse.

Conclusions The results of this study provide a prospectively validated standard laboratory biomarker index to estimate the transplant-related mortality risk after alloSCT. EASIX ≥3 taken before conditioning identifies a population of alloSCT recipients who have a more than twofold increased risk of treatment-related mortality.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The "Endothelial Activation and Stress Index" (EASIX; ((creatinine×lactate dehydrogenase)÷thrombocytes)) predicts survival in recipients of allogeneic hematopoietic stem cell transplantation (alloSCT). EASIX also predicted survival in patients with COVID-19 infection, sepsis, cancer or chimeric antigen receptor T-cell therapy.

WHAT THIS STUDY ADDS

⇒ This study defines and prospectively validates an EASIX cut-off ≥3 taken before conditioning to identify patients with a more than twofold increased risk of alloSCT-related mortality.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ EASIX ≥3 will more broadly be used in alloSCT and will be tested in combination with clinical scores to improve mortality risk assessment. This study will stimulate EASIX studies in different healthcare setting that are related to endothelial pathology, such as infection, inflammation, malignancies and immunotherapy.

BACKGROUND

The main clinical challenge of allogeneic stem cell transplantation (alloSCT) is high treatment-associated mortality (non-relapse mortality (NRM)). Prediction of NRM is currently done by defining comorbidities, disease-specific risks and donor-related factors with indices such as the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI),[1] the European Society for Blood and Marrow Transplantation (EBMT)-score,[2 3] the Dana-Farber Cancer Institute (DFCI)-score[4] and a combination of such scores.[5] Further improvement of pre-alloSCT risk assessment could facilitate clinical decision-making.

Endothelial dysfunction plays a crucial role in the pathophysiology of major complications

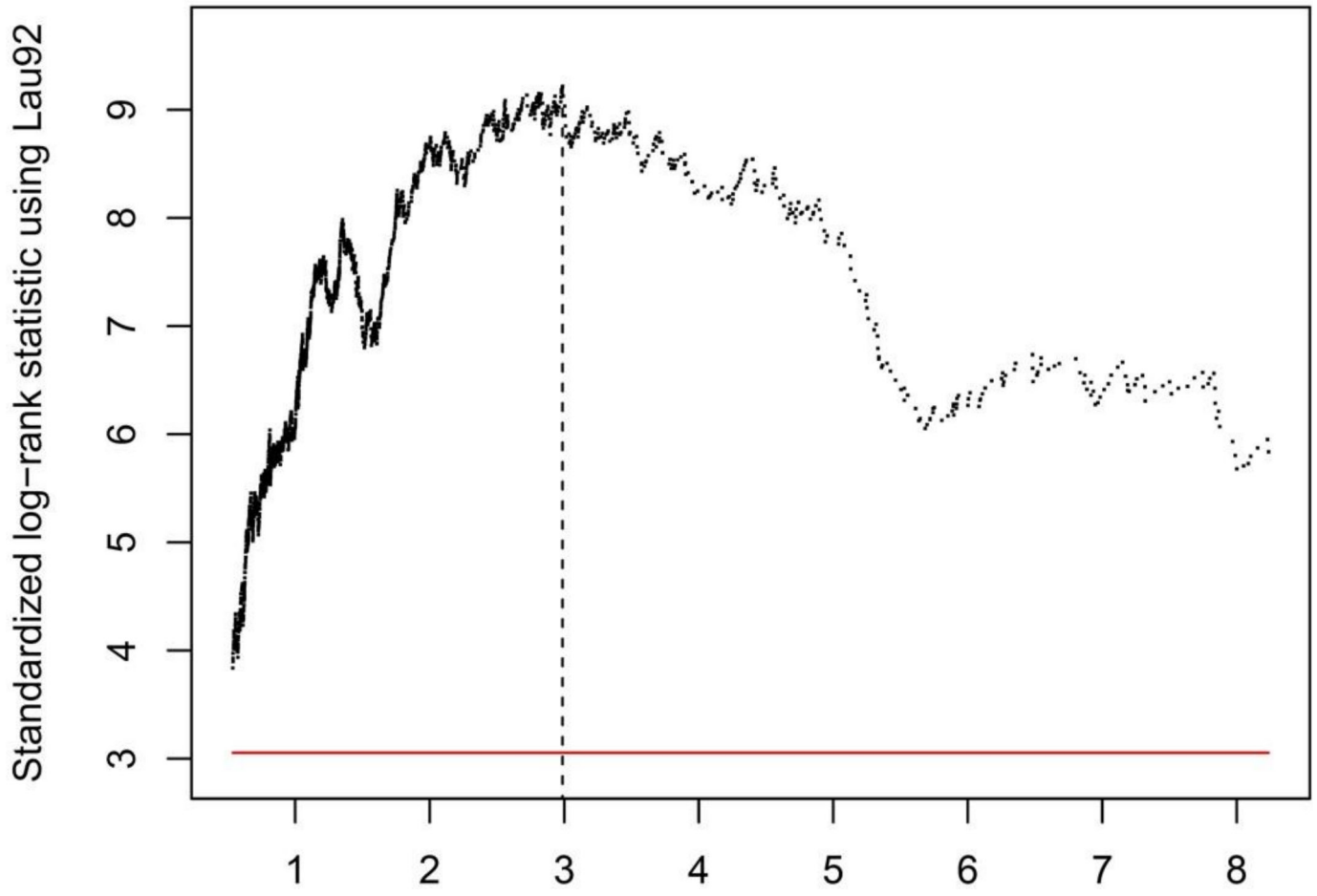


Figure 1 Definition of an optimal cut-off point for non-relapse mortality at Endothelial Activation and Stress Index-pre=3 in the retrospective cohort.

contributing to NRM of alloSCT, such as sepsis, graft-versus-host disease (GVHD), sinusoidal obstruction syndrome (SOS) and transplant-associated microangiopathy.[6–8] Risk assessment based on quantification of endothelial dysfunction prior to alloSCT is an attractive option that could help predicting alloSCT-associated mortality. Evidence is accumulating that pre-alloSCT measurement of patient-related endothelial risk factors, such as single-nucleotide-polymorphisms of the thrombomodulin and the CD40 ligand genes, complement activation-related genes, and angiopoetin-2 serum levels, can be used to predict outcome after acute GVHD.[9–12] However, general clinical application of these markers for alloSCT risk assessment in the near future is hindered by a lack of standardization and cost-effectiveness.

We have therefore established a biomarker panel related to endothelial dysfunction for pretransplant OS prediction that consists of standardized routine laboratory parameters in order to enable broad clinical use. The "Endothelial Activation and Stress Index" (EASIX; ((lactate dehydrogenase [LDH]×creatinine)/thrombocytes)) taken before start of conditioning has been recently shown to predict the risk of death after alloSCT (EASIX-pre).[13] In this previous project, the data analysis was performed with the continuous EASIX-pre score.

For this manuscript, we first analyzed a large retrospective alloSCT cohort to define an optimal EASIX-pre cut-off to predict NRM. The cut-off is very easy to use in clinical routine, as opposed to a continuous EASIX-pre score. We then prospectively validated the EASIX-pre cut-off within the EBMT network to facilitate broad clinical implementation.

METHODS

Retrospective study

The basic methodology and transplant procedures for the retrospective cohorts are described in more detail elsewhere.[13] For the present manuscript, we re-analyzed the retrospective data and included patients from four independent adult alloSCT cohorts. Cohort I contained 755 adult patients who had undergone alloSCT at the University of Heidelberg between 09/2001 and 06/2014. Cohort II was transplanted at the Charité, Campus Benjamin Franklin, Berlin between 08/1995 and 12/2011. Cohort III consisted of adult patients who had undergone alloSCT at the Seattle Fred Hutchinson Cancer Research Center between 01/2010 and 12/2013. Cohort IV consisted of adult patients transplanted between 01/2009 and 12/2013 at the University Hospital Essen.

Table 1 Patient characteristics

		EASIX			
Variable	**Level**	**<3 (n=241)**	**≥3 (n=74)**	**Overall (n=317)**	**P value**
Previous autologous transplantation(s)	No	213 (88.4%)	69 (93.2%)	284 (89.6%)	0.23
	Yes	28 (11.6%)	5 (6.8%)	33 (10.4%)	
Year of transplantation	Median (min–max)	2018 (2017–2020)	2018 (2017–2020)	2018 (2017–2020)	0.94
	(IQR)	(2018–2019)	(2018–2019)	(2018–2019)	
Type of donor 1	Identical	77 (32.5%)	23 (31.5%)	100 (32.1%)	0.81
	Sibling	128 (54%)	42 (57.5%)	172 (55.1%)	
	Unrelated	32 (13.5%)	8 (11%)	40 (12.8%)	
	Haplo missing	4	1	5	
Diagnosis	Acute leukemia	161 (66.8%)	35 (47.3%)	197 (62.1%)	<0.0001
	Lymphoma	42 (17.4%)	6 (8.1%)	48 (15.1%)	
	MDS or MPN	38 (15.8%)	33 (44.6%)	72 (22.7%)	
Complete remission at transplant	CR	163 (68.5%)	20 (27.4%)	184 (58.8%)	<0.0001
	No CR	75 (31.5%)	53 (72.6%)	129 (41.2%)	
	Missing	3	1	4	
DRI	Low–intermediate	182 (75.5%)	51 (68.9%)	235 (74.1%)	0.26
	High–very high	59 (24.5%)	23 (31.1%)	82 (25.9%)	
	Low	24 (10%)	3 (4.1%)	27 (8.5%)	
	Intermediate	158 (65.6%)	48 (64.9%)	208 (65.6%)	
	High	45 (18.7%)	16 (21.6%)	61 (19.2%)	
	Very high	14 (5.8%)	7 (9.5%)	21 (6.6%)	
Patient age (years)	Median (min–max) (IQR)	51.1 (19.3–73.5) (38.3–60.7)	58.8 (20.3–68.5) (51.3–63.6)	54.6 (19.3–73.5) (41.5–61.1)	0.0003
Patient sex	Male	133 (55.2%)	50 (67.6%)	183 (57.7%)	0.059
	Female	108 (44.8%)	24 (32.4%)	134 (42.3%)	
Donor 1 sex	Male	180 (75%)	50 (67.6%)	230 (72.8%)	0.21
	Female	60 (25%)	24 (32.4%)	86 (27.2%)	
	Missing	1	0	1	
Patient cytomegaly virus	Negative	50 (21%)	8 (11.1%)	59 (18.9%)	0.059
	Positive	188 (79%)	64 (88.9%)	253 (81.1%)	
	Missing	3	2	5	
Donor cytomegaly virus	Negative	89 (37.2%)	23 (31.1%)	114 (36.2%)	0.33
	Positive	150 (62.8%)	51 (68.9%)	201 (63.8%)	
	Missing	2	0	2	
Karnofsky score	≥90	133 (57.3%)	31 (43.7%)	165 (54.1%)	0.043
	<90	99 (42.7%)	40 (56.3%)	140 (45.9%)	
	Missing	9	3	12	
HCT-CI	0	109 (46.2%)	20 (27.8%)	129 (41.6%)	0.006
	1–2	69 (29.2%)	22 (30.6%)	91 (29.4%)	
	3+	58 (24.6%)	30 (41.7%)	90 (29%)	
	Missing	5	2	7	
Intensity of conditioning	RIC	85 (35.3%)	43 (58.1%)	129 (40.7%)	0.0005
	MAC	156 (64.7%)	31 (41.9%)	188 (59.3%)	

Continued

Table 1 Continued

		EASIX			
Variable	Level	<3 (n=241)	≥3 (n=74)	Overall (n=317)	P value
Total body irradiation	No	161 (66.8%)	64 (86.5%)	227 (71.6%)	0.001
	Yes	80 (33.2%)	10 (13.5%)	90 (28.4%)	
In vivo T-cell depletion	ATG	80 (33.2%)	27 (36.5%)	108 (34.1%)	0.6
	No	161 (66.8%)	47 (63.5%)	209 (65.9%)	

DRI, Disease Relapse Index; HCT-CI, Hematopoietic Cell Transplantation Comorbidity Index; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasms; RIC, reduced intensity conditioning.

Prospective study

Data source, study design and data collection

We asked EBMT centers performing more than 50 alloSCT per year if they were willing to participate in this prospective study. Nine centers in seven countries agreed to participate. Data were prospectively collected between 12/2017 and 3/2020 with a minimal follow-up of 365 days. Adults with acute leukemia, lymphoma or myelodysplastic syndrome (MDS) receiving a first alloSCT from peripheral blood were eligible. All types of conditioning and donors were allowed. Patients had to sign an informed consent document that permitted sharing of clinical data according to national rules. Basic data on patient and disease characteristics as well as longer term follow-up was taken from minimal essential data (MED-A) forms, which are submitted from all consecutive patients to the central EBMT registry. In addition, we designed registration and MED-B/C forms that were prospectively collected and specific to this study.

Endpoints and statistical analyses

Median follow-up time was estimated using the reverse Kaplan-Meier method. Primary endpoint was the incidence of NRM after alloSCT. Secondary endpoints were overall survival (OS), relapse-free survival (RFS), relapse incidence (RI), incidence and severity of acute GVHD and chronic GVHD.

NRM was defined as death without previous relapse. OS was defined as the time from alloSCT to death, regardless of the cause. RFS was defined as time from alloSCT to relapse or death from any cause. Acute GVHD was graded according to the modified Seattle-Glucksberg criteria[14] and chronic GVHD according to the revised Seattle criteria.[15] All outcomes were measured from the time of stem cell infusion. The probabilities of OS and RFS were calculated with the Kaplan-Meier test, and those of NRM, RI, acute and chronic GVHD, TMA, VOD and sepsis with the cumulative incidence estimator to accommodate for competing risks. For NRM, relapse was the competing risk, and for relapse, the competing risk was NRM. For acute and chronic GVHD, VOD, TMA and sepsis, death without the event and relapse were the competing risks.

For multivariate analysis, Cox proportional hazards regression models were used for OS and RFS. For competing outcomes like NRM, RI, GVHD and sepsis, cause-specific Cox proportional hazards regression models were used. Adjusting variables for multivariable analyses were: donor type (related vs unrelated), Disease Risk Index (DRI—divided in two categories: low and intermediate vs high and very high), patient age, sex (female to male vs other combination) and intensity of conditioning (reduced intensity conditioning (RIC) vs myeloablative conditioning (MAC)) (EBMT definition: MAC was defined as total body irradiation [TBI] >6 Gray or oral busulfan >8 mg/kg or intravenous busulfan >6.4 mg/kg). The definition of complete response excluded patients with incomplete regeneration of haematopoiesis (Cri).

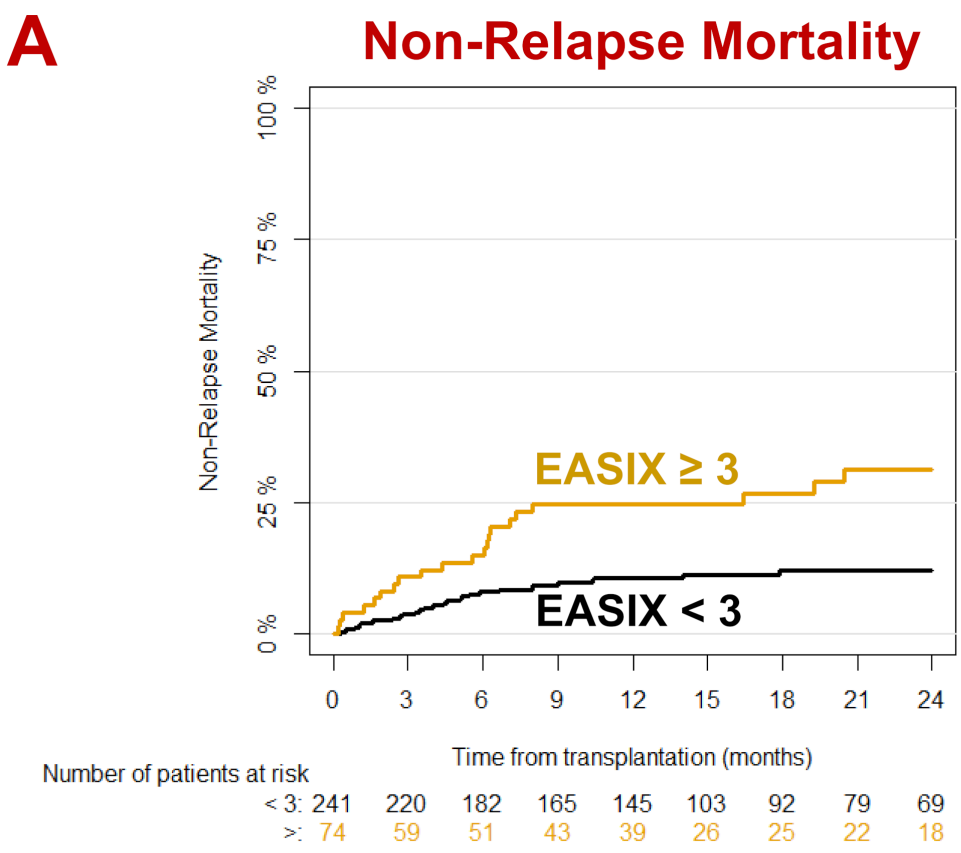
EASIX was calculated by the formula: LDH (U/L)×creatinine (mg/dL)/thrombocytes (nL). To identify an optimal EASIX-pre cut-off for predicting NRM, we used maximally selected log-rank statistics. In addition, we applied conditional inference survival trees to account for differences in the four retrospective cohorts.[16 17] The dichotomized EASIX-pre was then analyzed in univariable and multivariable analyses.

Results were expressed as the (cause-specific) HRs with 95% CI. Proportional hazards assumptions were checked systematically for all proposed models using the graphical test as proposed by Grambsch and Therneau.[18] Statistical analyses were performed with R V.4.04 (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

RESULTS

Defining an optimal EASIX-pre cut-off to predict NRM in retrospective cohorts

Patient characteristics of the training cohort were already published.[13] Median age of the combined adult cohorts I–IV was 53 (17–78) years, 842 (42%) were female patients, 761 (38%) had female donors. Matched related donors were used in 584 (29%), matched unrelated donors in 1074 (53%), mismatched donors in 330 (16%) of patients, whereas only 34 patients (2%) had haplo-identical donors. Diagnoses were mainly acute myeloid leukemia and MDSs (1260 (62%)), lymphoma (332 (16%)); acute lymphoblastic leukemia (183 (9%)) myeloproliferative neoplasms (MPN) (76 (4%)), multiple myeloma (152 (8%)) and aplastic anemia (18 (1%)). 601 (30%) of



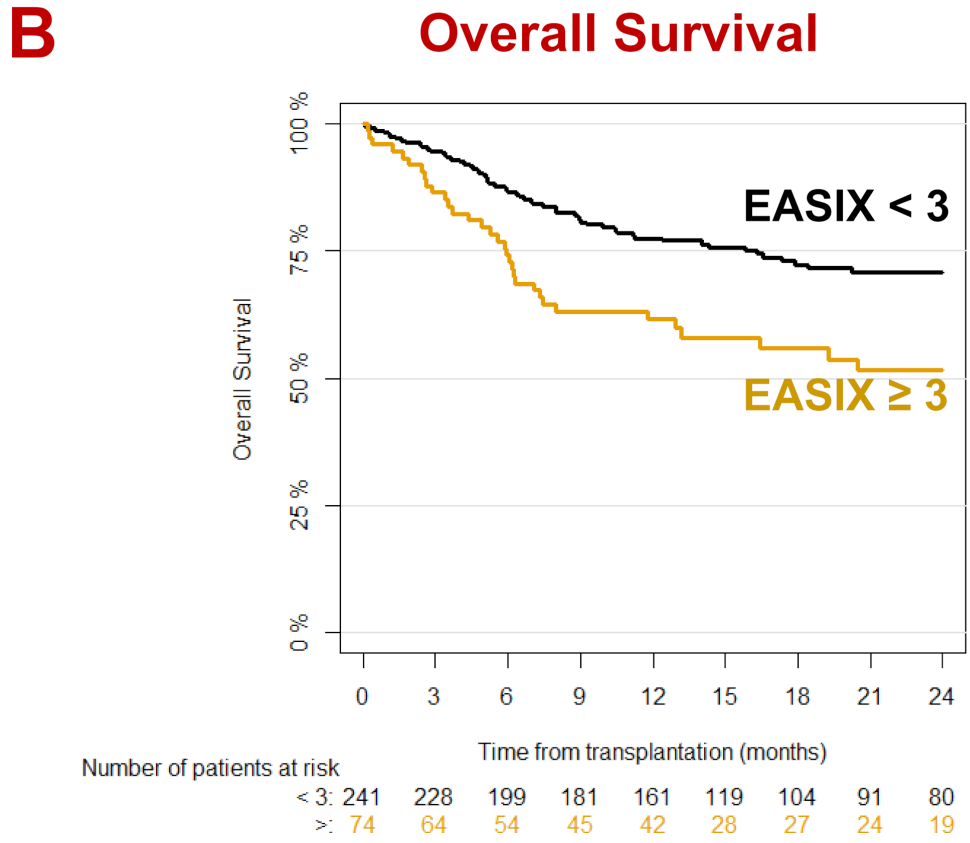


Figure 2 Univariate outcome graphs in patients with EASIX <3 versus EASIX ≥3 before allogeneic hematopoietic stem cell transplantation. EASIX, Endothelial Activation and Stress Index.

Table 2 Reasons for deaths

Cause of death	EASIX-pre low (n=63)	EASIX-pre high (n=33)
Original disease	39 (63%)	13 (39%)
Infection	15 (22%)	9 (27%)
GVHD	3 (5%)	3 (9%)
Multiorgan failure	0 (0%)	3 (9%)
Secondary malignancy	0 (0%)	2 (6%)
Other	5 (8%)	3 (9%)
Missing	1	0

EASIX, Endothelial Activation and Stress Index; GVHD, graft-versus-host disease.

patients had high disease risk, and 504 (25%) had intermediate disease risk. Stem cell sources were bone marrow in 156 (8%) and peripheral blood stem cells in all others. RIC was received by 1471 (73%) patients.

Using maximally selected log-rank statistics and conditional inference survival trees[16 17] with the endpoint NRM for the combined adult cohorts (n=2022) we identified an optimal cut-off point at EASIX-pre=3 (figure 1).

Prospective study

Patient characteristics

We enrolled 317 patients. The main patients and transplant characteristics that were included in the analysis are described in table 1. We used the last EASIX-pre score that was measured in the individual patients within 30 days before start of conditioning.

Patients were transplanted for acute leukemia (62.1%), MDS/MPN (22.7%) or lymphoma (15.1%), mainly from an unrelated donor (55.1%). Complete remission was achieved at transplant for 58.8%, leading to a higher proportion of low/intermediate DRI (74.1%). Patient median age was 54.6 years, with a majority of male recipients (57.7%) and donors (72.8%). MAC was more frequently performed (59.3%) than RIC, with high-dose TBI in 28.4%. ATG for GVHD prevention was given for 34.1%. Most parameters were balanced between the two cohorts. However, the following factors were higher in the EASIX-pre high group: patient age (median=58.8 vs 51.1 years, p<0.001), not in remission at transplant (72.6% vs 31.5%, p<0.001), diagnosis of MDS/MPN (44.6% vs 15.8%, p<0.001), RIC (58.1% vs 35.3%, p<0.001) and hematopoietic cell transplantation comorbidity index (HCT-CI ≥3, 41.7% vs 24.6%, p=0.006).

EASIX-pre is associated with NRM

The median follow-up time was 23.1 months (95% CI 18.8 to 24.4) in the low EASIX group and 23.6 months (95% CI 20.2 to 25.9) in the high EASIX group.

We found that 23% (n=74) of the 317 alloSCT recipients had EASIX ≥3 taken before conditioning. In univariate analysis NRM at 2 years was 31.1% (95% CI 20.1 to 42.8) in the high EASIX group (11.5% (95% CI 7.7 to 16.1) only in the low EASIX group) (figure 2A). Patients with high EASIX also had worse 2 years OS (51.6% (95% CI 40.6 to 65.6) vs 70.9% (95% CI 64.9 to 77.5)) (figure 2B) and 2 years progression-free survival (49.0% (95% CI 38.1 to 63.1) vs 61.4% (95% CI 55 to 68.5)). No statistically significant difference could be observed for the incidence of relapse. Major reasons for mortality were relapse of the original disease as well as infections in both groups (table 2).

However, NRM was responsible for death in 37% in the low EASIX group and in 61% in the high EASIX group, reflecting the increased NRM. To investigate if EASIX is associated with a certain type of NRM, we sub-classified NRM into infection-related, GVHD-related, multi-organ failure and secondary malignancy. TMA or VOD were not primary reasons for death. Results of table 2 show a higher percentage in all sub-categories in the high EASIX group. In multivariate analyses, we were able to validate the cut-off and found that EASIX ≥3 was associated with more than twofold increased risk for NRM (HR=2.18, 95% CI 1.2 to 3.94, p=0.01) (table 3).

Table 3 Multivariate analyses of non-relapse mortality

Variable	Level	HR	P value
EASIX before conditioning	Reference <3		
	≥3	2.18 (1.2 to 3.94)	0.01
Type of donor	Reference related donor Unrelated donor	0.59 (0.32 to 1.07)	0.082
Disease Relapse Index (DRI)	Reference: Low–intermediate High–very high	1.67 (0.88 to 3.16)	0.12
Patient age (5 years increment)		1.15 (1 to 1.32)	0.05
Donor recipient gender difference	Reference: Female to male Other combination	0.42 (0.22 to 0.82)	0.01
Intensity of conditioning	Reference: Reduced intensity Myeloablative	0.82 (0.44 to 1.55)	0.54

EASIX, Endothelial Activation and Stress Index.

Secondary outcome variables

There was no significant difference according to EASIX in incidence of acute GVHD II–IV (at d180: 22.1% (95% CI 17 to 27.7) vs 29.4% (95% CI 19.1 to 40.6) for EASIX <3 or >3 resp.). Interestingly, high-grade (3–4) acute GVHD differed in univariable analyses (at d180 5.8% (95% CI 3.2 to 9.3) vs 20.6% (95% CI 11.9 to 31) for EASIX <3 or ≥3, respectively). Multivariable Cox regression for high-grade acute GVHD was not possible due to low numbers of events. As expected, incidence of chronic GVHD did not differ between the two EASIX cohorts (at 24 months 15.5% (95% CI 7.8 to 25.6) vs 21.4% (95% CI 15.6 to 27.8) for EASIX <3 or ≥3, respectively).

DISCUSSION

The results of the current study demonstrate that EASIX-pre ≥3 identifies a population of patients at high risk for alloSCT-related mortality. After having tested EASIX-pre before in different alloSCT cohorts,[13] we now establish an easy to use cut-off. In the next step, we have validated this ≥3 cut-off in a multinational EBMT prospective study. EASIX-pre is now ready to be used in the clinical standard setting.

EASIX-pre has to be put in perspective with clinical scores estimating alloSCT-associated mortality. The HCT-CI focuses on patient-related factors and includes different pathological conditions.[1] The EBMT score consists of patient and donor data including histocompatibility, stage of disease, age and sex of donor and recipient, and time from diagnosis to transplantation.[2 3] A combination of both scores may even increase accuracy.[5] The DFCI score focuses on disease and disease status to predict mortality.[4] Comparing EASIX with the HCT-CI and EBMT scores, respectively, we observed an independent prognostic value of EASIX.[13] Interestingly, there was a tendency of improved prediction when these scores were applied in combination.[13] In the current analyses there was a higher share of HCT-CI high patients in the EASIX high cohort. However, the current study was not powered to explore synergies. Further analyses are needed to precisely define the synergies and overlaps between the scores.

EASIX is a prognostic rather than a diagnostic tool which is also emphasized by our observation that the marker does not associate with incidence of acute GVHD (II–IV), but has a connection to high-grade acute GVHD, that is, increased NRM after acute GVHD. EASIX was designed to be applicable with minimal costs or efforts in all transplantation centers. Endothelial dysfunction is a common physiopathological mechanism of several severe infectious and non-infectious alloSCT-related complications.[6–8]

Of note, we have previously shown the clinical utility of EASIX as a prognostic marker in patients with acute GVHD,[19] and for prediction of risk of sepsis,[20] SOS/VOD[21] and transplantation-associated microangiopathy.[13] Our results underline the clinical importance of endothelial dysfunction for complications after alloSCT. However, the clinical significance of EASIX as a prognostic tool is not restricted to the alloSCT setting. Recent data demonstrate that EASIX can be used also in other endothelium-related syndromes to predict mortality, such as lower-risk MDSs,[22] diffuse large B cell lymphoma,[23] multiple myeloma,[24] SARS-CoV-2 infections[25 26] or CAR-T cell therapy.[27 28]

A strength of our study is the simplicity of the approach, the retrospective validation in large cohorts of alloSCT recipients[13] as well as the current prospective validation of the clinical useful ≥3 EASIX-pre cut-off. A limitation and possible bias is that the conditioning regimens were variable and we do not have information why investigators decided on RIC in some patients. This bias can only be addressed in a randomized study. Another limitation is that the applicability of EASIX-pre has not been shown for pediatric transplants. This is less relevant here since our current study focused on adult patients only, but this also implies that EASIX-pre ≥3 is only ready to be used in the clinical standard setting for adult patients.

In summary, the results of this study provide a prospectively validated standard laboratory biomarker index to estimate transplant-related mortality after alloSCT. EASIX ≥3 taken before conditioning identifies a population of adult alloSCT recipients who have a more than twofold increased risk of treatment-related mortality.

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Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Charité Ethics Committee (approval number: EA2/24/17). Data collection for the EBMT registry was approved by the IRB and/or Ethics Committee in all centers. Written informed consent according to the Declaration of Helsinki was obtained in all eligible patients.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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