Journal for ImmunoTherapy of Cancer

EASIX-guided risk stratification for complications and outcome after CAR T-cell therapy with ide-cel in relapsed/refractory multiple myeloma

Jan H Frenking ,[1,2] Xiang Zhou,[3] Vivien Wagner,[3] Thomas Hielscher,[4] Joseph Kauer,[1,5] Elias K Mai,[1] Mirco J Friedrich,[1,6] Christian S Michel,[1] Marina Hajiyianni,[1] Iris Breitkreutz,[1] Patrick Costello,[7] Omar Nadeem,[7] Niels Weinhold,[1,2] Hartmut Goldschmidt,[1,8] Anita Schmitt,[1] Thomas Luft,[1] Michael Schmitt,[1] Carsten Müller-Tidow,[1,8] Max Topp,[3] Hermann Einsele,[3] Peter Dreger,[1] Nikhil C Munshi,[7] Adam S Sperling,[7,9] Leo Rasche,[3] Sandra Sauer,[1] Marc S Raab[1,2]

To cite: Frenking JH, Zhou X, Wagner V, *et al*. EASIX-guided risk stratification for complications and outcome after CAR T-cell therapy with ide-cel in relapsed/refractory multiple myeloma. *Journal for ImmunoTherapy of Cancer* 2024;**12**:e009220. doi:10.1136/jitc-2024-009220

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/jitc-2024-009220).

Accepted 08 September 2024

For numbered affiliations see end of article.

Correspondence to
Dr Jan H Frenking;
jan.frenking@med.uni-heidelberg.de

ABSTRACT

Background Chimeric antigen receptor (CAR) T-cell therapy has demonstrated significant benefits in the treatment of relapsed/refractory multiple myeloma (RRMM). However, these outcomes can be compromised by severe complications, including cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome (ICANS) and immune effector cell-associated hematotoxicity (ICAHT), predisposing for life-threatening infections.

Methods This retrospective observational study examined a total of 129 patients with RRMM who had received idecabtagene vicleucel (ide-cel) at two major myeloma centers in Germany and one center in the USA to assess the Endothelial Activation and Stress Index (EASIX) as a risk marker for an unfavorable clinical course and outcome after CAR T-cell therapy. EASIX is calculated by lactate dehydrogenase (U/L) × creatinine (mg/dL) / platelets (10^9 cells/L) and was determined before lymphodepletion (baseline) and at the day of CAR T-cell infusion (day 0). The analysis was extended to EASIX derivatives and the CAR-HEMATOTOX score.

Results An elevated baseline EASIX (>median) was identified as a risk marker for severe late ICAHT, manifesting with an impaired hematopoietic reconstitution and pronounced cytopenias during the late post-CAR-T period. Patients with high EASIX levels (>upper quartile) were particularly at risk, as evidenced by an increased rate of an aplastic phenotype of neutrophil recovery, severe late-onset infections and ICANS. Finally, we found associations between baseline EASIX and an inferior progression-free and overall survival. Moreover, the EASIX at day 0 also demonstrated potential to serve as a risk marker for post-CAR-T complications and adverse outcomes.

Conclusions In conclusion, EASIX aids in risk stratification at clinically relevant time points prior to CAR T-cell therapy with ide-cel. Increased EASIX levels might help clinicians to identify vulnerable patients to adapt peri-CAR-T management at an early stage.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The Endothelial Activation and Stress Index has emerged as a prognostic marker in various hematologic neoplasms and therapies. Most recently, the EASIX has been demonstrated to predict the development of severe cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS) following CD19-directed chimeric antigen receptor (CAR) T-cell therapy.

WHAT THIS STUDY ADDS

⇒ This is the first study investigating the EASIX as a risk marker for complications and adverse outcomes following anti-B-cell maturation antigen (BCMA) CAR T-cell therapy with idecabtagene vicleucel. We also describe for the first time associations with hematotoxicity and extend our model to other scoring systems and key pre-CAR-T time points for clinical decision-making. In summary, we found associations between EASIX and severe post-CAR-T cytopenias, late-onset infections, ICANS, inferior progression-free and overall survival.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our EASIX model has the potential to serve as a simple and rapid screening tool for identifying patients at risk for a broad spectrum of post-CAR-T complications and inferior outcomes, who could benefit from more intensive monitoring, prophylaxes and supportive measures. Future studies should further evaluate EASIX-guided risk stratification prior to other cellular and antibody-based immunotherapies.

BACKGROUND

Chimeric antigen receptor (CAR) T-cell therapy revolutionizes the treatment landscape of relapsed/refractory multiple

myeloma (RRMM). Idecabtagene vicleucel (ide-cel) is an autologous anti-B-cell maturation antigen (BCMA) targeting CAR T-cell product. The efficacy and safety of ide-cel in RRMM has been demonstrated in clinical trials[1 2] and in the real-world setting.[3]

The success of CAR T-cell therapy is hampered by the potential risk for severe toxicities including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS) and immune effector cell-associated hematotoxicity (ICAHT).[4–6] High-grade clinical manifestations of CRS and ICANS after CAR T-cell therapy with ide-cel are rare (5% and 3% grade ≥3 in the phase II trial, respectively),[1] but potentially life-threatening due to circulatory instability, hypoxia or neurological deficits. ICAHT represents the most common CAR T-cell-associated adverse effect and can manifest with severe, protracted and recurrent cytopenias during the early (≤30 days) and/or late (>30 days) post-CAR-T period.[6 7] As the severity of ICAHT is closely linked to prolonged hospitalization and severe infections, the most common cause of non-relapse mortality, it is important to identify risk factors and key drivers of this complication.[5 7–9] An important step towards a reliable risk stratification has been achieved through implementation of the CAR-HEMATOTOX score by Rejeski and colleagues.[5] The score was developed to predict the duration of severe neutropenia in patients with relapsed/refractory large B-cell lymphoma undergoing anti-CD19 CAR T-cell therapy.[5] Recent studies, however, suggested applicability to a broader context, including anti-BCMA CAR T-cell therapy.[10 11]

Additional markers and scoring systems could further improve and facilitate risk stratification and help identify the full spectrum of patients at risk for adverse clinical outcomes after CAR T-cell therapy. Many severe complications following immunotherapies have been reported to be associated with endothelial dysfunction.[12 13] The Endothelial Activation and Stress Index (EASIX) includes high lactate dehydrogenase (LDH), high creatinine and low platelet counts as validated indicators for endothelial dysfunction and is calculated with the simple formula LDH (U/L) × creatinine (mg/dL) / platelets (10^9 cells/L).[12 14–16] The EASIX was originally developed to predict overall survival (OS) in patients with acute graft-versus-host disease,[14] but has since been reported as a prognostic marker in the context of allogeneic stem-cell transplantation in general,[15] sepsis,[16] myelodysplastic syndrome[17] and multiple myeloma.[18] Several groups have demonstrated the potential of the EASIX and its variants to predict the risk for severe CRS, ICANS and inferior survival following CAR T-cell therapy in patients with B-cell neoplasias.[12 19–22] Moreover, recent data points to a link between an aplastic phenotype of neutrophil recovery and progressive endothelial dysfunction.[13]

So far, associations between EASIX and post-CAR-T cytopenias as well as the potential of EASIX-based risk stratification in the context of anti-BCMA CAR T-cell therapy remain unexplored. Moreover, a comparative analysis of the EASIX and other scores as a risk marker at different time points prior to ide-cel infusion has not yet been conducted. Therefore, the aim of this study was to address this knowledge gap and assess the EASIX as a risk marker for major complications and adverse outcomes following BCMA-directed CAR T-cell therapy with ide-cel.

METHODS

Patient selection and data collection

This multicenter retrospective observational study included a total of 129 patients with RRMM. Until May 2023, 63 patients had received ide-cel at Heidelberg University Hospital (n=30) or University Hospital of Würzburg (n=33) (German cohort), and 66 patients at the Dana-Farber Cancer Institute (US cohort). Data cut-off was 25 September 2023. All patients with available data were included in the further analysis. Patients had received prior lymphodepletion with fludarabine/cyclophosphamide (n=125) or bendamustine (n=4). Institutional standard operating procedures for post-CAR-T prophylaxes and toxicity management are listed in online supplemental table S1. Clinical data were extracted from the electronic patient management software and the original medical records whenever available. Laboratory values prior to lymphodepletion and at the day of CAR-T-cell infusion (day 0) were collected with a leniency period of up to 5 and 2 days, respectively. The observation period for post-CAR-T complications between day 0 and day 30 was referred to as the early post-CAR-T period, and the period between day 31 and 90 was referred to as the late post-CAR-T period.[6 9] For analysis of post-CAR-T cytopenias, all patients with repetitive blood cell count measurements (≥2 time points) were included, irrespective of the cause of cytopenia. Missing data on complications were due to an incomplete follow-up period, external follow-up with limited data access or loss to follow-up and are detailed in online supplemental table S3. Study results were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for cohort studies.

Classifications and grading systems

Clinical response, disease stage, drug refractoriness and prior lines of therapy were defined according to international guidelines.[23–25] Extramedullary disease manifestations were classified as bone-associated or extraosseous, bone-independent soft tissue masses.[26] High risk cytogenetic abnormality was defined by the presence of del(17p), t(4;14) and/or t(14;16) as described in previous publications.[1 3] Chromosome 1q gain/amplification was included if explicitly mentioned.[27] CRS and ICANS were graded as recommended by the American Society for Transplantation and Cellular Therapy.[4] Cytopenias and infections were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) V.5.0. CTC grade ≥3 thrombocytopenia (platelets <50 x 10^9/L), anemia (hemoglobin <80g/L) and infections were

defined as severe. Late neutropenia was further specified based on the absolute neutrophil count (ANC) cut-offs for late ICAHT in the current consensus guidelines.[6] Severe late ICAHT included grade 3 and 4.[6] The phenotypes of neutrophil recovery (*quick*, *intermittent*, *aplastic*) were defined according to Rejeski *et al*.[5] Causes of death and non-relapse mortality were classified as previously described.[8 28]

Scores

The EASIX and its derivatives (modified EASIX [m-EASIX], EASIX-F and EASIX-FC) were determined according to the literature.[14 19 20] Log_2-transformed values were used for the primary statistical analysis and data visualization if necessary.[14 15] The median or upper quartile (Q_3) was used to form EASIX groups, with rounding to the second decimal place. The CAR-HEMATOTOX score (CAR-HTX) was determined according to Rejeski *et al*.[5] A score <2 was considered as low, a score ≥2 as high.[5]

Statistical analysis

R (V.4.4.1), GraphPad Prism (V.10.2.3) and Microsoft Excel (V.16.87) were used for statistical data analysis and visualization. The entire dataset with all cohorts was used for the primary analyses.[29] Statistical tests and subgroup analyses were applied to examine differences between the German and US cohorts. Non-parametric Mann-Whitney test was used to compare continuous variables. Percentages were compared with Fisher's exact test. Longitudinal laboratory markers were compared between groups using a linear mixed model with random patient effect and group, time and group–time interaction as fixed effects. Contrast tests based on estimated marginal means were used to compare groups across time points, at individual time points and for interaction between group and time points. P values of pairwise group comparisons were adjusted for multiple testing using Tukey's method, and for testing at individual time points, p values were additionally adjusted using Holm's method. Univariate and multivariate logistic regression analyses were performed using binary or continuous variables. Correlations between continuous variables were described by Spearman correlation coefficient (r). Simple linear regression was used to visualize data and obtain a best-fit line. Receiver operating characteristic (ROC) curve analysis was used to evaluate test characteristics. Optimal cut-off values were selected according to the highest Youden Index. Survival data were analyzed by univariate and multivariate Cox regression and log-rank test. All p-values were two-sided and considered as statistically significant at p<0.05.

RESULTS

Patient and disease characteristics

Patient and disease characteristics are listed in table 1.

In the total cohort (n=129), the median age at CAR T-cell therapy was 64 years (range: 34–83). Forty-two (33%) patients were female. Of the patients with available data, 9% had ISS stage III (n=10/108), 40% had high risk cytogenetic aberrations (n=49/123), 20% had a bone marrow infiltration ≥50% (n=14/71) and 38% had extramedullary disease (n=48/126), including 16 (13%) cases of bone-associated and 32 (25%) cases of extraosseous soft tissue masses. Patients had received a median of five prior therapy lines. Triple-class and penta-drug refractory disease were found in 107 (83%) and 41 (32%) patients, respectively. Patient-related and disease-related differences between the German and US cohorts are outlined in table 1. Of note, official approval requirements for ide-cel and general treatment algorithms are different in both countries.

Efficacy

CAR T-cell therapy with ide-cel induced an overall response rate of 78% (n=101) (online supplemental figure S1A; online supplemental table S2). Forty-seven (36%) patients achieved a complete response or better. At a median follow-up of 9.6 months (95% CI: 7.9 to 11.6), the median progression-free survival (PFS) was 8.6 months (95% CI: 6.7 to 11.9), and the median OS was not reached (online supplemental figure S1D, E). Efficacy results were comparable between the German and US cohorts (online supplemental figure S1; online supplemental table S2).

CRS and ICANS

Detailed information on post-CAR-T complications, supportive and prophylactic measures are provided in online supplemental table S3. One hundred and nine patients (84%) experienced CRS, including mostly grade 1 (n=67; 52%) and grade 2 (n=41; 32%) events (figure 1A). One (1%) patient was affected by CRS grade 3. The US cohort showed a trend towards less pronounced CRS events (p=0.04). ICANS was reported in 11 (9%) patients, including three grade 3 events (2%) and one grade 4 event (1%) (figure 1B). Tocilizumab and dexamethasone were administered in 66 (51%) and 57 (44%) patients, respectively.

Cytopenias

Baseline cytopenias prior to lymphodepletion are summarized in online supplemental table S4 and were mostly limited to CTC grades 1–2. An overview of the frequency and CTC grades of post-CAR-T cytopenias is given in online supplemental table S5. Interestingly, the US cohort had a lower rate of CTC grade ≥3 neutropenia during the early post-CAR-T period (65% vs 92%; p=0.0006), with concurrent evidence of a higher rate of early (p=0.0009) and prophylactic (p<0.0001) granulocyte colony-stimulating factor (G-CSF) use. A significant proportion of patients showed high-grade cytopenias during the late post-CAR-T period, with CTC grade ≥3 neutropenia, anemia and thrombocytopenia occurring in 39% (n=42/107), 14% (n=15/109) and 34% (n=37/109) of evaluable patients in the total cohort, respectively.

Table 1 Patient and disease characteristics

	Total cohort n=129	German cohort n=63	US cohort n=66	P
Age, years				
Median (range)	64 (34–83)	60 (34–77)	66 (35–83)	**0.007**
≥70, No. (%)	36 (28)	14 (22)	22 (33)	0.17
Sex, No. (%)				
Male	87 (67)	45 (71)	42 (64)	0.36
Female	42 (33)	18 (29)	24 (36)	
ECOG*, No. (%)				
0–1	111 (96)	63 (100)	48 (91)	**0.02**
2–3	5 (4)	0 (0)	5 (9)	
Unknown	13	0	13	
ISS stage*, No. (%)				
I	63 (58)	37 (71)	26 (46)	**0.03**
II	35 (32)	11 (21)	24 (43)	
III	10 (9)	4 (8)	6 (11)	
Unknown	21	11	10	
R-ISS stage*, No. (%)				
I	24 (23)	18 (35)	6 (11)	**0.009**
II	75 (71)	31 (61)	44 (81)	
III	6 (6)	2 (4)	4[7]	
Unknown	24	12	12	
Extramedullary disease*, No. (%)				
Yes	48 (38)	30 (50)	18 (27)	**0.01**
Bone-associated	16 (13)	13 (22)	3 (5)	
Extraosseous	32 (25)	17 (28)	15 (23)	
No	78 (62)	30 (50)	48 (73)	
Unknown	3	3	0	
Cytogenetics, No. (%)				
Standard risk	74 (60)	27 (45)	47 (75)	**0.0009**
High risk	49 (40)	33 (55)	16 (25)	
del(17p)	30 (24)	20 (33)	10 (16)	
t(4;14)	19 (15)	12 (20)	7 (11)	
t(14;16)	5 (4)	3 (5)	2 (3)	
High risk with 1q	74 (60)	44 (73)	30 (48)	**0.006**
1q+	54 (44)	30 (50)	24 (38)	
Unknown	6	3	3	
Bone marrow burden†, No. (%)				
<50%	57 (80)	20 (80)	37 (80)	>0.99
≥50%	14 (20)	5 (20)	9 (20)	
Unknown	58	38	20	
Prior lines of therapy, median (95% CI)	5 (5-6)	5 (5-6)	6 (5-6)	0.67
Prior therapies, No. (%)				
Double-class refractory‡	114 (88)	48 (76)	66 (100)	**<0.0001**
Triple-class refractory§	107 (83)	42 (67)	65 (98)	**<0.0001**
Penta-drug exposed¶	100 (78)	50 (79)	50 (76)	0.68

Continued

Table 1 Continued

	Total cohort n=129	German cohort n=63	US cohort n=66	P
Penta-drug refractory¶	41 (32)	11 (17)	30 (45)	**0.0007**
Autologous SCT	116 (90)	61 (97)	55 (83)	**0.02**
Allogeneic SCT	12 (9)	12 (19)	0 (0)	**0.0001**
BCMA-targeted therapy	22 (17)	4 (6)	18 (27)	**0.002**
Belantamab mafodotin	21 (16)	3 (5)	18 (27)	**0.0006**
Bispecific antibody	4 (3)	3 (5)	1 (2)	0.36
Teclistamab	2 (2)	1 (2)	1 (2)	>0.99
Talquetamab	2 (2)	2 (3)	0 (0)	0.24
Systemic bridging therapy**, No. (%)				
Yes	111 (86)	59 (94)	52 (79)	**0.02**
Immunomodulatory agent	50 (39)	36 (57)	14 (21)	**<0.0001**
Proteasome inhibitor	71 (55)	40 (63)	31 (47)	0.08
Anti-CD38 antibody	36 (28)	25 (40)	11 (17)	**0.006**
Classical cytotoxic agent	61 (47)	39 (62)	22 (33)	**0.002**
No	18 (14)	4 (6)	14 (21)	
Radiotherapy	2 (2)	0 (0)	2 (3)	0.50
Watch-and-wait	16 (12)	4 (6)	12 (18)	0.06
Lymphodepletion, No. (%)				
Fludarabine/cyclophosphamide	125 (97)	63 (100)	62 (94)	0.12
Bendamustine	4 (3)	0 (0)	4 (6)	
Vein-to-vein time, days, median (range)	49 (35–138)	56 (42–138)	45 (35–113)	**<0.0001**
Time from initial diagnosis to CAR T-cell therapy, years, median (range)	6.2 (0.6–17.6)	6.4 (1.4–17.6)	5.5 (0.6–14.4)	0.19

*Determined prior to lymphodepletion (baseline).
†Last bone marrow status determined within 90 days prior to CAR T-cell therapy.
‡Refractory to an immunomodulatory agent and a proteasome inhibitor.
§Refractory to an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 monoclonal antibody.
¶ Exposed/refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab.
**Systemic treatment administered between leukapheresis and lymphodepletion (at least one drug).
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; ECOG, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; R-ISS, Revised International Staging System; SCT, stem cell transplant.

To further characterize late hematotoxicity, patients were classified according to the ICAHT consensus guidelines as described in the Methods section and based on late neutrophil counts (figure 1C). After day 30, 60% of the patients met the definition for late ICAHT (n=64/107) and 21% for severe late ICAHT (grade ≥3; n=22/107). Neutrophil recovery over time and the corresponding ANC nadir values for patients with grade 1–2, grade 3–4 or without late ICAHT are shown in figure 1D and online supplemental figure S2A. The severe late ICAHT group was characterized by a significantly impaired neutrophil recovery, which was already indicated during the early period and led to a pronounced, second drop after a short-term plateau. Since ICAHT grading is based solely on neutrophil counts, we also analyzed the corresponding recovery of platelet and hemoglobin levels over time (figure 1E, F). Similar to neutrophil recovery, we observed a lymphodepletion-associated drop, followed by a recovery tendency. Severe late ICAHT was associated with a pronounced second decline, characterized by significantly lower platelet (median 15 x 10^9/L vs 110 x 10^9/L; p<0.0001) (online supplemental figure S2B) and hemoglobin nadir values (median 84g/L vs 107 g/L; p<0.0001) (online supplemental figure S2C) compared with all others, resulting in a significantly increased rate of severe thrombocytopenia (77% vs 22%; OR: 11.81; 95% CI: 3.86 to 31.34; p<0.0001) and severe anemia (45% vs 6%; OR: 13.33; 95% CI: 3.70 to 41.59; p<0.0001). Average ANC, platelet and hemoglobin levels across time points were significantly different between all three groups. Moreover, there was a significant interaction between group and time points indicating different longitudinal patterns of blood cell counts, driven by the severe late ICAHT group. Further details are provided in online supplemental table S6. Compared with the other patients with available data (n=68), the severe late ICAHT

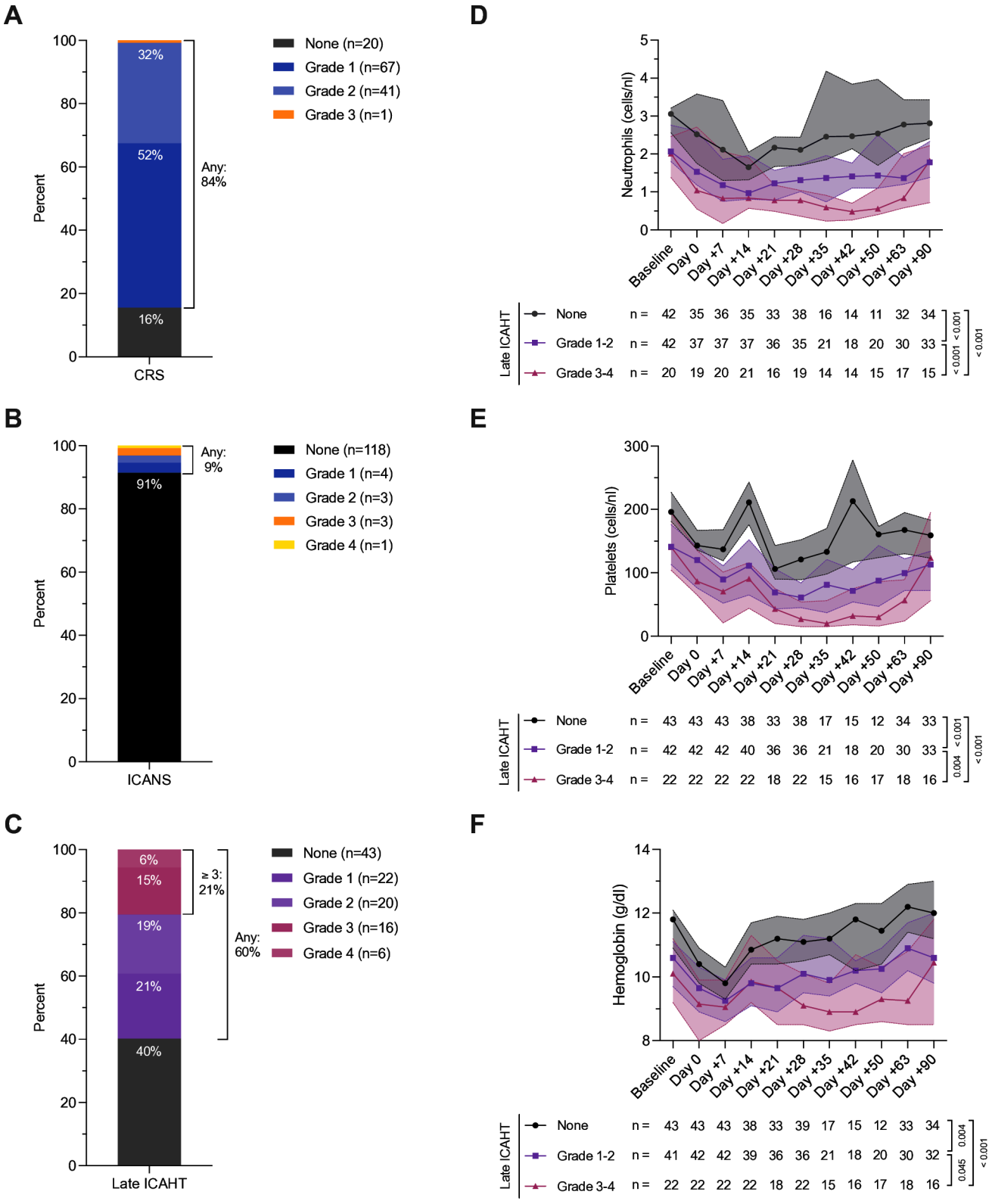

Figure 1 Frequency and severity of toxicities after CAR T-cell therapy in the total cohort. (A) CRS; (B) ICANS; (C) Late ICAHT. (D–F) Median absolute neutrophil count (D), platelet count (E) and hemoglobin levels (F) over time depending on late ICAHT grade. The filled area illustrates the corresponding 95% CIs. Measured events per group and time point are provided in the table below. P values are shown to the right of the table and refer to pairwise group comparisons across time points. Further statistical analyses using a linear mixed model are summarized in online supplemental table S6. Baseline, prior to lymphodepletion. Day 0, day of CAR T-cell infusion. CAR, chimeric antigen receptor; CRS, Cytokine-release syndrome; ICAHT, immune effector cell-associated hematotoxicity; ICANS, immune effector cell-associated neurotoxicity syndrome.

group (n=14) showed a significantly increased need for supportive measures after day 30, including G-CSF stimulation (71% vs 15%; p<0.0001), red blood cell transfusions (29% vs 4%; p=0.01) and platelet transfusions (36% vs 4%; p=0.003).

EASIX is associated with severe late cytopenias

To assess associations between baseline variables and late post-CAR-T cytopenias, we first determined the individual EASIX components, as well as blood cell counts, inflammatory and other laboratory parameters prior to lymphodepletion (baseline) and calculated the EASIX, its derivatives and the CAR-HEMATOTOX for all patients with available data (table 2). As ferritin values were not available for the US cohort, analyses of ferritin-based scores prior to lymphodepletion were restricted to the German cohort unless otherwise stated.

The median baseline EASIX was determined to be 1.26, the upper quartile (Q_3) was 2.15. Accordingly, the following groups were derived: >median (n=62) versus ≤median (n=64) and >Q_3 (n=31) versus ≤Q_3 (n=95), respectively. A comparison of patient and disease characteristics, complications and outcomes between baseline EASIX groups is provided in online supplemental tables S7 and S8. The main disease-related differences among patients with elevated (>median) or high (>Q_3) EASIX levels compared with the others included ISS/R-ISS stage, baseline cytopenias, glomerular filtration rate and the frequency of bridging therapies. The corresponding laboratory values and scores at day 0 are shown in online supplemental table S9.

When testing the correlation of the baseline EASIX components or the EASIX score with the late nadir values of ANC, platelets and hemoglobin, we found significant associations between the EASIX and all three endpoints (r=−0.39, p<0.0001; r=−0.52, p<0.0001; r=−0.38, p<0.0001) (figure 2A–C), whereas the correlations between the individual EASIX parameters and the nadirs were generally weaker. Correlation heatmaps including additional laboratory parameters and time points are shown in online supplemental figure S3. In a logistic regression model, the log_2-transformed baseline EASIX emerged as a significant predictor of late ICAHT (OR: 2.11; 95% CI: 1.33 to 3.65; p=0.004) and severe late ICAHT (grade ≥3) (OR: 1.51; 95% CI: 1.09 to 2.26; p=0.02). Detailed results of the univariate and multivariate analyses are presented in online supplemental tables S10 and S11. Baseline EASIX values were significantly higher in the severe late ICAHT group (n=21) compared with patients without severe late ICAHT (n=83) (median 1.78 vs 1.12; p=0.002) (figure 2D). The corresponding ROC analysis showed an area under the curve (AUC) of 0.72 (95% CI: 0.61 to 0.82; p=0.002), and the median baseline EASIX (1.26) as a cut-off achieved a sensitivity of 71% and a specificity of 58% (figure 2E). The group with an elevated baseline EASIX (>median; n=50/104) was characterized by a higher rate of late ICAHT (80% vs 43%; OR: 5.39; 95% CI: 2.16 to 13.42; p=0.0001) and severe late ICAHT (30% vs 11%; OR: 3.43; 95% CI: 1.24 to 9.76; p=0.03) (figure 2F). The impaired hematopoietic reconstitution in the elevated EASIX group is further illustrated by significantly lower ANC (median 0.96 x 10^9/L vs 1.71 x 10^9/L; p<0.0001), platelet (median 52 x 10^9/L vs 136 x 10^9/L; p<0.0001) and hemoglobin (median 99 g/L vs 109 g/L; p=0.003) nadir values during the late post-CAR-T period (figure 2G–I), resulting in a significantly higher rate of G-CSF stimulation (33% vs 14%; OR: 2.89; 95% CI: 1.00 to 7.41; p=0.05), severe late thrombocytopenia (50% vs 17%; OR: 5.00; 95% CI: 2.10 to 11.39; p=0.0004) and anemia (23% vs 6%; OR: 5.10; 95% CI: 1.43 to 17.61; p=0.01) (online supplemental table S7). Of note, associations between EASIX and severe late ICAHT were not restricted to the baseline time point, but also seen for the log_2-transformed EASIX at day 0 (OR: 1.79; 95% CI: 1.24 to 2.87; p=0.006) (online supplemental table S11). The corresponding ROC analysis showed a comparable AUC value (AUC: 0.77; 95% CI: 0.64 to 0.90; p=0.0004) to the baseline EASIX (figure 2E).

EASIX is associated with the neutrophil recovery phenotype

To further specify associations between EASIX and post-CAR-T cytopenias and consider qualitative differences in neutrophil recovery, we classified the evaluable 104 patients according to the three phenotypes recently proposed by Rejeski and colleagues.[5] Fifty (48%), 46 (44%) and 8 (8%) patients were assigned to the *quick*, *intermittent* and *aplastic* phenotype, respectively. A logistic regression analysis with an aplastic phenotype as a binary endpoint is shown in online supplemental table S12. Patients with an *aplastic* phenotype of neutrophil recovery showed significantly higher baseline EASIX values compared with all other patients (median 2.37 vs 1.22; p=0.004) (figure 3A). The corresponding ROC analysis demonstrated an AUC of 0.80 (95% CI: 0.67 to 0.93; p=0.005) (figure 3B). In the group with high baseline EASIX values (>Q_3), 21% of the patients (n=5/24) exhibited an aplastic phenotype, compared with 4% in the EASIX<Q_3 group (n=3/80) (OR 6.75; 95% CI 1.53 to 26.62; p=0.02) (figure 3C). When evaluating the test characteristics of the EASIX at day 0, we also observed a high AUC (AUC: 0.83; 95% CI 0.66 to 1.00; p=0.002) (figure 3B).

EASIX and CAR-HEMATOTOX score

Given the similar endpoint of both scores, we then compared the baseline EASIX values between the CAR-HTX^{low} (n=43) and CAR-HTX^{high} (n=13) groups in the German cohort and the patients in the US cohort who were attributable to the CAR-HTX^{high} group based on the available laboratory values (n=20). Patients in the CAR-HTX^{high} group showed significantly higher baseline EASIX values (median 2.07 vs 1.18; p=0.009 and median 3.15 vs 1.18; p=0.0001, respectively) (figure 3D). Moreover, we observed significant correlations between the baseline EASIX and the individual CAR-HTX scores (r=0.54; p<0.0001; n=52) (figure 3E), which were also

Table 2 Laboratory parameters and scores prior to lymphodepletion (baseline)

	Total cohort N=129	German cohort n=63	US cohort n=66	P
Laboratory parameters prior to lymphodepletion (baseline), median (range)				
LDH, U/L	213 (101–1717), n=126	228 (101–1131)	204 (117–1717), n=63	0.07
Creatinine, mg/dL	1.0 (0.40–4.13)	1.02 (0.40–1.77)	0.94 (0.49–4.13)	0.28
Platelet count, x10^9/L	168 (8–349)	178 (20–344)	149 (8–349)	0.22
Absolute neutrophil count, x10^9/L	2.54 (0.43–7.67), n=126	2.72 (0.76–7.67), n=60	2.49 (0.43–5.63)	0.18
Hemoglobin, g/L	108 (61–145), n=128	107 (75–143)	109 (61–145), n=65	0.87
CRP, mg/dL	0.27 (0.03–10.85), n=116	0.27 (0.1–5.21)	0.29 (0.03–10.85), n=53	0.91
Ferritin, ng/mL	198 (10–4494), n=58	143 (10–4494), n=55	2684 (1013–3869), n = 3[a]	
B2-MG, mg/L	2.9 (1.29–27.6), n=117	3.0 (1.5–7.9), n=52	2.8 (1.29–27.6), n=65	0.92
eGFR, mL/min	75 (16–117)	75 (38–114)	74 (16–117), n=65	0.58
>60, No. (%)	95 (74)	48 (76)	47 (71)	0.36
30–60, No. (%)	31 (24)	15 (24)	16 (24)	
<30, No. (%)	3 (2)	0 (0)	3 (5)	
Scores prior to lymphodepletion (baseline)				
EASIX, median (Q_1–Q_3)	1.26 (0.90–2.15), n=126	1.26 (0.93–1.80)	1.26 (0.87–2.73), n=63	>0.99
>median (>1.26), No. (%)	62 (49)	31 (49)	31 (49)	>0.99
>Q_3 (>2.15), No. (%)	31 (25)	11 (17)	20 (32)	0.10
Modified EASIX, median (Q_1–Q_3)	0.34 (0.19–1.10), n=115	0.34 (0.23–0.97)	0.36 (0.17–1.70), n=52	0.76
>6.2, No. (%)	11 (10)	5 (8)	6 (12)	0.54
EASIX-F, No. (%)				
Low	30 (50)	30 (55)	0 (0)	
Intermediate	22 (37)	21 (38)	1 (20)	
High	8 (13)	4 (7)	4 (80)	
Unknown	69	8	61[a]	
EASIX-FC, No. (%)				
Low	40 (69)	40 (73)	0 (0)	
Intermediate	11 (19)	10 (18)	1 (33)	
High	7 (12)	5 (9)	2 (67)	
Unknown	71	8	63[a]	
CAR-HEMATOTOX, No. (%)				
Low	43 (56)	43 (77)	0 (0)	
High	34 (44)	13 (23)	21 (100)	
Unknown	52	7	45[a]	

Due to missing data for the US cohort, further analyses of ferritin and ferritin-based scores prior to lymphodepletion were only performed for the German cohort, unless stated otherwise.
B2-MG, beta-2-microglobulin; CAR, chimeric antigen receptor; CRP, C reactive protein; EASIX, Endothelial Activation and Stress Index; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; Q_1, first/lower quartile (25th percentile); Q_3, third/upper quartile (75th percentile).

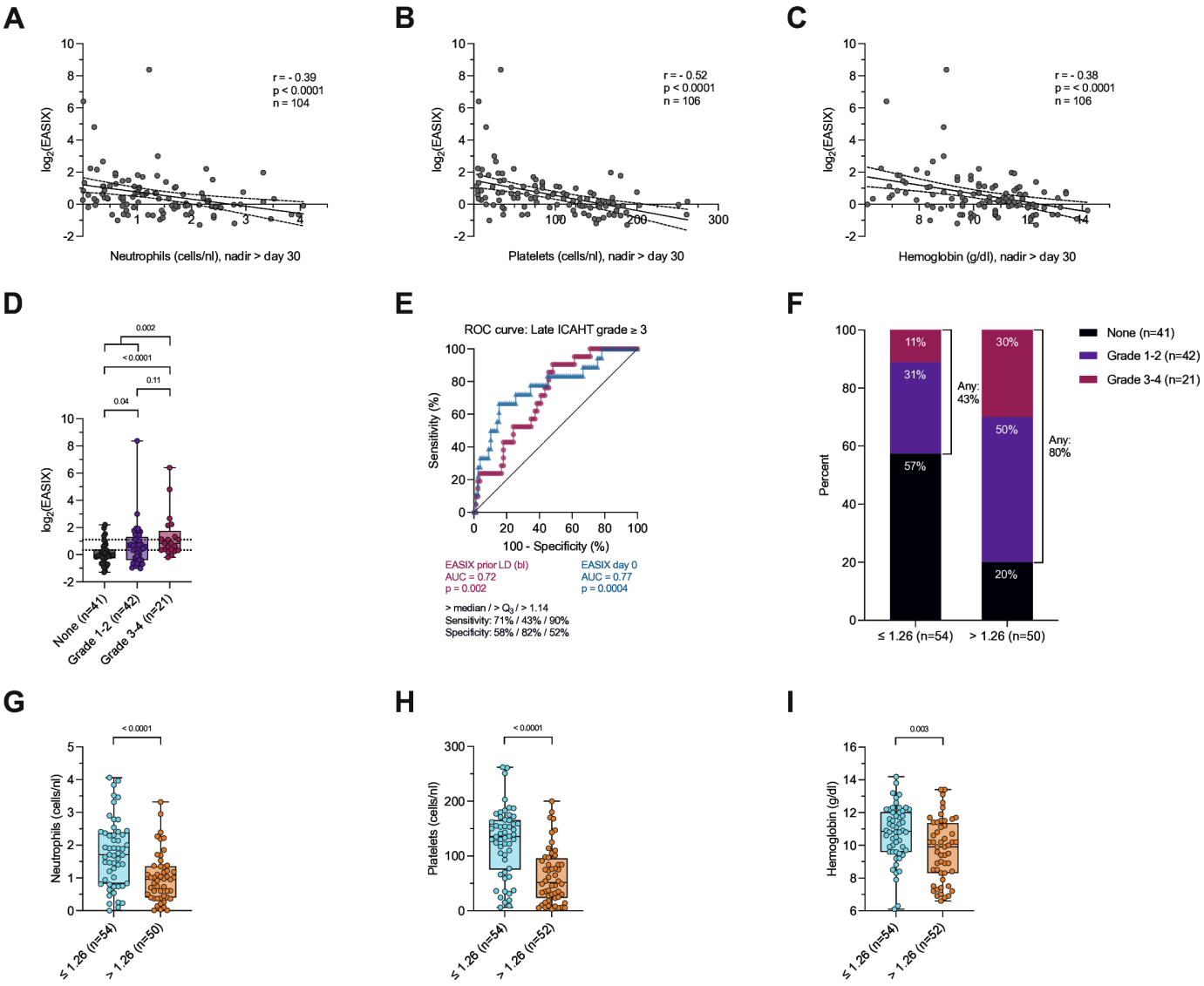

Figure 2 EASIX is associated with severe late cytopenias. (A–C) Graph showing the association between baseline log_2(EASIX) (prior to lymphodepletion) and late ANC (A), platelet count (B) and hemoglobin (C) nadir values. Best-fit line and 95% confidence bands were obtained by simple linear regression. Coefficient (r) and p values are based on Spearman correlation analysis. (D) Baseline log_2(EASIX) values depending on late ICAHT grade. Median (left to right): −0.03 vs 0.63 vs 0.83. P values of the group comparisons are shown at the top. The dashed lines indicate the median and the upper quartile of the baseline EASIX. (E) ROC curves to assess the potential of the baseline (bl) EASIX (prior to lymphodepletion (LD)) (red) and the EASIX at day 0 (day of CAR T-cell infusion) (blue) to identify patients at risk for severe late ICAHT (grade ≥3). AUC values, p values and sensitivity/specificity for selected baseline EASIX cut-off values (median, upper quartile [Q_3], optimal cut-off) are provided below. (F) Frequency and severity of late ICAHT depending on baseline EASIX group (≤median [≤1.26] vs >median [>1.26]). (G–I) Blood cell count nadir values during the late post-CAR-T period depending on baseline EASIX group (≤median [≤1.26] vs >median [>1.26]). P values of the group comparisons are shown at the top. Late ANC nadir values (G), median (left to right): 1.71/nL vs 0.96/nL. Late platelet count nadir values (H), median (left to right): 135.5/nL vs 51.5/nL. Late hemoglobin nadir values (I), median (left to right): 10.85 g/dL vs 9.90 g/dL. ANC, absolute neutrophil count; AUC, area under the curve; CAR, chimeric antigen receptor; EASIX, Endothelial Activation and Stress Index; ICAHT, immune effector cell-associated hematotoxicity; ROC, receiver operating characteristic.

seen at day 0 (r=0.56; p<0.0001; n=92). Significantly increased rates of high CAR-HTX scores were found when comparing evaluable patients with an elevated baseline EASIX (>median; n=11/28; 39%) and an EASIX ≤median (n=2/28; 7%) (OR: 8.41; 95% CI: 1.83 to 40.28; p=0.01) or a high baseline EASIX (>Q_3; n=6/10; 60%) and an EASIX ≤Q_3 (n=7/46; 15%) (OR: 8.36; 95% CI: 2.03 to 30.19; p=0.007), respectively (figure 3F; online supplemental table S7).

Detailed information on associations between the CAR-HTX score at different time points and the post-CAR-T clinical course are provided in online supplemental tables S10 - S18. Despite partial overlaps between CAR-HTX- and EASIX-based groups prior to lymphodepletion,

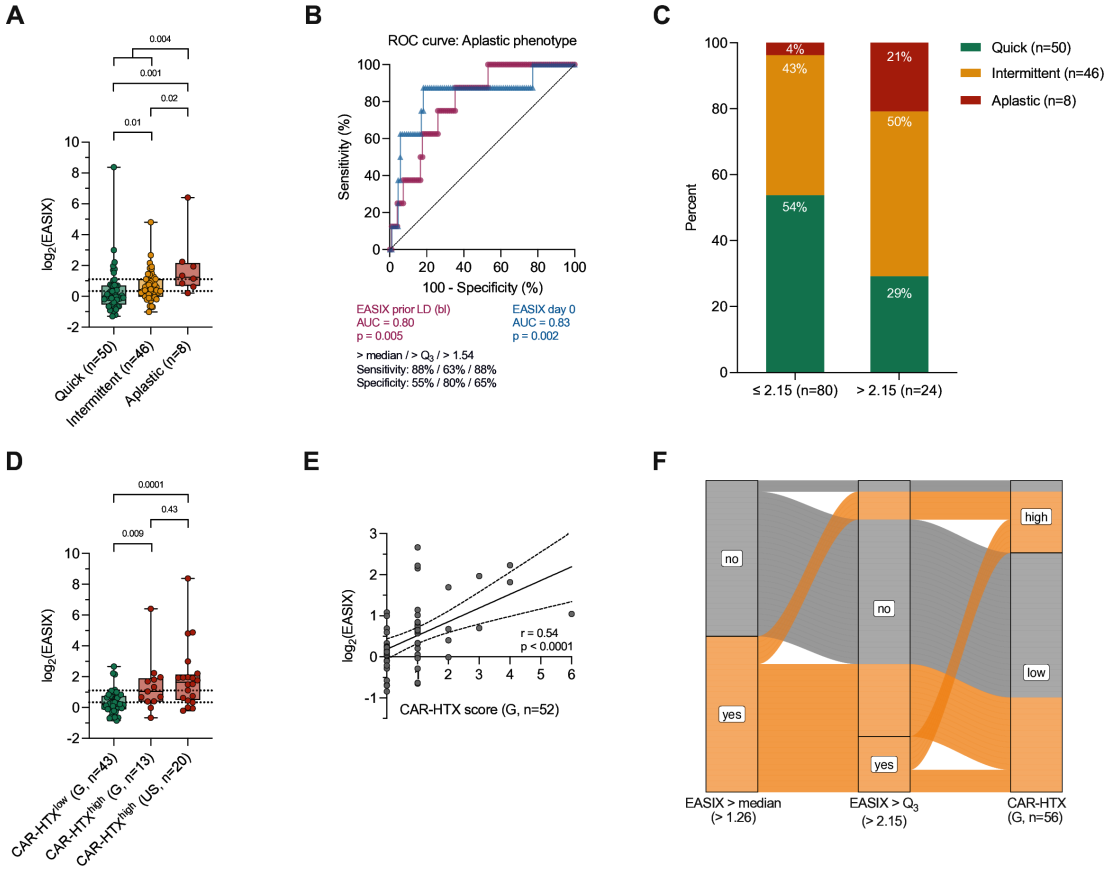

Figure 3 EASIX is associated with the neutrophil recovery phenotype and the CAR-HEMATOTOX (CAR-HTX) score. (A) Baseline log_2(EASIX) values (prior to lymphodepletion) depending on the phenotype of neutrophil recovery (*quick*, *intermittent* or *aplastic*). Median (left to right): −0.03 vs 0.43 vs 1.24. P values of the group comparisons are shown at the top. The dashed lines indicate the median and the upper quartile of the baseline EASIX. (B) ROC curves to assess the potential of the baseline (bl) EASIX (prior to lymphodepletion (LD)) (red) and the EASIX at day 0 (day of CAR T-cell infusion) (blue) to identify patients at risk for an *aplastic* phenotype of neutrophil recovery. AUC values, p values and sensitivity/specificity for selected baseline EASIX cut-off values (median, upper quartile [Q_3], optimal cut-off) are provided below. (C) Distribution of the *quick*, *intermittent* and *aplastic* phenotype of neutrophil recovery depending on baseline EASIX group (≤upper quartile [≤2.15] vs >upper quartile [>2.15]). (D) Comparison of patients with a low (<2) and a high (≥2) CAR-HTX regarding baseline log_2(EASIX) values in the German cohort (G) and the US cohort (US). Median (left to right): 0.24 vs 1.05 vs 1.65. P values of the group comparisons are shown at the top. The dashed lines indicate the median and the upper quartile of the baseline EASIX. (E) Graph showing the association between baseline log_2(EASIX) (prior to lymphodepletion) and exact CAR-HTX score for all patients with available data in the German cohort. (G) Best-fit line and 95% confidence bands were obtained by simple linear regression. Coefficient (r) and p values are based on Spearman correlation analysis. (F) Alluvial plot showing the individual patient distribution and associations regarding (left to right) baseline EASIX group>median (>1.26) (yes (orange) vs no (gray)), baseline EASIX group>upper quartile (>Q_3; >2.15) (yes vs no) and baseline CAR-HTX (high vs low) in the German cohort (G) for all patients with available CAR-HTX. AUC, area under the curve; CAR, chimeric antigen receptor; EASIX, Endothelial Activation and Stress Index; ROC, receiver operating characteristic.

we still observed differences in the associations with the investigated endpoints and assigned risk. For example, a proportion of patients affected by severe cytopenias or other complications had a low CAR-HTX, but elevated or high baseline EASIX levels (online supplemental figure S4).

EASIX and risk for severe late-onset infections, ICANS and medical interventions

We then evaluated associations between the EASIX parameters and other clinically relevant complications following CAR T-cell therapy. The corresponding univariate and multivariate logistic regression analyses including patient and disease characteristics are summarized in online supplemental tables S13–S15. Fifteen out of 113 evaluable patients were affected by a severe late-onset infection (CTC grade ≥3). These patients had significantly higher baseline EASIX values (median 2.21 vs 1.20; p=0.003) compared with non-affected patients (figure 4A). The ROC analysis provided comparable AUC values for the EASIX before lymphodepletion and at day 0 (figure 4B). The frequency of severe late-onset infections was significantly increased in the group with a high baseline EASIX (>Q_3; n=8/25; 32%) compared with patients with an EASIX ≤Q_3 (n=7/88; 8%) (OR:

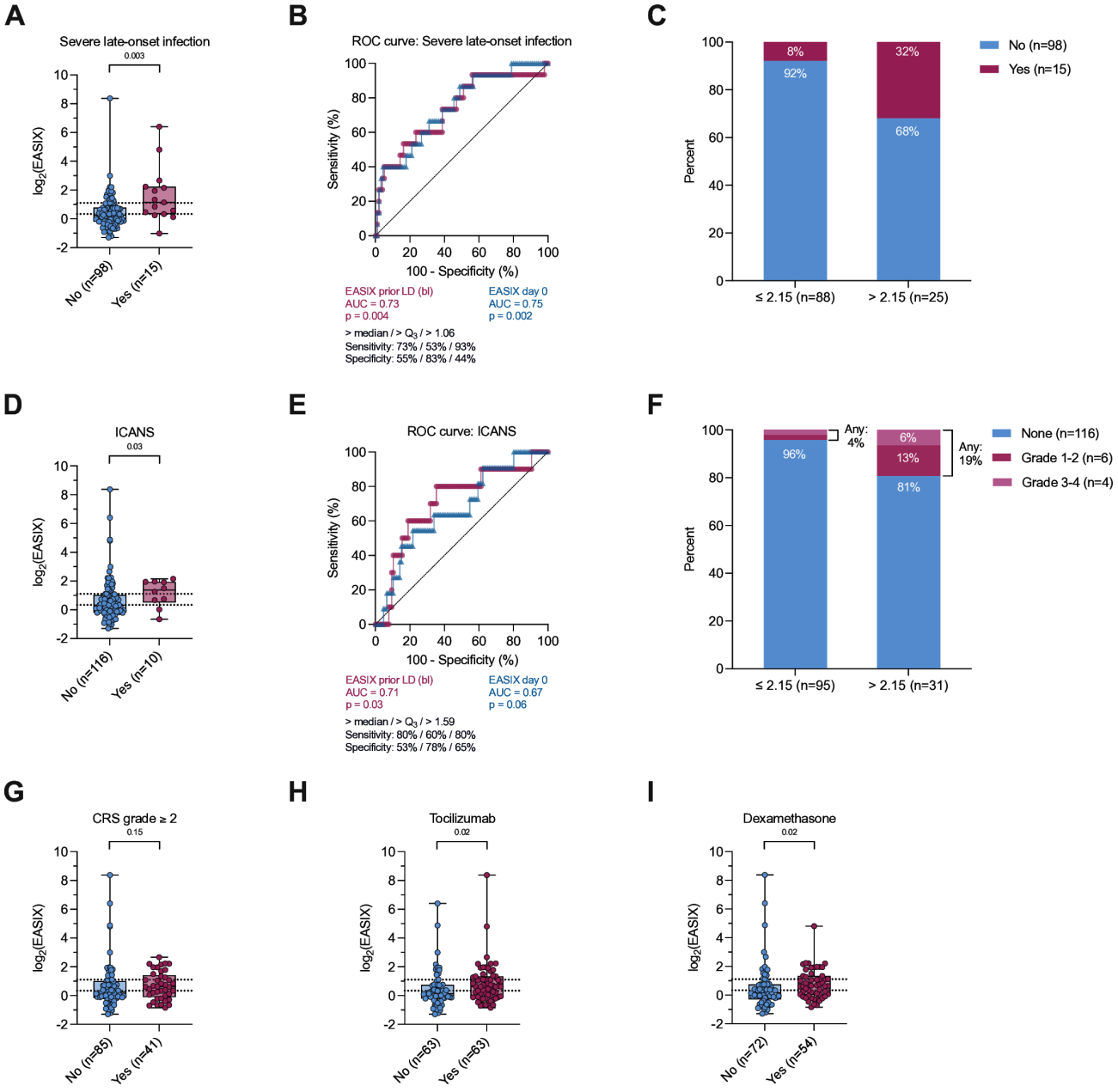

Figure 4 EASIX is associated with severe late-onset infections, ICANS and medical interventions. (A) Comparison of patients with and without late-onset severe infection (Common Terminology Criteria (CTC) grade ≥3) regarding baseline log_2(EASIX) values (prior to lymphodepletion). Median (left to right): 0.26 vs 1.14. P value of the group comparison is shown at the top. The dashed lines indicate the median and the upper quartile of the baseline EASIX. (B.) ROC curves to assess the potential of the baseline (bl) EASIX (prior to lymphodepletion (LD)) (red) and the EASIX at day 0 (day of CAR T-cell infusion) (blue) to identify patients at risk for a severe late-onset infection. AUC values, p values and sensitivity/specificity for selected baseline EASIX cut-off values (median, upper quartile [Q_3], optimal cut-off) are provided below. (C) Frequency of late-onset severe infections depending on baseline EASIX group (≤ upper quartile [≤2.15] vs >upper quartile [>2.15]). (D) Comparison of patients with and without ICANS regarding baseline log_2(EASIX) values. Median (left to right): 0.33 vs 1.38. P value of the group comparison is shown at the top. The dashed lines indicate the median and the upper quartile of the baseline EASIX. (E) ROC curves to assess the potential of the baseline EASIX (prior to LD) (red) and the EASIX at day 0 (day of CAR T-cell infusion) (blue) to identify patients at risk for ICANS (any grade). AUC values, p values and sensitivity/specificity for selected baseline EASIX cut-off values (median, Q_3, optimal cut-off) are provided below. (F) Frequency and severity of ICANS depending on baseline EASIX group (≤upper quartile [≤2.15] vs >upper quartile [>2.15]). (G–I) Comparison of patients with and without CRS grade ≥2, tocilizumab and dexamethasone treatment due to CAR T-cell associated toxicities regarding baseline log_2(EASIX) values. P values of the group comparisons are shown at the top. The dashed lines indicate the median and the upper quartile of the baseline EASIX. CRS grade ≥2 (G), median (left to right): 0.24 vs 0.61. Tocilizumab (H), median (left to right): 0.14 vs 0.63. Dexamethasone (I),median (left to right): 0.17 vs 0.64. AUC, area under the curve; CAR, chimeric antigen receptor; CRS, cytokine release syndrome; EASIX, Endothelial Activation and Stress Index; ICANS, immune effector cell-associated neurotoxicity syndrome; ROC, Receiver operating characteristic.

5.45; 95% CI: 1.80 to 16.11; p=0.005) (figure 4C). Moreover, patients who were affected by ICANS (any grade; n=10) showed significantly higher baseline EASIX values compared with the others (n=116) (median 2.61 vs 1.26; p=0.03) (figure 4D). The results of the ROC analysis favored the baseline EASIX as a risk marker (figure 4E). The group with a high baseline EASIX (>Q_3) was characterized by a significantly increased rate of ICANS events (n=6/31; 19%) compared with the EASIX ≤Q_3 group (n=4/95; 4%) (OR: 5.46; 95% CI: 1.49 to 17.90; p=0.01) (figure 4F). While no association between EASIX and CRS grade ≥2 was found (figure 4G), we observed that patients with a need for medical interventions had significantly higher baseline EASIX values (figure 4H–I), and increased rates of tocilizumab and dexamethasone administrations were found among patients with elevated EASIX levels (61% vs 39%; OR: 2.47; 95% CI: 1.21 to 4.92; p=0.02 and 53% vs 33%; OR: 2.33; 95% CI: 1.13 to 4.70; p=0.03, respectively) (online supplemental table S8). An overview of all ROC analyses performed is given in online supplemental figure S5. A comparison of the test characteristics of the EASIX and the m-EASIX at the two pre-CAR-T time points demonstrated a general superiority of the EASIX score for the investigated endpoints (online supplemental figure S6). Associations between the other EASIX derivatives and complications are shown in online supplemental table S10–S15.

EASIX is associated with inferior outcomes

Finally, we examined associations between patient and disease characteristics, laboratory parameters, scores and clinical outcomes (online supplemental tables S16–S18). No associations between EASIX and response status before or after CAR T-cell therapy were found (online supplemental table S16; online supplemental figure S7). Results of the univariate Cox regression analysis of PFS are summarized in figure 5A. High baseline EASIX levels (>Q_3) were found to be prognostically unfavorable (HR: 2.05; 95% CI: 1.21 to 3.48; log-rank p=0.007; C-index=0.58) (figure 5A, B). The associations between ISS stage III (HR: 2.76; 95% CI: 1.32 to 5.77; p=0.007), extraosseous disease (HR: 2.34; 95% CI: 1.31 to 4.19; p=0.004), high EASIX levels (HR: 2.03; 95% CI: 1.13 to 3.64; p=0.02) and an inferior PFS remained significant in a multivariate model. Moreover, patients with high EASIX levels showed an inferior OS (HR: 4.85; 95% CI: 2.35 to 10.00; log-rank p<0.0001; C-index=0.68) (figure 5C, D), driven by a high rate of death in the first 6 months after CAR T-cell infusion (n=8/15) and also seen in the subcohorts (online supplemental figure S8B, D). A multivariate analysis confirmed the negative prognostic significance of ISS stage III (HR: 4.42; 95% CI: 1.62 to 12.10; p=0.004), extraosseous disease (HR: 3.42; 95% CI: 1.44 to 8.17; p=0.006) and a high baseline EASIX (HR: 3.89; 95% CI: 1.71 to 8.83; p=0.001). Under consideration of the limited case numbers, no significant differences were found in the distribution of causes of death and non-relapse mortality between the EASIX groups (online supplemental table S8). In addition to the baseline time point, we also found strong associations between the EASIX at day 0 and post-CAR-T outcomes (figure 5A, C; online supplemental figure S8E, F). Further analyses of score-based risk groups at different time points are provided in online supplemental tables S17 and S18.

DISCUSSION

Our real-world data analysis confirmed the clinical efficacy and safety of ide-cel in RRMM. We included cohorts from two German centers and one US center, representing two countries with widespread use of CAR T-cells in RRMM. While overall efficacy based on response rates and survival times were similar between the German and US cohorts, we observed significant differences in the incidence of complications. This is most likely explained by differences in patient and disease characteristics, but also by center-specific management of post-CAR-T prophylaxes and toxicities. For example, prophylactic G-CSF administration, as described in the literature,[30] was used in the US cohort and associated with a decreased rate of high-grade neutropenia during the early post-CAR-T period.

With the aim of predicting severe complications following CAR T-cell therapy with ide-cel, we employed the EASIX score originally developed for similar purposes in the allogeneic transplant setting. We demonstrated associations between EASIX at two pre-CAR-T time points and life-threatening complications and inferior outcomes after ide-cel infusion. To our knowledge, this is the first study investigating EASIX-based risk stratification in this context. Former studies have focused on CD19-directed CAR T-cell therapy in lymphomas and associations between EASIX and severe CRS/ICANS.[12 19 20] We extended our analysis by including post-CAR-T cytopenia as an endpoint, the most common adverse event after CAR T-cell therapy.[6]

High-grade cytopenias were frequently observed and not restricted to the early post-CAR-T period. We identified a fraction of patients with severe late ICAHT, defined by deep neutropenia after day 30 and associated with severe anemia and thrombocytopenia, leading to a high need for supportive measures and complicating outpatient care. The EASIX allowed for a simple risk evaluation based on LDH, creatinine and platelet count. Patients with elevated EASIX levels showed a significantly higher rate of severe late cytopenias. The high relevance of baseline platelet count for prediction of post-CAR-T cytopenias is a well-described phenomenon[5 31] and could be related to intensive prior therapies and disease-associated suppression of hematopoiesis. Of note, we observed significantly higher rates of bridging therapies among patients with increased EASIX levels, whereas bone marrow disease burden and baseline remission status were comparable between groups. LDH is a well-established prognostic factor in multiple myeloma and regarded as an indicator of highly proliferative disease activity and extramedullary tumor masses.[23 32 33] Although no correlation between

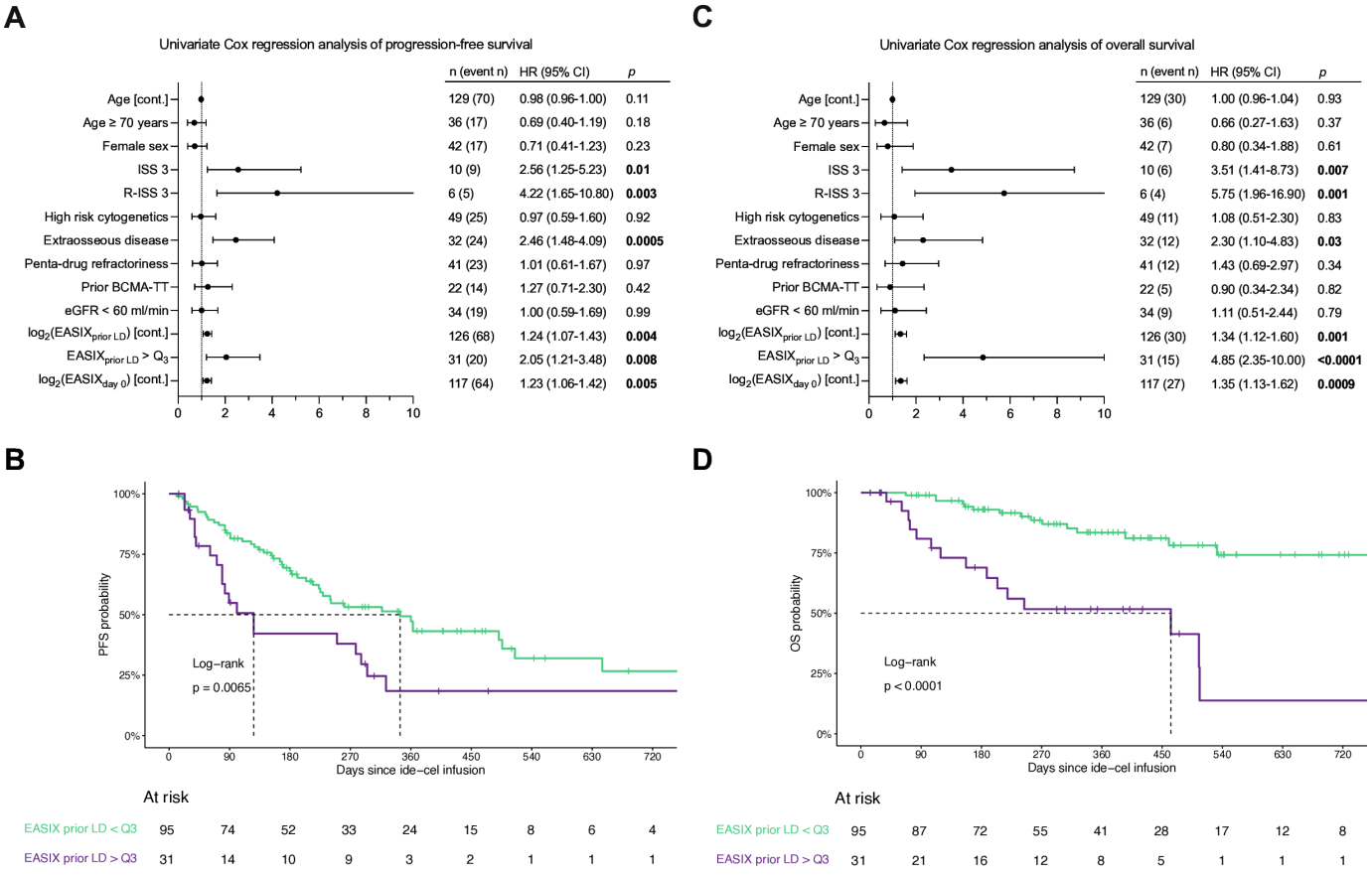

Figure 5 EASIX is associated with inferior outcomes after CAR T-cell therapy. (A) Forest plot showing the results of the univariate Cox regression analysis of PFS in the total cohort. The plot shows the respective HR and 95% CI. Included continuous and binary variables: age (continuous), age ≥70 years, female sex, ISS stage 3, R-ISS 3, high risk cytogenetics, extraosseous disease, penta-drug refractoriness, prior BCMA-TT, eGFR <60 mL/min, log_2(EASIX) prior to lymphodepletion (LD) (continuous), EASIX prior to LD>upper quartile (Q_3) and log_2(EASIX) at day 0 (day of CAR T-cell infusion) (continuous). (B) Kaplan-Meier estimates of the probability of PFS in days since ide-cel infusion for the baseline EASIX (prior to LD) ≤ Q_3 (≤2.15) group (green) (median PFS 344 days; 95% CI: 225 to 515) and the baseline EASIX>Q_3 (>2.15) group (violet) (median PFS 126 days; 95% CI: 79 to 323) in the total cohort. (C) Forest plot showing the results of the univariate Cox regression analysis of OS. The plot shows the respective HR and 95% CI. Included continuous and binary variables are shown above. (D) Kaplan-Meier estimates of the probability of OS in days since ide-cel infusion for the baseline EASIX (prior to LD) ≤ Q_3 (≤2.15) group (green) (median OS NR) and the baseline EASIX>Q_3 (>2.15) group (violet) (median OS 463 days; 95% CI: 188 to NR) in the total cohort. BCMA-TT, B-cell maturation antigen-targeted therapy; CAR, chimeric antigen receptor; EASIX, Endothelial Activation and Stress Index; eGFR, estimated glomerular filtration rate; ide-cel, idecabtagene vicleucel; ISS, International Staging System; NR, not reached; OS, overall survival; PFS, progression-free survival; R-ISS Revised International Staging System stage.

LDH and duration of severe neutropenia during the post-CAR-T phase has been found in the context of anti-CD19 CAR T-cell therapy,[5] Rejeski and colleagues have reported associations between elevated LDH levels and an aplastic phenotype of neutrophil recovery.[11 13] Baseline creatinine showed an impact on late cytopenias and infections in our analysis. Renal impairment might reflect disease type, higher disease aggressiveness, comorbidities and intensive pretreatment. In line with this hypothesis, we observed a correlation between baseline creatinine and beta-2 microglobulin, a marker of high tumor mass in multiple myeloma.[23]

In addition to disease-related factors, the common interpretation of the EASIX as an indicator of endothelial stress and homeostasis provides an additional explanation for the observed associations.[12 15] Endothelial cells represent an important component of the bone marrow niche contributing to maintenance, expansion and regeneration of hematopoietic stem cells,[34–36] and endothelial dysfunction and corresponding serum markers have been found to be associated with an aplastic phenotype of neutrophil recovery after CD19 CAR T-cell therapy.[13] Consistently, patients with high EASIX levels showed a higher rate of aplastic phenotypes in our analysis.

The importance of severe, long-lasting neutropenia and endothelial dysfunction in the development of life-threatening infections has been well demonstrated by Rejeski and colleagues.[8 37] It therefore appears plausible that patients with high EASIX levels had a significantly increased risk for late-onset severe infections. These patients could therefore particularly benefit from prolonged anti-infective prophylaxis, early intravenous

immunoglobulin substitution, more regular monitoring of infection parameters and intensified use of growth factors.

Previous studies have demonstrated the potential of the EASIX and its derivatives as risk markers for advanced CRS and ICANS,[12 19 20] although in a different disease context. In line with these findings, our analysis showed associations between baseline EASIX and increased rates of ICANS and medical interventions. Considering EASIX as a marker of endothelial damage, it is important to note that endothelial and complement dysfunction are regarded as pathogenetic drivers of CAR-T-associated neurotoxicity, and different studies have shown associations with corresponding serum markers.[12 38–40]

Most importantly, we found strong associations between high EASIX levels and an inferior PFS and particularly OS, driven by a high rate of early death. High EASIX levels implicated a higher rate of an aplastic phenotype of neutrophil recovery, which has been shown to be associated with adverse outcomes after CD19-directed CAR T-cell therapy.[13] The link between increased EASIX levels, endothelial dysfunction and non-relapse mortality has been extensively described in the context of allogeneic stem cell transplantation,[15] and more recently, also in the context of CAR T-cell therapy for large B-cell lymphoma.[41] Due to the limited event rate in our cohort, further studies are needed to validate the EASIX as a risk marker specifically for non-relapse mortality after anti-BCMA CAR T-cell therapy.

In addition to the EASIX, we also included established EASIX derivatives and the CAR-HEMATOTOX score in our analysis. We observed partial overlaps between the different score-based risk groups and varying degrees of association with the selected clinical endpoints. For example, the group with high baseline EASIX levels included an increased proportion of patients with a high CAR-HEMATOTOX, which is an established scoring system to risk stratify for an aplastic phenotype. The partial overlap between both risk groups is at least in parts explained by the fact that both scores include platelet count as a marker of hematopoetic reserve. A major difference is that the EASIX includes parameters known to mirror disease burden and aggressiveness in RRMM, whereas the CAR-HEMATOTOX, similarly to the EASIX derivatives, focuses on baseline inflammation. Among evaluable patients, we found significant associations between baseline CAR-HEMATOTOX and late ICAHT. However, no associations were observed between the baseline score and other endpoints of interest, acknowledging a relevant proportion of patients who had to be excluded from the analysis due to missing data. The extent and relevance of inflammation might vary depending on the composition of the patient population, disease, CAR construct and endpoint. For example, the m-EASIX showed a strong association with PFS and OS, but weaker associations with the examined post-CAR-T complications. Compared with the other scores, one of the general strengths of the EASIX is simplicity and the usage of widely available laboratory markers to predict severe late complications affecting survival. The two cut-off values (median and upper quartile) allow for a stepwise risk stratification approach and help to cover a broad spectrum of clinically relevant endpoints. A potential weakness is the integration of laboratory parameters which may be age-, sex- and assay-dependent. Nevertheless, the score has been validated for numerous diseases, treatments and endpoints in the past years.

Key limitations of our study are the retrospective design and the limited case and event numbers. In addition, the lack of baseline ferritin values for the US cohort limited our analysis of ferritin-based scores prior to lymphodepletion. The combined analysis of cohorts from three independent centers for the other endpoints, however, is a strength of the analysis and increases generalizability. Further studies are needed to evaluate the benefits and disadvantages of different scoring systems and to prospectively validate the EASIX and the derived cut-off values in larger, external cohorts prior to implementation in clinical routine.

In conclusion, the EASIX represents a quick and simple screening tool to identify vulnerable patients and predict major complications and adverse clinical outcomes after CAR T-cell therapy with ide-cel. The EASIX could therefore facilitate clinical decision-making prior to lymphodepletion and at day 0 in the future. Patients with low EASIX levels might be suitable candidates for outpatient CAR T-cell therapy. In contrast, patients with elevated, and even more those with high EASIX levels might particularly benefit from hospitalization, closer monitoring after discharge and intensified use of supportive and prophylactic measures. Future studies across different entities and time points should explore the potential of the EASIX as a risk marker in the context of CAR T-cell and other immunotherapies.

Author affiliations
[1]Department of Medicine V, University Hospital and Medical Faculty Heidelberg, Heidelberg, Baden-Württemberg, Germany
[2]Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center, Heidelberg, Baden-Württemberg, Germany
[3]Internal Medicine II, University Hospital of Würzburg, Würzburg, Bayern, Germany
[4]Division of Biostatistics, German Cancer Research Center, Heidelberg, Baden-Württemberg, Germany
[5]Molecular Medicine Partnership Unit, Heidelberg, Baden-Württemberg, Germany
[6]Eli and Edythe L Broad Institute of Harvard and MIT, Cambridge, Massachusetts, USA
[7]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts, USA
[8]National Center for Tumor Diseases, Heidelberg, Baden-Württemberg, Germany
[9]Division of Hematology, Brigham and Women's Hospital, Boston, Massachusetts, USA

Acknowledgements We would like to thank all patients and the personnel at the participating centers who contributed to this work.

Contributors Conceptualization: JF, MSR, SS. Methodology: JF, TH, MSR, JK, XZ, TL. Investigation: JF, XZ, VW, PC, MH, JK. Analysis and visualization: JF, TH. Funding acquisition: MSR. Project administration: JF, MSR, SS. Supervision: MSR, SS, LR, ASp, NCM, PD, ON, HE, MT, CM-T, MS, TL, ASchmitt, HG, NW, MJF, EKM, CSM, IB. Writing – original draft: JF. Writing – review & editing: MSR, ASperling,

PD, TL, NW, ON, EKM. Guarantor: MSR. All authors read and approved the final manuscript.

Funding JF is funded through the IMS and Paula and Rodger Riney Foundation. MSR has received research funding from the Dietmar Hopp Foundation. ASp was supported by grants from the NCI (K08CA252174) and DOD (CA210827). XZ has received research funding from the DFG, IZKF Würzburg and BZKF.

Competing interests JF has received honoraria from BMS and Stemline and travel and congress participation grants from Janssen-Cilag. XZ declares advisory services for and has received travel support from SkylineDx. JK has received honoraria from AstraZeneca. EKM declares a consulting or advisory role for Amgen, BMS/Celgene, GlaxoSmithKline, Janssen-Cilag, Pfizer, Sanofi, Stemline and Takeda. He has received honoraria from Amgen, BMS/Celgene, GlaxoSmithKline, Janssen-Cilag, Pfizer, Sanofi, Stemline and Takeda, research funding from BMS/Celgene, GlaxoSmithKline, Janssen-Cilag, Sanofi and Takeda and travel support from BMS/Celgene, GlaxoSmithKline, Janssen-Cilag, Sanofi, Stemline and Takeda. MJF declares consulting activity for Pfizer and Kerna Ventures. CSM has received honoraria and travel support from Janssen-Cilag. IB has received honoraria from Oncopeptide and travel support from Janssen. ON reports receiving consulting fees from Janssen, BMS, Takeda, GPCR therapeutics, Sanofi and Pfizer. AS has received travel grants from Hexal and Jazz Pharmaceuticals and research grants from Therakos/Mallinckrodt. She is a consultant for Janssen-Cilag and BMS and co-founder of TolerogenixX Ltd. AS is part-time employee of TolerogenixX Ltd. MS declares an advisory role or expert testimony for MSD, Novartis, BMS and Pierre Fabre. He is co-founder and shareholder of TolerogenixX GmbH, Heidelberg. He has received financial support for research on biosimilars and travel grants from Hexal, financial support of educational activities and conference participation and travels grants from Kite and BMS, collaborative research grants from Novartis and funding for collaborative research from Apogenix. MT has received research funding from Kite, Regeneron and Roche. He is an advisory board member for AstraZeneca, BMS, Incyte, Janssen and Novartis. HE declares a consulting or advisory role for BMS/Celgene, Janssen, Amgen, Takeda, Sanofi, GSK, Novartis and Roche. He has received research funding from BMS/Celgene, Janssen, Amgen, GSK, Sanofi and Novartis, honoraria from BMS/Celgene, Janssen, Amgen, Takeda, Sanofi, GSK, Novartis and travel support from BMS/Celgene, Janssen and Amgen. PD reports consultancy for AbbVie, AstraZeneca, Beigene, BMS, Gilead, Miltenyi, Novartis and Riemser. He is member of the speakers' bureau for AbbVie, AstraZeneca, BeiGene, BMS, Gilead, Novartis, Riemser and Roche and has received research support from Riemser (all to institution). NCM reports receiving personal fees from BMS, Janssen, Amgen, Takeda, OncoPep, AbbVie, Karyopharm, Novartis, Legend, Raqia, Adaptive Biotechnology, and Pfizer outside the submitted work. He has intellectual property licensed to OncoPep and held stocks in C4 Therapeutics. ASp reports receiving consulting fees from Novartis and Roche. LR consulted for Janssen, Amgen, GSK, Pfizer, BMS, Sanofi, and received honoraria from Janssen, GSK, Pfizer, BMS, Sanofi and received research funding from Skyline Dx and BMS. SS has received travel grants or honoraria for presentations from Celgene, BMS, Janssen, Takeda and Amgen. MSR declares a consulting or advisory role for BMS, Amgen, GSK, Janssen, Sanofi, Pfizer, AbbVie and Takeda. He has received research funding from BMS, Janssen, Sanofi and Heidelberg Pharma, travel support from BMS, Amgen and Janssen and honoraria from BMS, Janssen, AbbVie and Sanofi.

Patient consent for publication Not applicable.

Ethics approval This study was approved by institutional committees and boards (Ethics Committee of the Medical Faculty of Heidelberg University [S-096/2017] and Dana-Farber IRB [18-340]) and conducted according to the Declaration of Helsinki. Written informed consent was obtained from all patients. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The datasets analyzed during the current study are available from the corresponding author on reasonable request.

ORCID iD

Jan H Frenking http://orcid.org/0009-0001-9682-2601

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