REGULAR ARTICLE

blood advances

Applying the EHA/EBMT grading for ICAHT after CAR-T: comparative incidence and association with infections and mortality

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Key Points

- The novel EHA/EBMT grading of ICAHT closely reflects the extent of hematological toxicity following BCMA- and CD19-directed CAR-T therapy.
- Severe ICAHT was associated with transfusion use, an increased rate of severe infections and adverse treatment outcomes with high NRM.

Cytopenias represent the most common side effect of CAR T-cell therapy (CAR-T) and can predispose for severe infectious complications. Current grading systems, such as the Common Terminology Criteria for Adverse Events (CTCAE), neither reflect the unique quality of post–CAR-T neutrophil recovery, nor do they reflect the inherent risk of infections due to protracted neutropenia. For this reason, a novel EHA/EBMT consensus grading was recently developed for Immune Effector Cell-Associated HematoToxicity (ICAHT). In this multicenter, observational study, we applied the grading system to a large real-world cohort of 549 patients treated with BCMA- or CD19-directed CAR-T for refractory B-cell malignancies (112 multiple myeloma [MM], 334 large B-cell lymphoma [LBCL], 103 mantle cell lymphoma [MCL]) and examined the clinical sequelae of severe (≥3°) ICAHT. The ICAHT grading was strongly associated with the cumulative duration of severe neutropenia ($r = 0.92$, $P < .0001$), the presence of multilineage cytopenias, and the use of platelet and red blood cell transfusions. We noted an increased rate of severe ICAHT in patients with MCL vs those with LBCL and MM (28% vs 23% vs 15%). Severe ICAHT was associated with a higher rate of severe infections (49% vs 13%, $P < .0001$), increased nonrelapse mortality (14% vs 4%, $P < .0001$), and inferior survival outcomes (1-year progression-free survival: 35% vs 51%, 1-year overall survival: 52% vs 73%, both $P < .0001$). Importantly, the ICAHT grading demonstrated superior capacity to predict severe infections compared with the CTCAE grading (c-index 0.73 vs 0.55, $P < .0001$ vs nonsignificant). Taken together, these data highlight the clinical relevance of the novel grading system and support the reporting of ICAHT severity in clinical trials evaluating CAR-T therapies.

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All data needed to evaluate the conclusions in the paper are present in the manuscript and/or the supplementary Materials. Original data available upon reasonable request to the corresponding authors.

The full-text version of this article contains a data supplement.

Introduction

Chimeric antigen receptor T-cell (CAR-T) therapy has emerged as a powerful treatment modality for a range of advanced B-cell malignancies but is associated with a unique toxicity profile.[1-6] Next to cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) as prototypical side effects, hematological toxicity represents the most common side effect of CAR-T therapy.[7,8] Cytopenias are qualitatively unique because of their biphasic trajectory and can be long-lasting in nature.[9-12] Importantly, profound neutropenia can incur significant morbidity and mortality by predisposing patients undergoing cell therapy to clinically relevant infectious complications.[11,13-17] The recurrent quality of cytopenia can prolong hospital stays or result in additional hospitalizations due to infections. Notably, a high frequency of hematotoxicity has been observed across CAR products and disease entities, irrespective of target antigen (eg, CD19, CD22, BCMA) and costimulatory domain (eg, 4-1BB, CD28z).[8,11,18-21] Current grading systems, such as the Common Terminology Criteria for Adverse Events (CTCAE) describe cytopenias predominantly in quantitative terms by assigning severity grades according to cytopenia depth. However, the cumulative risk of secondary complications such as infections primarily increases with the respective duration of observed cytopenia.[15,22]

In an international survey of >50 experienced CAR-T centers, we observed significant heterogeneity in the grading and management of post–CAR-T cytopenias.[23] To better assess cytopenias and the potential risk of severe infections, the European Hematology Association (EHA) and the European Society for Blood and Marrow Transplantation (EBMT) recently introduced a novel grading system for Immune Effector Cell-Associated HematoToxicity (ICAHT), which incorporates both the depth and duration of neutropenia.[8] Importantly, the novel EHA/EBMT grading system for ICAHT provides a more distinct description of hematotoxicity, separating early (day 0-30) vs late ICAHT (after day 30). The consensus guidelines document further provides severity-based best practice recommendations for both the diagnostic workup and management of ICAHT (eg, G-CSF, anti-infective prophylaxis, stem cell boosts).[24]

Because of the standardized severity criteria, the novel ICAHT grading enables harmonized comparisons across disease entities. In this study, we applied the grading to a large, multicenter, retrospective patient cohort that was treated with different CAR constructs across multiple refractory B-cell malignancies (eg, large B-cell lymphoma [LBCL], mantle cell lymphoma [MCL], and multiple myeloma [MM]). Moreover, we examined the rate of infections and treatment outcomes in relation to ICAHT severity.

Methods

Patient cohort

The grading system for early ICAHT (Table 1) was applied to a real-world cohort of 549 patients treated with BCMA- or CD19-directed CAR T-cells for relapsed/refractory B-cell malignancies (112 MM, 334 LBCL, and 103 MCL) across 12 international CAR-T centers (supplementary Methods).[18,19,25] A uniform data collection form with an embedded data dictionary was provided to all participating centers by the coordinating center (LMU Munich), along with an example of guidelines for data collection. All sites returned data to the coordinating center. A quality control check was performed by the coordinating center and queries were issued for missing data or data that did not follow the format specified in the data collection form. All retrospective data were collected with institutional review board approval. Examples: LMU Munich: Project Nr. 19-817; Lyon: CNIL, approval No. 18-076, Mayo: 21-006535, Moffitt Cancer Center: Advarra Pro00046602.

Table 1. EHA/EBMT consensus grading for early ICAHT

Grading	I	II	III	IV
Early ICAHT (d 0-30)				
ANC ≤ 500/μL	<7 d	7-13 d	≥14 d	Never above 500/μL
ANC ≤ 100/μL	-	-	≥7 d	≥14 d
Late ICAHT (after d +30)*				
ANC ≤ 1500/μL	x			
ANC ≤ 1000/μL		x		
ANC ≤ 500/μL			x	
ANC ≤ 100/μL				x

Because of incomplete data and loss to follow-up, only early ICAHT grades were assessed in this study. Data on late ICAHT grades were not available in this study.
*measured ≥2 time points, or nontransient neutropenia

Hematological toxicity and management

Hematotoxicity end points included the total cumulative duration of severe neutropenia (absolute neutrophil count [ANC] <500/μL, day 0-60) and the phenotypes of neutrophil recovery (quick vs intermittent vs aplastic), as previously described.[11,22] Severe thrombocytopenia was defined as a platelet count <50 G/L, whereas severe anemia was defined as a hemoglobin <8 g/dL or requiring transfusion with packed red blood cells. Neutropenia was defined as severe (ANC <500/μL) or profound (ANC <100/μL) based on the joint American Society of Clinical Oncology/Infectious Diseases Society of America (ASCO/IDSA) consensus guidelines for cancer-related infection risk.[22] Patient-individual data concerning management strategies for hematotoxicity including the use of G-CSF, thrombopoietin agonists, and hematopoietic stem cell boosts were collected.

Assessment of other toxicities

CRS and ICANS were graded according to the American Society For Transplantation and Cellular Therapy (ASTCT) consensus criteria.[26] Toxicity management followed institutional guidelines.[15,27] Infections were studied until day +90 after CAR-T infusion and were graded on a 5-grade scale as mild, moderate, severe, life-threatening, or fatal.[15,17-19,28] Severe infections (grade 3 or higher) were defined as requiring intravenous anti-infective therapy and/or hospitalization. Infectious events were either characterized based on microbiologic or histopathologic data or as a clinical syndrome of infection (eg, pneumonia, cellulitis, cystitis) based on retrospective chart review. In the absence of microbiologic evidence, asymptomatic neutropenic fever was not considered an infection event.

Clinical outcomes

Kaplan-Meier estimates for progression-free survival (PFS) and overall survival (OS) were calculated from the time of CAR-T infusion. NRM was defined as death following CAR-T without

evidence of relapse or progression. Severe (≥3°) vs nonsevere (0-2°) ICAHT groups were compared by log-rank test. In a subgroup analysis, we compared survival outcomes in patients with absent (0°), mild-to-moderate (1-2°), and severe (≥3°) ICAHT. Univariate Cox regressions were applied to study hazard ratios (HRs) comparing different ICAHT severity groups.

Statistical considerations

Univariate and multivariable analyses were performed using binary logistic regression, studying severe vs nonsevere ICAHT as the binary outcome. All covariates with a $P < .2$ on univariate analysis were included in the multivariable model. Statistical significance between groups was explored by the Mann-Whitney test for continuous variables and Fisher exact test for comparison of percentages. Receiver operating characteristic (ROC) analysis was performed to compare the discrimination of the ICAHT vs CTCAE grading for severe infections (eg, grade 3 or higher). Statistical analysis and data visualization were performed using GraphPad Prism (v9.0), SPSS (IBM, v28.0), and R Statistical Software (v4.1.2).

Results

Overview of baseline features and coincident toxicity according to ICAHT severity

The overall distribution of mild (1°), moderate (2°), severe (3°), and life-threatening (4°) ICAHT was 36%, 29%, 17%, and 5% (Figure 1a). Only 70 patients (13%) did not exhibit ICAHT of any grade. An overview of baseline features comparing patients with severe (grade 3 or higher, n = 125) vs nonsevere ICAHT (absent or grade 1-2, n = 424) is provided in Table 2. Patients that subsequently developed severe or life-threatening ICAHT displayed elevated serum inflammatory markers and pronounced cytopenia at baseline, reflected by increased CAR-HEMATOTOX scores (median 3 vs 1, $P < .001$).[11,15,29] The severe ICAHT group also showed significantly elevated serum LDH levels (median 272 vs 235 U/L, $P < .001$), increased ECOG performance status (≥2: 20% vs 11%, $P = .02$), and more frequent bone marrow (BM) infiltration (36% vs 18%, $P < .001$). Furthermore, the CD28z costimulatory domain was associated with severe ICAHT, consistent with prior reports (Table 2).[30,31] In contrast, neither the number of prior treatment lines nor prior autologous stem cell transplantation (SCT) were associated with severe hematotoxicity.

In terms of coincident toxicity after CAR-T infusion, both severe CRS (ASTCT grade 3 or higher: 15% vs 5%, $P < .001$) and ICANS (≥3°: 26% vs 13%, $P < .001$) were more common in patients with severe ICAHT (supplementary Table 1). Accordingly, patients with severe hematotoxicity often received additional immunosuppressive agents for toxicity management, such as glucocorticoids (52% vs 43%, $P = .07$) or the IL-6 receptor antagonist tocilizumab (75% vs 60%, $P = .002$). Furthermore, intensive care admission was more frequent for the severe ICAHT group (23% vs 4%, $P < .001$). On multivariable binary

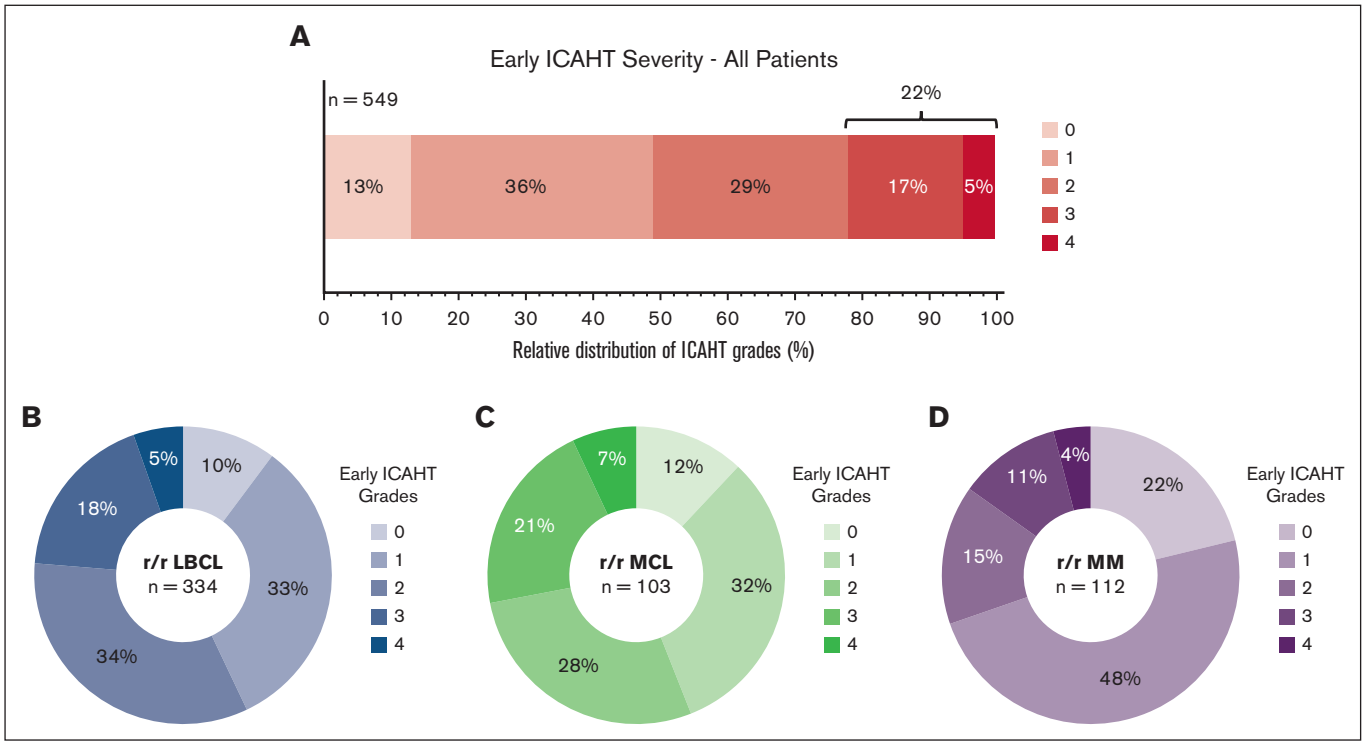


Figure 1. ICAHT severity across disease entities. (A-D) Relative distribution of ICAHT severity grades across the entire study population (A) and for patients with relapsed/refractory (r/r) LBCL (B), mantle cell lymphoma (C), and MM (D).

Table 2. Baseline patient characteristics

Characteristic	*All patients (n = 549)*	ICAHT severity		*P* value
		Nonsevere (n = 424)	Severe (n = 125)	
Demographic features				
Age, y (95% CI)	65 (64-65)	65 (64-65)	65 (63-66)	.65
Gender, female – n (%)	208 (38%)	155 (37%)	53 (42%)	.25
ECOG PS at lymphodepletion				
Median (IQR)	1 (0-1)	1 (0-1)	1 (1-1)	**<.001**
PS ≥2 – n (%)	73 (13%)	48 (11%)	25 (20%)	**.02**
Disease features				
LBCL	334 (60.8%)	255 (60.1%)	79 (63.2%)	.06
MM	112 (20.4%)	95 (22.4%)	17 (13.6%)	
MCL	103 (18.8%)	74 (17.5%)	29 (23.2%)	
BM involvement – n (%)	113/520 (22%)	71/404 (18%)	42/116 (36%)	**<.001**
Serum LDH (U/l), 95% CI	243 (235-255)	235 (221-243)	272 (259-308)	**<.001**
CAR product features				
CD28z (axi-cel, brexu-cel)	306 (56%)	224 (53%)	82 (66%)	**.01**
4-1BB (tisa-cel, ide-cel, cilta-cel)	243 (44%)	200 (47%)	43 (34%)	
Prior therapy				
Median lines of prior therapy (95% CI)	4 (3-4)	3.5 (3-4)	4 (3-4)	.35
Prior autologous SCT – n (%)	218 (40%)	171 (40%)	47 (38%)	.60
CAR-HEMATOTOX components (Rejeski et al[11])				
Median C-reactive protein (mg/dl), 95% CI	0.84 (0.66-1.04)	0.96 (0.80-1.16)	2.03 (1.29-3.10)	**<.001**
Median ferritin (ng/ml), 95% CI	356 (318-421)	307 (254-354)	828 (583-1157)	**<.001**
Median ANC (/µl), 95% CI	2560 (2370-2720)	2830 (2600-3060)	1400 (1140-1770)	**<.001**
Median platelet count (G/l), 95% CI	152 (144-158)	164 (156-174)	93 (79-115)	**<.001**
Median hemoglobin (g/dl), 95% CI	10.5 (10.3-10.7)	10.8 (10.6-11.1)	9.1 (8.8-9.6)	**<.001**
Median CAR-HEMATOTOX score, 95% CI	1 (1-2)	1 (1-1)	3 (3-4)	**<.001**
CAR-HEMATOTOX score ≥2, n – %	266 (48%)	154 (36%)	112 (90%)	**<.001**

P-values <0.05 are highlighted in bold.

Patient baseline characteristics before CAR-T infusion. All laboratory values were determined before lymphodepleting chemotherapy with a leniency period of 3 days. ECOG: Eastern Cooperative Oncology Group. PS, performance status; IQR, interquartile range; LD, lymphodepletion chemotherapy. If a measurement was not available for all patients, the denominator is indicated in the table.

logistic regression, costimulatory domain (CD28z > 4-1BB), low platelet count, low ANC, low hemoglobin, increased serum ferritin, and the presence of BM infiltration were retained as independent risk factors for severe ICAHT (supplementary Table 2).

Severe ICAHT is more frequent in patients with MCL

When comparing ICAHT grades across disease entities, we noted a numeric trend toward increased grade ≥3 ICAHT in patients with MCL compared with those with LBCL or MM (28% vs 23% vs 15%, Figure 1b-d). Although MCL was linked to severe ICAHT on univariate analysis (HR = 2.2, 95% confidence interval [CI] 1.1-4.3), this did not extend to the multivariable analysis accounting for other pertinent risk factors, such as BM infiltration, serum inflammatory markers, and baseline cytopenia (*P* >. 9; supplementary Table 2). Among the patients with LBCL, we noted an increase in ICAHT severity with axi-cel compared with tisa-cel (*P* = .0015; supplementary Figure 1).

ICAHT severity is closely correlated with multilineage cytopenias and the need for transfusions and other supportive measures

As expected, based on the grading criteria, we noted a strong positive correlation between ICAHT severity and the cumulative duration of severe neutropenia (r = 0.92, *P* < .001; supplementary Figure 2a). Cubic spline analysis showed a particular increase in the duration of neutropenia beginning with grade 3 ICAHT (supplementary Figure 2b). Accordingly, the median cumulative duration of severe neutropenia was markedly increased in patients with severe and life-threatening ICAHT (19 and 52 days, respectively; Figure 2a). In terms of the quality of neutrophil recovery following CAR-T, the aplastic phenotype was more common in the patients with grade ≥3 ICAHT (Figure 2b).[11] In contrast, quick recovery was the dominant phenotype in patients without ICAHT (0°: 87%) and with mild ICAHT (1°: 52%).

Though the ICAHT grading is entirely based on neutrophil counts, patients with severe ICAHT also observed coincident multilineage

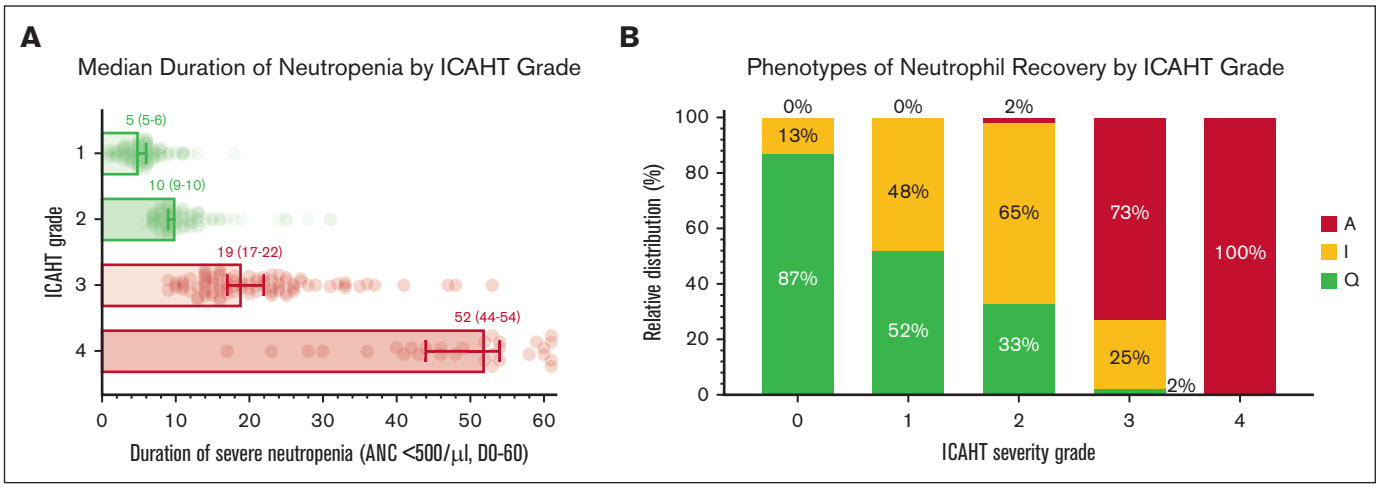


Figure 2. Impact of ICAHT severity on the duration of severe neutropenia and neutrophil recovery phenotypes. (A) Median duration of severe neutropenia (ANC <500/µL) between CAR-T infusion and day 60 by ICAHT severity grade. Whiskers indicate the 95% CI. (B) Distribution of neutrophil recovery phenotypes for each ICAHT grade ("quick" [Q] vs "intermittent" [I]vs "aplastic" [A]; for definitions see Rejeski et al[11]).

cytopenias, including severe thrombocytopenia (90% vs 46%, $P < .001$) and severe anemia (92% vs 49%, $P < .001$; Table 3). In terms of management, the severe ICAHT group more commonly received G-CSF (72% vs 44%, $P = .01$) or needed platelets (85% vs 21%, $P < .001$) and packed red blood cell transfusions (86% vs 41%, $P < .001$). Moreover, a higher proportion of patients received TPO mimetics such as eltrombopag or romiplostim (12% vs 2%, $P < .001$) or hematopoietic stem cell boosts (6% vs 0.2%, $P < .001$).[32,33]

Patients with severe or life-threatening ICAHT more commonly develop infectious complications particularly fatal infections

Next, we examined the influence of ICAHT severity on early infectious events. Notably, patients with severe ICAHT displayed a significantly increased rate of severe infections (49% vs 13%, $P < .0001$, Figure 3a) and severe bacterial infections (36% vs 8%, $P < .0001$, Figure 3b). A high rate of life-threatening (10%) and fatal infections (9%) was noted in the severe ICAHT group. Of the 11 fatal infections that occurred in the setting of severe or life-threatening ICAHT during the first 90 days, most were of fungal (n = 5) or bacterial origin (n = 4). In contrast, only 2 patients (0.5%) with absent or mild-to-moderate ICAHT died of an infection during the first 90 days after CAR-T infusion (both viral infections). Overall, these observations translated into a markedly increased 1-year NRM rate in the severe ICAHT group (14% vs 4.5%, log-rank $P < .0001$, Figure 4a), primarily attributable to fatal infections (Figure 4b).

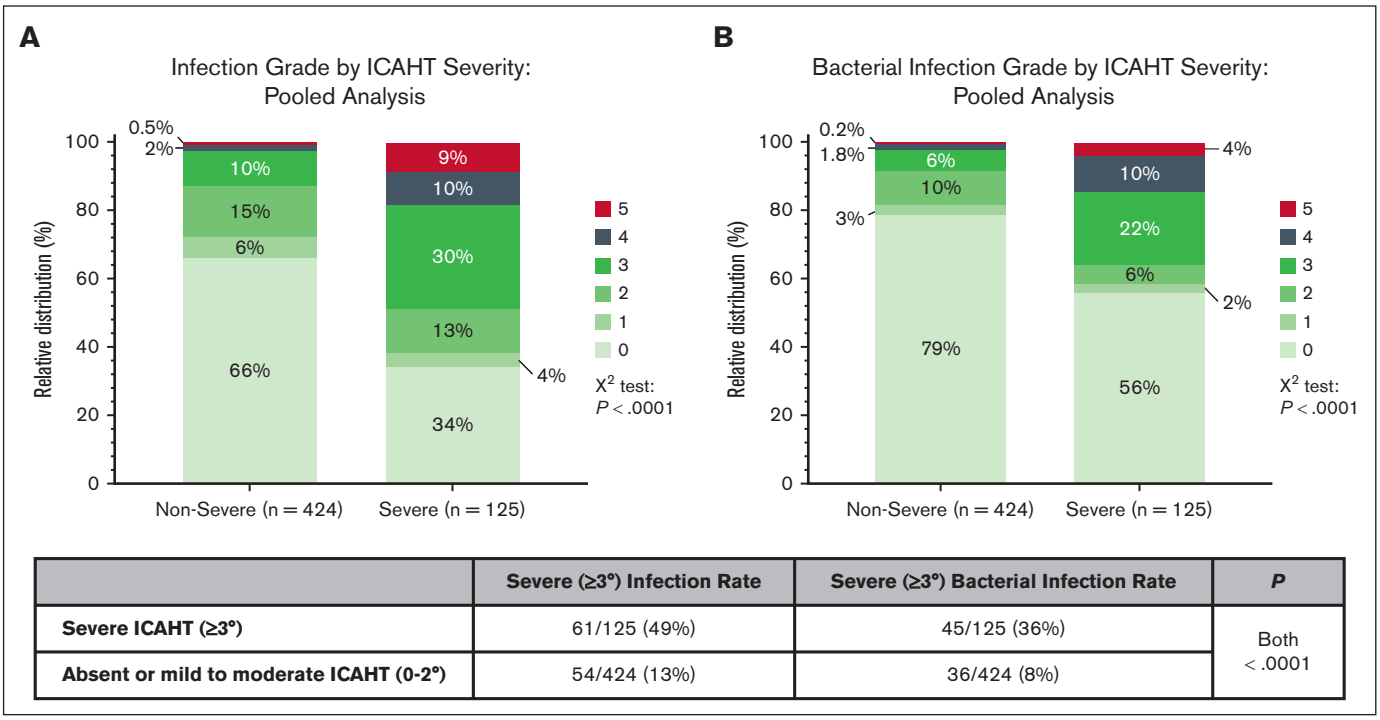
Superior discrimination for infectious events with the ICAHT grading compared with CTCAE grading criteria

Regarding the predictive capacity for severe infectious events, the ICAHT grading was superior to the CTCAE grading of neutropenia

Table 3. Hematotoxicity and management

Characteristic	All patients (n = 549)	ICAHT severity		P value
		Nonsevere (n = 424)	Severe (n = 125)	
Coincident thrombocytopenia				
Severe thrombocytopenia (platelet count < 50 G/L), day 0-100	229/401 (57%)	139/301 (46%)	90/100 (90%)	**<.001**
Platelet transfusion day 0-100	149/401 (37%)	64/301 (21%)	85/100 (85%)	**<.001**
Coincident anemia				
Severe anemia (Hb <8 g/dL), d 0-100	240/401 (60%)	148/301 (49%)	92/100 (92%)	**<.001**
pRBC transfusion day 0-100	209/401 (52%)	123/301 (41%)	86/100 (86%)	**<.001**
Supportive therapies – n (%)				
Granulocyte colony stimulating factor (G-CSF) use	277 (50%)	187 (44%)	90 (72%)	**.01**
Thrombopoetin (TPO) agonist use	25 (5%)	10 (2%)	15 (12%)	**<.001**
CD34+ Stem cell boost	9 (2%)	1 (0.2%)	8 (6%)	**<.001**

Overview of cytopenia incidence rates and concomitant management strategies during the first 100 days after brexu-cel infusion stratified by CAR-HEMATOTOX score. Data on anemia, thrombocytopenia and transfusions were available in 401 patients. *P* values determined by Fisher exact test for categorical variables.



	Severe (≥3°) Infection Rate	Severe (≥3°) Bacterial Infection Rate	*P*
Severe ICAHT (≥3°)	61/125 (49%)	45/125 (36%)	Both < .0001
Absent or mild to moderate ICAHT (0-2°)	54/424 (13%)	36/424 (8%)	

Figure 3. Severe ICAHT is associated with an increased rate of infection. (A-B) Relative distribution of infection grades for all infection subtypes (A) and for bacterial infections only (B) comparing patients without (grade 0-2) vs with severe ICAHT (grade ≥3). The respective infection grades (1-5°) are color-coded; *P* values were determined by χ^2 test. A table summarizes the rate of severe infections (grade 3 or higher) and severe bacterial infections by ICAHT severity (*P* value as determined by Fisher exact test).

(C-index 0.73 vs 0.55, $P < .0001$ vs nonsignificant, Figure 5a). On receiver operating characteristic analysis, optimal discrimination for severe infections was noted for grade 3 ICAHT (sensitivity 54%, specificity 86%). A potential explanation for the poor discriminatory capacity of the CTCAE grading lies in the fact that most patients (87.2%) developed CTCAE grade 4 neutropenia, making it difficult to distinguish specific subgroups (Figure 5b). Nonetheless, the small number of patients with absent or grade 1-3 neutropenia according to CTCAE criteria did display a lower rate of severe infections, as expected (supplementary Table 3).

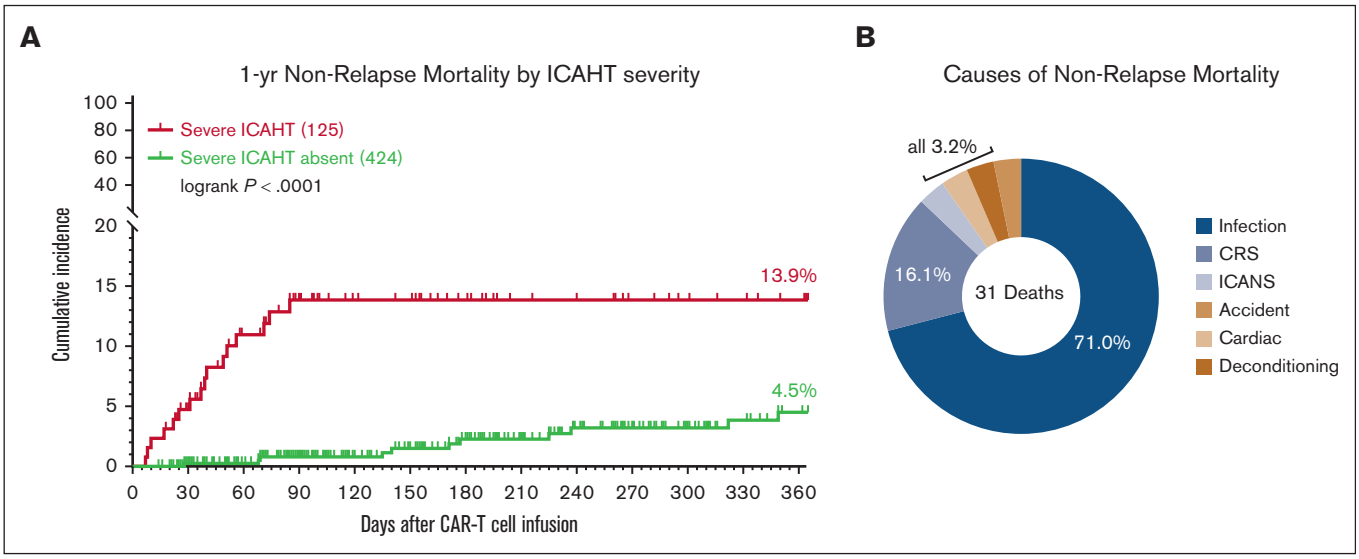


Figure 4. ICAHT severity is associated with increased NRM and extended hospital duration. (A) 1-year nonrelapse mortality (NRM) according to ICAHT severity. The p-value of the Mantel-Cox log-rank test comparing severe vs nonsevere ICAHT is depicted. (B) Overview of the determined causes of death unrelated to lymphoma progression across all time points for the entire study cohort (total n = 560 patients).

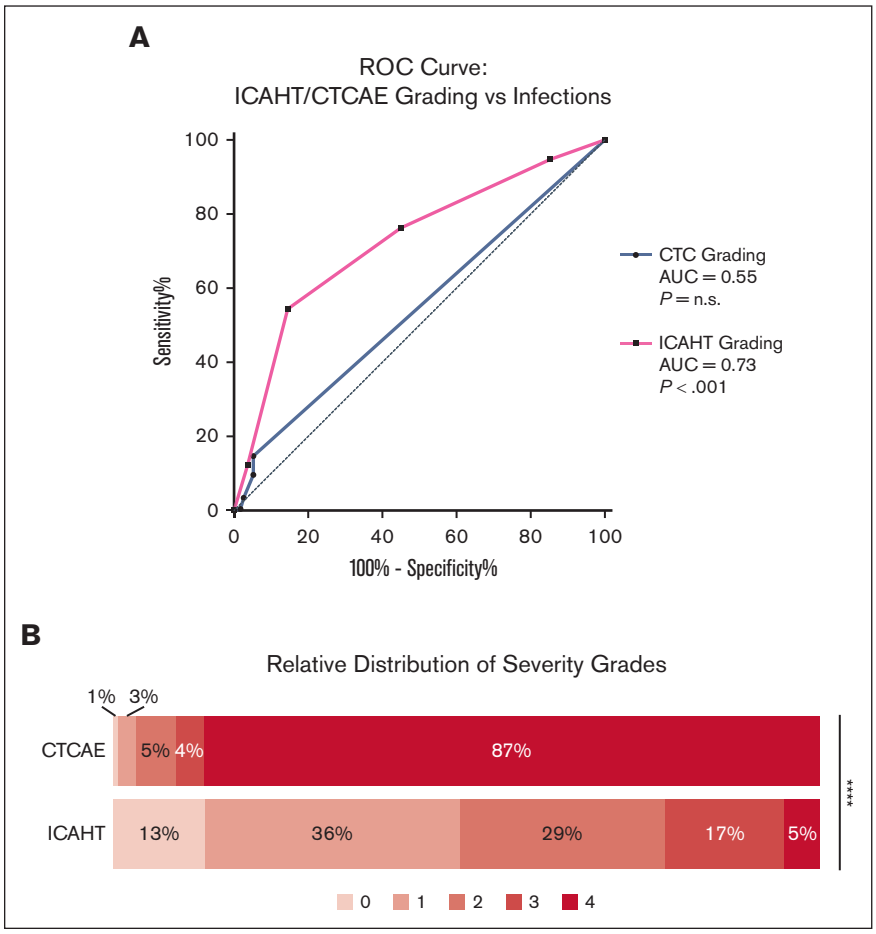


Figure 5. Superior discrimination for severe infections with the novel ICAHT grading compared with CTCAE grading. (A) Receiver operating characteristic (ROC) analysis studying the influence of the ICAHT (pink) and CTCAE (blue) grading on the binary outcome of severe infection during the first 90 days after CAR T-cell infusion. The area under the curve (AUC) and *P* value are provided. (B) Relative distribution of severity grades for CTCAE grading of neutropenia (top) vs ICAHT grading (bottom). The *P* value of the χ^2 test is depicted.

ICAHT severity is linked to extended hospitalization and inferior survival outcomes

Importantly, the presence of severe or life-threatening ICAHT was associated with prolonged hospital stays (median 21 vs 16 days, $P < .0001$, Fig. S3). In terms of treatment outcomes, the severe ICAHT group exhibited inferior PFS compared to the patients without severe ICAHT (1-year PFS 35% vs 51%, log-rank $P < .0001$, $HR_{PFS} = 1.9$, 95% CI 1.5-2.4; Figure 6a). Furthermore, they exhibited lower OS (1-year OS 52% vs 73%, log-rank $P < .0001$, $HR_{OS} = 2.3$, 95% CI 1.7-3.1; Figure 6b). When examining subgroups, we noted improved PFS in the patients with mild-to-moderate ICAHT compared to those with a complete absence of cytopenias (Figure 6c). However, the survival advantage for low-grade hematotoxicity did not extend to OS (Figure 6d).

Discussion

In conclusion, these data highlight the clinical relevance of the novel EHA/EBMT ICAHT grading system. ICAHT severity was closely associated with multilineage cytopenias, transfusion dependence, and the more common use of supportive measures such as growth factor support and hematopoietic stem cell boosts. More importantly, patients with severe and life-threatening ICAHT displayed an increased infection incidence and adverse treatment outcomes with high NRM.

The multivariable analysis suggests that the observed disease-specific differences in ICAHT severity (eg, higher incidence in patients with MCL) more fundamentally reflect variant usage of CD28z-harboring CAR products, as well as the extent of systemic inflammation and impaired hematopoietic function at baseline. For example, patients with LBCL receiving axi-cel displayed more pronounced hematotoxicity when compared to those receiving tisa-cel, in line with a recent matched comparison of both CAR-T products by Bachy and colleagues.[30] In terms of prior therapies, we did not observe an association between ICAHT severity and the prior administration of autologous SCT, which has been implicated as a risk factor for hematotoxicity in other studies.[9,13] However, we did note an association between the presence of baseline cytopenias and ICAHT severity, which may indicate a preexisting insult to the hematopoietic stem and progenitor compartment due to prior cytotoxic therapies, especially bridging therapy.[34]

One of the major deficits of the current CTCAE grading lies in the fact that most patients who received CAR-T therapy displayed grade 3 or 4 neutropenia (>90%, Figure 5b), mostly as an expected consequence of lymphodepleting chemotherapy. A grading system wherein essentially all patients are classified as

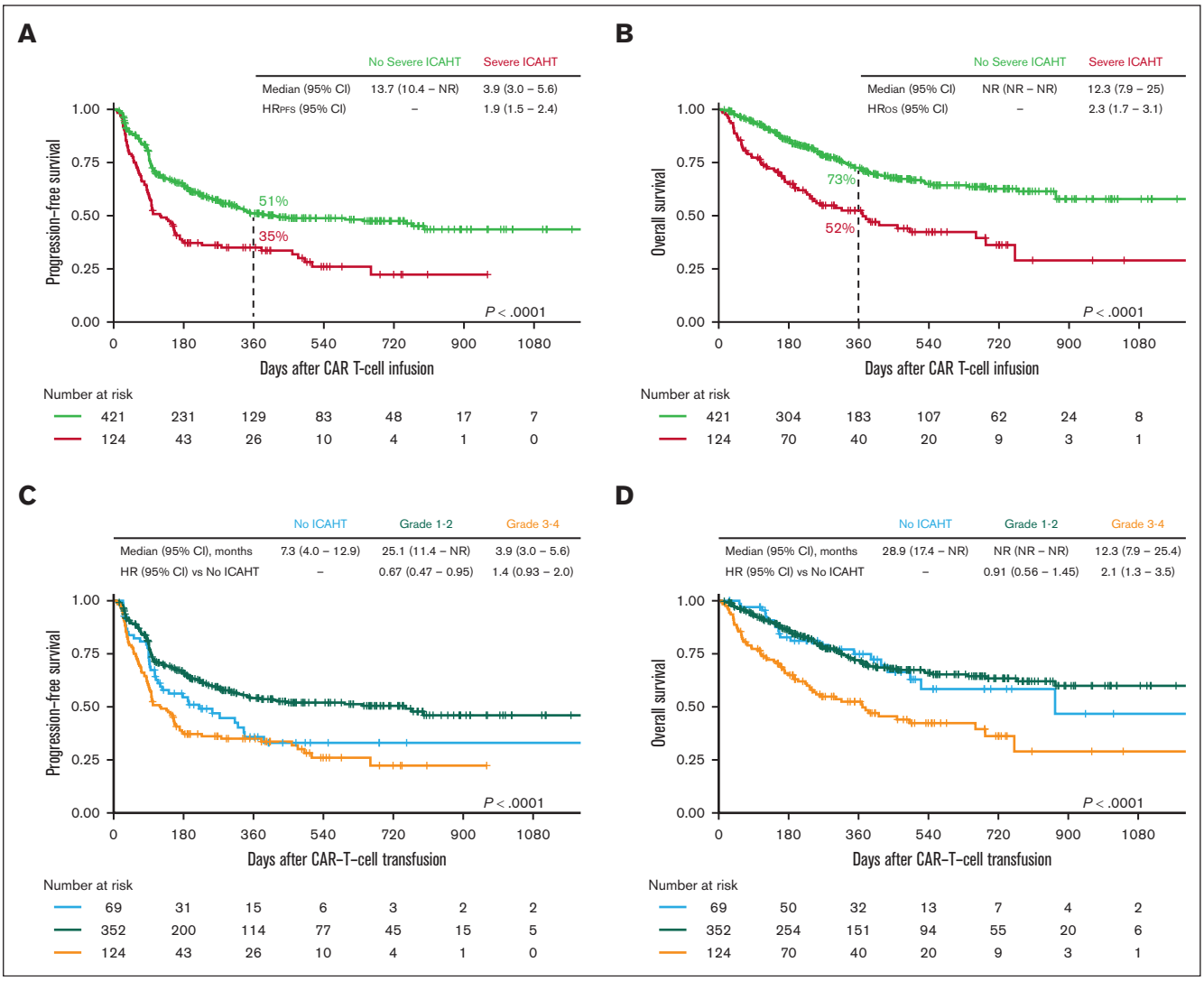


Figure 6. Patients with severe ICAHT show poor survival outcomes. (**A-B**) Kaplan-Meier estimates of PFS (**A**) and OS (**B**) comparing patients with grade 3-4 ICAHT (red) vs absent or grade 1-2 ICAHT (green). The *P* value of the log-rank test is shown on the bottom right of the graph. The median PFS and OS in months and HR of the univariate Cox regression model are superimposed above each graph. (**C-D**) Subgroup analysis of PFS (**C**) and OS (**D**) stratified by 3 ICAHT severity groups. Absent hematotoxicity (grade 0, blue) was compared with mild-to-moderate (grade 1-2, dark green) and severe-to-life-threatening ICAHT (grade 3-4, yellow). The *P* value of the log-rank test and the HRs using absent ICAHT (grade 0) as the reference are depicted.

having severe hematotoxicity once a certain count threshold is met is not particularly useful in clinical practice. Specifically, it is difficult to discern with the CTCAE grading system at what time point after CAR-T infusion certain diagnostic and therapeutic measures are to be initiated. In contrast, the ICAHT grading more closely mirrors the true clinical severity of hematotoxicity, as reflected by the increased infection rate, the need for platelet and red blood cell transfusions, and escalated supportive measures, including the use of TPO agonists and hematopoietic stem cell boosts. Furthermore, severe manifestations of ICAHT were linked to the clinically relevant aplastic neutrophil recovery phenotype, recently demonstrated to be associated with poor treatment outcomes as well as baseline immune dysregulation and an HLH-like inflammatory signature after infusion.[25] We noted a particular increment in the duration of severe neutropenia beginning with grade 3 ICAHT, indicating that patients with absent count recovery above an ANC >500/μL around day +14 and especially at day +30, are more likely to encounter long-lasting and potentially even irreversible bone marrow aplasia. Our analysis provides empiric evidence for the expected incidence rate of grade 4 (eg, life-threatening) ICAHT, which was ~5% across all studied patients. As noted in the consensus guidelines manuscript, these patients require close monitoring for infections and carry a very high risk of morbidity and mortality.[8] As spontaneous count recovery may prove elusive, allogeneic SCT can be considered, though this likely only applies to very few patients and needs to be discussed on a case-by-case basis.

In our analysis, the novel EHA/EBMT ICAHT grading was closely linked to the main complication of hematotoxicity, namely infectious complications, which drive NRM after CAR-T therapy.[15,35,36] The increased infection incidence in patients with grade ≥3 ICAHT is

likely a consequence of the profound immune deficits conferred by sustained neutropenia, combined with the underlying immune dysregulation observed in patients developing severe hematotoxicity.[15,17,29,37] For example, patients who received CAR-T with severe BM aplasia commonly also exhibit profound B-cell aplasia and T-cell lymphopenia.[25] Additional immunosuppressive factors may relate to coincident high-grade CRS or ICANS and the concomitant toxicity management, particularly the extended use of high-dose corticosteroids.[15] The poor survival in the severe ICAHT group highlights that an increased toxicity burden (particularly high-grade toxicity) and inferior treatment outcomes often go hand-in-hand.[15,37,38] In contrast, mild-to-moderate toxicity has been associated with favorable outcomes across multiple immunotherapy platforms, including cellular therapies, allogeneic stem cell transplantation, and immune checkpoint inhibition.[39-41] Accordingly, the patients with grade 1 or 2 ICAHT exhibited excellent treatment outcomes in our study.

Key limitations of this study include the retrospective nature and the absence of reporting of late ICAHT grades (beyond day +30), which were not available for most cases because of a loss of follow-up and/or lack of high-quality data after day 30. Although this study incorporated a broad population of patients treated with CAR T-cells in a real-world setting across multiple countries, this comes with the caveat of considerable heterogeneity in terms of underlying patient features, treatment setting, and toxicity management. Furthermore, we did not have available data for pediatric patients or for patients treated with CAR-T for indolent lymphoma or B-cell precursor acute lymphoblastic leukemia.

Still, these data provide the expected incidence rates of early ICAHT severity across several disease entities. One of the major advantages of the ICAHT grading relates to the harmonized reporting of hematotoxicity across different disease contexts, indications, and treatment settings using the same nomenclature. Importantly, such standardized reporting could also inform hematotoxicity management protocols. Specifically, institutions may use thresholds in the expected rate of grade ≥3 ICAHT to guide their decision-making concerning the administration of anti-infective prophylaxis, G-CSF support, TPO mimetics, and hematopoietic stem cell boosts.[33,42,43] Furthermore, existing risk-stratification tools such as the CAR-HEMATOTOX score may be further optimized by modelling for severe or life-threatening ICAHT as a clinically relevant end point. Regulatory bodies such as the United States Food and Drug Administration or European Medicines Agency may consider mandating the reporting of ICAHT grades in emerging CAR-T studies so as to uncover toxicity signals and enable cross-trials comparisons of this important side effect of cell therapy. Future work may also explore the utility of the ICAHT grading in the context of bispecific antibody therapies, particularly considering the high frequency of cytopenias with CD3xCD20 and CD3xBCMA bispecifics.[44-48]

In conclusion, the new EHA/EBMT consensus grading provides a framework for evaluating hematotoxicity after CD19- and BCMA-directed CAR-T. We demonstrate clinically meaningful sequelae in the patients who developed severe or life-threatening ICAHT. These findings therefore argue for the reporting of ICAHT grades both in the real-world setting and in clinical trials evaluating established and novel CAR constructs.

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Authorship

Contribution: K.R. and M.S. conceptualized the study; Investigation: K.R., Y.W., D.K.H., G.I., E.B., R.B., O.P., F.M., W.B., J.M., R.M., V.L.B., P.B., F.L.L., Y.L., M.D.J., and M.S. conducted the investigation; K.R. performed formal analysis and visualization; K.R. and M.S. performed methodology and wrote the original raft; K.R., Y.W., D.K.H., G.I., E.B., R.B., O.P., F.M., W.B., J.M., R.M., V.L.B., P.B., F.L.L., Y.L., M.D.J., and M.S. reviewed and edited; and all authors read and approved the final manuscript.

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