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Prospective Validation of CAR-HEMATOTOX and a Simplified Version Predict Survival in Patients with Large B-Cell Lymphoma Treated with Anti-CD19 CAR T-Cells: Data from CART-SIE Study

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A B S T R A C T

Background: Anti-CD19 CAR T-cells have revolutionized outcomes in relapsed/refractory large B-cell lymphomas. Long-term follow-up underscored the role of hematological toxicity in nonrelapse mortality, largely driven by infections, leading to the development of the CAR-HEMATOTOX (HT) score for predicting neutropenia. The European scientific community (EHA/EBMT) later reached a consensus, defining a new entity: immune effector cell–associated hematotoxicity (ICAHT).

Aims: To validate the ability of the HT score to predict ICAHT and survival.

Methods: The CART-SIE is an ongoing multicenter prospective observational study collecting data on patients affected by B-cell lymphoma treated with commercial anti-CD19 CAR T-cells (ClinicalTrials.gov ID: NCT06339255).

Results: Since 2019 to 2024, 1002 consecutive patients were enrolled. Out of 746 patients infused, the HT score at infusion was evaluable in 389. Median age was 59 years (48-66). Patients with high HT score had greater disease burden and a greater need for bridge therapy. Patients with a HT^{HIGH} score had a 4-fold higher risk of experiencing late ICAHT of grade≥3 (OR = 3.99, 95% CI = 1.16-13.77, P = .03). Patients with a HT^{HIGH} score also showed lower overall response rates (ORR) and complete response rates (CRR) at 90 days (CRR at 90 days: 59% HT^{LOW} versus 38% HT^{HIGH}, OR = 0.42, 95% CI = 0.27-0.66, P = .0002; ORR at 90 days: 67% HT^{LOW} versus 49% HT^{HIGH}, OR = 0.47, 95% CI = 0.29-0.74, P = .001). Adjusted logistic models confirmed that the effect of HT score was independent from baseline characteristics. With a median follow-up of 18 months, patients with a HT^{HIGH} score have lower OS and PFS (1-year OS: 78% HT^{LOW} versus 62% HT^{HIGH}, P = .0002; 1-year PFS: 49% versus 39%, P = .003). Adjusted Cox models confirmed that HT was an independent prognostic factor for OS. A high HT-score was found to be associated with higher risk of secondary primary malignancy (HR=2.8, 95% CI = 1.03-7.8, P = .04). A simplified version of HT (simpleHT), based solely on the platelet count and C-reactive protein at infusion, was calculated for 560 patients and proved significant in predicting both OS and PFS (1-year was 72% $simpleHT^{LOW}$ versus 37% $simpleHT^{HIGH}$, $P < .0001$, 1-year PFS was 48% $simpleHT^{LOW}$ versus 22% $simpleHT^{HIGH}$, $P < .0001$).

Conclusion: In our prospective real-world study, we validated the ability of the HT score to predict ICAHT and survival. SimpleHT identified a population at very high risk with an impaired progression free and overall survival.

INTRODUCTION

Anti-CD19 CAR T-cells have become part of the therapeutic algorithm for patients affected by relapsed/refractory B-cell lymphoma. Long-term follow-up data [1,2] and real-world experiences [3–7] have demonstrated, on one hand, a 40% cure rate, but, on the other, a significant hematologic toxicity in the context of nonrelapse mortality (NRM) primarily driven by infections [6,8].

The clinical risk of hematologic toxicity has prompted the development of the CAR-HEMATOTOX [9] (HT score) scoring system. This model, based on simple blood count parameters and inflammatory markers, allows for the prediction of neutropenia and, according to more recent reports, also correlates with the risk of infections and survival [10].

Subsequently, the European scientific community, under the aegis of the European Hematology Association (EHA) and the European Society for Blood and Marrow Transplantation (EBMT), reached a consensus in defining a new nosological entity: the immune effector cell-associated hematotoxicity (ICAHT) [11].

Given the potential widespread use of the HT score, its validation in independent real world cohorts has become critically important, especially regarding its predictive ability for the newly defined nosological entity ICAHT. The primary aim of this study is to validate the score in a large independent cohort of patients.

Considering that the HT score incorporates parameters reflecting both the hematopoietic reserve and the inflammatory status of patients at the time of infusion, factors that may correlate with disease burden, a secondary objective of our research was to conduct an exploratory analysis to assess whether the score could predict response rates and survival outcomes. Finally, a simplified version of the HT score (SimpleHT), which considers only platelets and C-reactive protein, was tested.

METHODS

The CART-SIE is an ongoing prospective, multicenter, observational study that collects data from patients affected by B-cell lymphoma treated with commercial at 21 centers across Italy.

Eligible patients for the present analysis are those with relapsed or refractory aggressive large B-cell lymphomas (LBCL), including DLBCL (not otherwise specified, high-grade B-cell lymphoma (HGBL), DLBCL arising from transformed follicular lymphoma), and primary mediastinal B-cell lymphoma (PMBCL).

Response was assessed according to the Lugano 2014 criteria [12]. Cytokine release syndrome (CRS) and neurotoxicity (Immune effector-cell associated neurotoxicity: ICANS) were graded according to the American Society for Transplantation and Cellular Therapy consensus [13]. Hematological toxicity was defined and graded based on the consensus outlined by the EHA and the EBMT [11]. Specifically, late and severe immune effector cell-associated haematotoxicity (ICAHT) is characterized by persistent neutropenia (at least two consecutive measurements), severe (ANC $\leq$500/μL) and late (occurring more than 30 days after CAR T-cell infusion).

HT score was calculated at baseline (i.e., before lymphodepletive chemotherapy) according to Rejeski et al. [9]. Specifically, as per Rejeski et al., patients were classified as high-risk when the score was $\geq$2 points.

SimpleHT classified patients as high-risk if they had PLT $\leq$ 175,000/μL and CRP $\geq$ 3 mg/dL at baseline, using the same cut-offs as in the original study [9]. The decision to use platelets and C-reactive protein was driven by the strong association of these two parameters with both toxicity and outcome, as demonstrated since the earliest studies [8,14], along with the greater availability of these data in our database, in which ferritin, likely due to its higher cost compared to CRP, was measured less systematically in some centers.

The study adhered to the Declaration of Helsinki and followed good clinical practice guidelines, with ethical approval obtained from institutional review boards at each site (INT 180/19, approval number 431/DG, 2019, ClinicalTrials.gov ID: NCT06339255). Written informed consent was obtained from all patients.

Patients, disease and treatment characteristics were summarized using standard descriptive statistics. Differences in distributions were tested using Kruskal-Wallis rank sum test for continuous variables and Fisher's exact test for categorical variables. The incidence of adverse events (ICAHT, severe thrombocytopenia, CRS and ICANS), as well as overall response rate (ORR) and complete response rate (CRR) were analysed as binary outcomes using logistic regression. The predictive power of these models was evaluated using sentivity, sensibility and area under the curve (AUC) parameters. Overall survival (OS), progression-free survival (PFS) and duration of response (DOR) were analysed using Kaplan-Meier curves and Cox models. The incidence of secondary neoplasms was analysed in the context of competing events using cumulative incidence estimates and univariable Fine and Gray models, with death as the competing event.

In order to evaluate the significance of HEMATOTOX independently from other risk factors, its effect on each outcome was adjusted by a linear predictor resulting from a model which included stage, bulky disease, histology, disease status, IPI, and bridging therapy.

De-identified data collected in this study are available upon request from the corresponding author.

RESULTS

Since 2019 to July 2024, a total of 1,002 patients were enrolled in the CART-SIE study, of whom 746 were infused and evaluable. Among the 746 infused patients, 628 had LBCL, and the HT score

Table 1
Patients Characteristics

	Simplified HT score				CAR HEMATOTOX (HT)			
	Total N=560	Low N=465	High N=95	p	Total N=389	Low N=138	High N=251	*P*
Age (yrs. median)	59 (48-66)	58 (48-67)	60 (49-65)	.67	59 (48-66)	57 (46-66)	60 (49-66)	.41
Sex (female)	207 (37%)	174 (37%)	33 (35%)	.64	133 (34%)	42 (30%)	91 (36%)	.27
Histology				.29				.35
- DLBCL	379 (68%)	308 (66%)	71 (75%)		266 (68%)	95 (69%)	171 (68%)	
- HGBL	110 (20%)	95 (20%)	15 (16%)		71 (18%)	21 (15%)	50 (20%)	
- PMBCL	71 (13%)	62 (13%)	9 (10%)		52 (13%)	22 (16%)	30 (12%)	
Refractory disease	404 (74%)	333 (73%)	71 (76%)	.61	285 (75%)	103 (77%)	182 (74%)	.62
Stage (advanced[#])	**382 (69%)**	**302 (66%)**	**80 (86%)**	**<.01**	**268 (70%)**	**77 (57%)**	**191 (77%)**	**<.01**
IPI (≥3)	**223 (41%)**	**172 (38%)**	**51 (56%)**	**.002**	**159 (43%)**	**43 (33%)**	**116 (48%)**	**.004**
Bulky disease	**197 (36%)**	**152 (33%)**	**45 (49%)**	**.004**	**135 (35%)**	**39 (28%)**	**96 (39%)**	**.05**
LDH>ULN baseline LDH missing	**199 (46%)** 127	**154 (42%)** 102	**45 (64%)** 25	**<.01**	**134 (44%)** 81	**32 (29%)** 28	**102 (52%)** 53	**<.01**
Product infused:				.91				.92
- Axi-cel	318 (57%)	265 (57%)	53 (56%)		219 (56%)	77 (56%)	142 (57%)	
- Tisa-cel	242 (43%)	200 (43%)	42 (44%)		170 (44%)	61 (44%)	109 (43%)	
Vein-to-vein time	1.6 mth	1.6 mth	1.6 mth	.79	1.6 mth	1.7 mth	1.6 mth	.48
Previous lines:				.34				.31
- 1	13 (2%)	9 (2%)	4 (5%)		11 (3%)	5 (4%)	6 (2%)	
- 2	351 (63%)	297 (64%)	54 (57%)		245 (63%)	91 (66%)	154 (62%)	
- ≥3	196 (35%)	159 (34%)	37 (38%)		133 (34%)	42 (30%)	91 (36%)	
Previous ASCT	150 (27%)	129 (28%)	21 (22%)	.31	110 (28%)	41 (30%)	69 (27%)	.64
Bridging therapy	**455 (81%)**	**370 (80%)**	**85 (90%)**	**.01**	**324 (84%)**	**104 (75%)**	**220 (88%)**	**.002**
Bridging failure*	**219 (44%)**	**159 (38%)**	**60 (71%)**	**<.01**	149 (43%)	47 (39%)	102 (45%)	.62

Stage advanced[#] defined as Ann Arbor III and IV, Bridging failure* defined as Progressive Disease after bridge.
ASCT, autologous stem cell transplantation; DLBCL, diffuse large B-cell lymphom; HGBL, high grade B-cell lymphoma; IPI, international prognostic index; LDH, lactate-dehydrogenase; mth, months; PMBCL, primary mediastinal B-cell lymphoma.

could be calculated at the baseline for 389 of them. The simplified version of the score (SimpleHT) was available for 560 patients (*Supplementary Figure 1*).

Table 1 describes the characteristics of all 560 analyzed patients and the 389 patients for whom the HT score was calculated. The median age of the population was 59 years (48-66), and 37% (207/560) of the patients were female. Histologies were equally distributed between the two identified risk groups. Both the HT score and its simplified version are able to distinguish between two populations, where the high-risk population is characterized by a greater disease burden in terms of stage (advanced stage: 57% HT^{LOW} versus 77% in HT^{HIGH}, $P < .001$), lactate dehydrogenase at baseline (LDH > upper level normality: 29% HT^{LOW} versus 52% in HT^{HIGH}, $P = .004$), presence of bulky disease (>5 cm for the longest diameter of the largest node or mass present: 28% HT^{LOW} versus 39% in HT^{HIGH}, $P = .04$), and a greater need for bridging therapy (75% HT^{LOW} versus 88% in HT^{HIGH}, $P = .002$).

Supplementary Table 1 provides the characteristics of the 239 patients for whom the CAR-HEMATOTOX score could not be calculated.

Hematotoxicity and HT score validation –In the global population, the incidence of any grade of late ICAHT was 38%, with only 16% of these cases being grade ≥3. The incidence of severe thrombocytopenia (PLT <50,000/μL on two consecutive measurements more than 30 days after CAR T-cell infusion) was 8.6%, while only 0.2% of patients exhibited severe anemia (Hb <8 g/dL on two consecutive measurements more than 30 days after CAR T-cell infusion).

The HT score was confirmed to be capable of predicting both late grade ≥ 3 ICAHT and early

ICAHT. Patients with a HT^{HIGH} score at infusion showed a fourfold increased risk of developing severe late ICAHT compared to those with a HT^{LOW} score (OR = 3.99, 95% CI = 1.16-13.77, *P* = .03).

Patients with HT^{LOW} demonstrated a significantly lower rate of early ICAHT and severe thrombocytopenia: 36% HT^{LOW} versus 54% HT^{HIGH} (OR = 2.12, 95% CI = 1.36-3.29, *P* = .0009) for early ICAHT and 2.4% HT^{LOW} versus 13% HT^{HIGH} (OR = 6.02, 95% CI = 1.79-20.27, *P* = .0038) for severe thrombocytopenia.

A multivariable logistic model was fitted, adjusting for baseline characteristics, and confirmed the independent effect of the score in predicting hematotoxicity (late ICAHT grade ≥3: HR = 3.23, 95% CI = 1.1-14, *P* = .04, *Supplementary Table 2*).

The discriminatory ability of the model in predicting late grade ≥ 3 ICAHT was confirmed, although the suboptimal specificity values suggest it functions more as a screening test rather than a diagnostic one (sensitivity = 86%, specificity = 39%, positive:negative likelihood ratio = 1.41:0.36, AUC 62.5).

Efficacy and outcomes –Globally the overall response rates and complete response rates were 55% and 47% respectively (*Supplementary Table 3*). The complete and overall response rates were significantly higher in patients with a HT^{LOW} score compared to those with a HT^{HIGH}, respectively CRR at 90 days: 59% HT^{LOW} versus 38% HT^{HIGH}, (OR = 0.42, 95% CI = 0.27-0.66, *P* = .0002), and ORR at 90 days: 67% HT^{LOW} versus 49% HT^{HIGH}, (OR = 0.47, 95% CI = 0.29-0.74, *P* = .001). Multivariable logistic models were fitted, adjusting for baseline characteristics, and confirmed the independent effect of the score also in predicting response rates (*Supplementary Table 2*).

With a median follow-up of 18 months for the overall cohort of 560 patients, the 1-year OS and PFS were 67% and 44% (median OS = not reached, median PFS = 6.3 months), respectively while the 1-year DOR was 58% (median DOR = 24 months) (*Supplementary Figure 2*).

The OS, PFS, and DOR were found to be entirely comparable across the global cohort of 628 patients (*Supplementary Figure 3*), the cohort of 560 patients for whom the simplified score was calculated, and the cohort of 389 patients for whom the CAR-HEMATOTOX score was determined.

OS and PFS were significantly better in patients with a HT^{LOW} score compared to those with a HT^{HIGH}. Specifically, the 1-year OS was 78% for patients with a HT^{LOW} score versus 62% for those with a HT^{HIGH} score (log-rank *P* = .0002, Figure 1 –*Panel A*), while the 1-year PFS was 49% for patients with a HT^{LOW} score and 39% for those with HT^{HIGH} score (log-rank *P* = .003, Figure 1 –*Panel B*). Multivariable Cox models were fitted, adjusting for baseline characteristics, and confirmed the independent effect of the HT score in predicting PFS and OS (OS: HR = 1.91, 95% CI = 1.29-2.81, *P* < .001, *Supplementary Table 4*).

Toxicity and Secondary Primary Malignancies –Globally the incidence of any grade/grade ≥3 CRS and ICANS were respectively 83%/9% and 24%/7%. Patients with HT^{HIGH} demonstrated a higher incidence of CRS of any grades compared to patients with HT^{LOW} (73% HT^{LOW} versus 86% in HT^{HIGH}, OR = 2.2, 95% CI = 1.3-3.7, *P* = .003). No statistically significant differences were observed in terms of grade ≥ 3 CRS, ICANS, or NRM. Specifically, the 1-year NRM for the entire cohort was 4.1% (4.1% for both HT^{HIGH} and HT^{LOW} groups). Among the 23 deaths, approximately half (N = 10, 44%) were caused by infections, including 3 COVID-19 infections. No statistically significant excess of infectious mortality was observed between patients with HT^{HIGH} and HT^{LOW} (2% in both risk groups).

Patients were also evaluated for development of secondary primary malignancies (SPM) after CAR-T cells; SPMs were documented in 5.7% of patients; the most frequent were myeloid malignancies (15/22), with a median time from infusion to diagnosis of 11.7 months (range 4.8-19.1).

Among the 7 patients who developed SPMs other than myeloid malignancies, diagnoses included follicular T-helper cell proliferation (1 case), T-large granular lymphocyte (T-LGL) leukemia (1 case), prostate cancer (1 case), Epstein-Barr virus (EBV)-positive carcinoma (1 case), Hodgkin lymphoma (2 cases) and colon cancer (1 case).

The subset of patients who developed SPMs had a median age of 61 years (range: 53.3-66.8 years), with 41% having received more than two prior lines of therapy and 45% having undergone autologous stem cell transplantation.

The 2-year cumulative incidence of second malignancies was 10% (95% CI = 6.1-16) for all SPMs and 7.6% (95% CI = 4-13) for myeloid malignancies.

From univariable Fine and Gray models, a high HT score was found to be associated with a higher risk for occurrence of SPM (HR 2.82, 95% CI = 1.03-7.76, *P* = .04), along with age (HR 1.03, 95% CI = 1-1.07, *P* = .04), Ann Arbor Stage III-IV (HR 5.46, 95% CI = 1.27-23.5, *P* = .02), bone marrow involvement

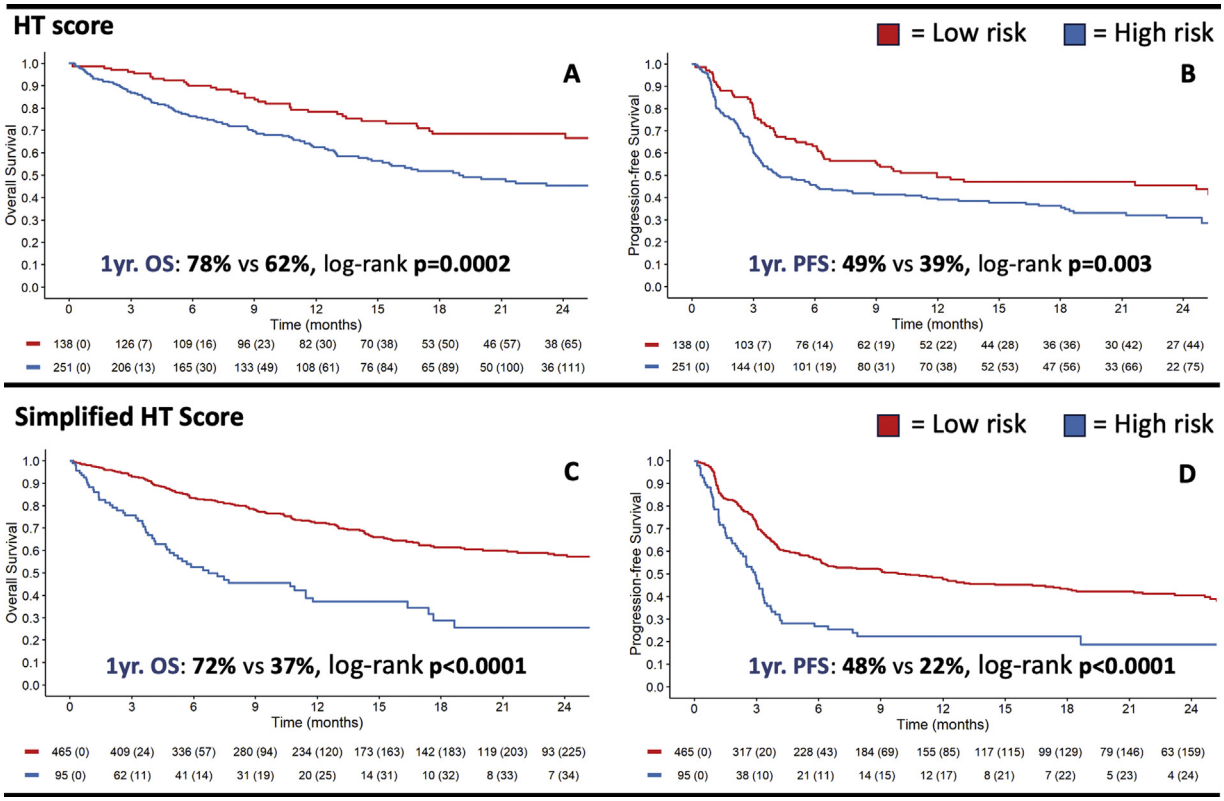

Figure 1. Overall (OS) and Progression free survival (PFS) according to HT score and simplified HT score.

(HR 4.86, 95% CI = 1.37-17.3, P = .015) and severe thrombocytopenia (HR 3.15, 95% CI = 1.18-8.44, P = .02). Finally, a trend towards higher risk for development of myeloid malignancies was also found in patients with HT^{HIGH} score (HR = 3.39, 95% CI = 0.96-12), although it was not statistically significant (P = .06).

Simple-HT –The simplified version of the score, based on only CRP and platelets, demonstrated discriminatory capacity for severe late ICAHT (5% SimpleHT^{LOW} versus 12% SimpleHT^{HIGH}, OR = 2.55, 95% CI = 1.1-6, P = .03).

The complete and overall response rates were significantly higher in patients with a SimpleHT-^{LOW} score compared to those with a SimpleHT^{HIGH}, respectively CRR at 90 days: 51% SimpleHT^{LOW} versus 23% SimpleHT^{HIGH}, (OR = 0.30, 95% CI = 0.17-0.52, P < .001), and ORR at 90 days: 60% SimpleHT^{LOW} versus 31% SimpleHT^{HIGH}, (OR = 0.31, 95% CI = 0.18-0.52, P < .001). Multivariable logistic models were fitted, adjusting for baseline characteristics, and confirmed the independent effect of the score also in predicting response rates (*Supplementary Table 5*).

Interestingly, patients with a SimpleHT^{HIGH} score had worse OS and PFS compared to those with a SimpleHT^{LOW}: 1-year OS was 72% SimpleHT^{LOW} versus 37% in SimpleHT^{HIGH} (log-rank P < .0001, Figure 1) and 1-year PFS was 48% SimpleHT^{LOW} versus 22% SimpleHT^{HIGH} (log-rank P < .0001, Figure 1).

Multivariable Cox models were fitted, adjusting for baseline characteristics, and confirmed the independent effect of the Simple-HT score in predicting PFS and OS (OS: HR = 1.87, 95% CI = 1.87-3.55, P < .001, *Supplementary Table 6*). A trend indicating higher nonrelapse mortality in patients with a SimpleHT^{HIGH} score was identified but did not reach statistical significance (1-years NRM: SimpleHT^{HIGH} 11%, 95% CI = 4-21% versus SimpleHT^{LOW} = 3%, 95% CI = 1.3-5.4%).

DISCUSSION

To the best of our knowledge, this report represents the largest cohort published to date regarding hematologic toxicity in patients affected by B-cell lymphoma treated with axi-cel and tisa-cel, in a real-world setting.

The incidence of both early and late cytopenias in general and the incidence of ICAHT in particular observed in our cohort, is consistent with previously reports [15]. Our work, for the first time, validated HT-score in a large cohort of patients in the context of a prospective real-world setting, as a useful tool for predicting hematologic toxicity. The sensitivity and specificity data of HT-score,

position it as a useful screening test both clinically and scientifically. Clinically, the score can be used to guide diagnostic workups or implement preventive measures against infections such as prophylactic use of G-CSF and antimicrobial prophylaxis. Scientifically, the score helps to define a population that will need further study to understand the mechanisms underlying CAR T-cell hematologic toxicity, with the aim of reducing toxicity and improving sustainability.

With a nonrelapse mortality at 1 year of 4.1%, our data align with those reported in the literature [16]. The trend towards higher NRM in patients with HT^{HIGH} observed in previous studies [10] was not confirmed in our cohort, although the relative rarity of the event makes it difficult to draw definitive conclusions.

Similarly, no statistically significant difference in infectious mortality was observed based on the HT score. It is worth noting that, due to the nature of our study as a prospective multicenter national study, granular data on infection rates were not collected. As a result, it was not possible to validate the previous observation that a HT^{HIGH} score correlates with a higher rate of severe infections [10].

The increase in the number of enrolled patients and the extended follow-up period has not substantially altered the incidence of secondary malignancies compared to that previously reported by Barone et al. [17], and remains consistent with data from the FDA Adverse Events Reporting System [18]. Myeloid neoplasms among secondary malignancies are of particular interest, both due to their higher incidence [17,18] compared to other secondary malignancies and their unclear etiopathogenic mechanisms. In the presence of correlation between high HT-score and occurrence of secondary primary malignancies, preexisting impaired hematopoietic reserve and inflammation supposedly contribute to the development of subsequent neoplasms. Once again, the utility of the HT score lies in identifying a high-risk population on which future research will focus. It is clear that investigating the presence of pre-existing MDS or exploring a potential causal relationship between CAR T-cell therapy and the development of secondary primary malignancies is beyond the scope and statistical power of our study.

With an overall survival and progression-free survival at 1-year of 62% and 39% in the HT^{HIGH} population, our study aligns with the findings reported by Rejeski et al. [10] in a smaller cohort. Notably, the simplified version of the score can identify an ultra-high-risk population with an OS and PFS of only 37% and 22%, respectively. The strong correlation between HT score and SimpleHT with both overall and progression free survival provides clinicians with two very simple tools that, by describing overall hematopoietic reserve and inflammation, enable effective risk stratification and they can also be used to design future studies.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2025.01.888.

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