## Title

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**CLINICAL RESEARCH**
*Cardio-oncology*

# Biomarkers and cardiovascular outcomes in chimeric antigen receptor T-cell therapy recipients

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## Abstract

**Aims** Chimeric antigen receptor T-cell therapy (CAR-T) harnesses a patient's immune system to target cancer. There are sparse existing data characterizing death outcomes after CAR-T-related cardiotoxicity. This study examines the association between CAR-T-related severe cardiovascular events (SCE) and mortality.

**Methods and results** From a multi-centre registry of 202 patients receiving anti-CD19 CAR-T, covariates including standard baseline cardiovascular and cancer parameters and biomarkers were collected. Severe cardiovascular events were defined as a composite of heart failure, cardiogenic shock, or myocardial infarction. Thirty-three patients experienced SCE, and 108 patients died during a median follow-up of 297 (interquartile range 104–647) days. Those that did and did not die after CAR-T were similar in age, sex, and prior anthracycline use. Those who died had higher peak interleukin (IL)-6 and ferritin levels after CAR-T infusion, and those who experienced SCE had higher peak IL-6, C-reactive protein (CRP), ferritin, and troponin levels. The day-100 and 1-year Kaplan–Meier overall mortality estimates were 18% and 43%, respectively, while the non-relapse mortality (NRM) cumulative incidence rates were 3.5% and 6.7%, respectively. In a Cox model, SCE occurrence following CAR-T was independently associated with increased overall mortality risk [hazard ratio (HR) 2.8, 95% confidence interval (CI) 1.6–

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4.7] after adjusting for age, cancer type and burden, anthracycline use, cytokine release syndrome grade ≥ 2, pre-existing heart failure, hypertension, and African American ancestry; SCEs were independently associated with increased NRM (HR 3.5, 95% CI 1.4–8.8) after adjusting for cancer burden.

**Conclusion** Chimeric antigen receptor T-cell therapy recipients who experience SCE have higher overall mortality and NRM and higher peak levels of IL-6, CRP, ferritin, and troponin.

## Structured Graphical Abstract

### Key Question

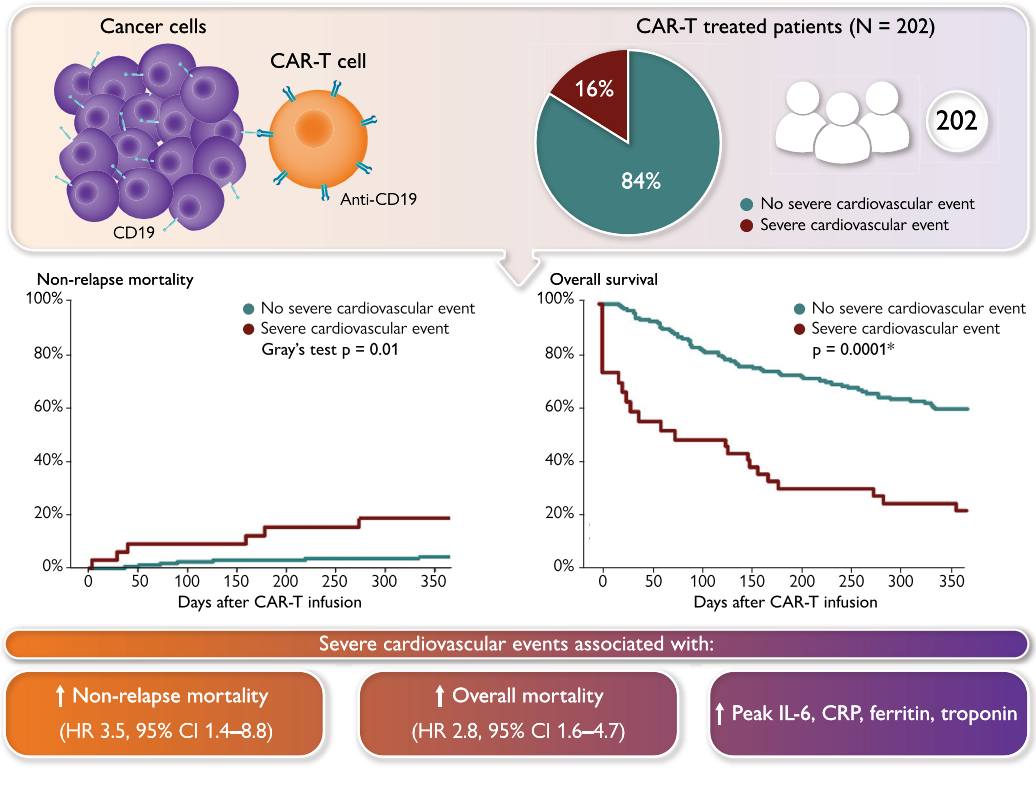
Severe cardiovascular events (SCE), including heart failure, cardiogenic shock or myocardial infarction, are common following chimeric antigen receptor T-cell (CAR-T) therapy for cancer. However, data are limited on whether or not SCE following CAR-T infusion are associated with increased mortality.

### Key Finding

SCE following CAR-T infusion were associated with increased overall mortality and with non-relapse mortality (NRM) defined as death without recurrence or progression of malignancy from time of CAR-T infusion. SCE were also associated with higher peak levels of IL-6, CRP, ferritin and troponin.

### Take Home Message

Patients who experience SCE after CAR-T infusion have increased risk of mortality. The data support investigating strategies to mitigate CAR-T related cardiotoxicity, including the role of biomarkers for early detection and treatment of cardiovascular events.




Cancer patients treated with chimeric antigen receptor T-cell therapy (CAR-T) who experience severe cardiovascular events have higher overall mortality and non-relapse mortality and higher peak levels of IL-6, CRP, ferritin, and troponin. The overall survival was graphed as the Simon—Makuch curve. Non-relapse mortality was graphed as cumulative incidence. IL-6, interleukin-6; CRP, C-reactive protein; HR, hazard ratio; CI, confidence interval. **P*-value is from the score test provided by the univariable time-dependent Cox model.

**Keywords** Cardio-oncology • CAR-T cells • Chimeric antigen receptor • Cancer • Mortality • Cardiovascular events

# Introduction

Chimeric antigen receptor T-cell therapy (CAR-T) targeting CD19 is a Food and Drug Administration–approved form of gene-modified cell therapy with encouraging outcomes in patients with relapsed or refractory lymphomas and leukaemias.[1–4] Chimeric antigen receptor T-cell therapy can induce durable complete remissions with re-programmed T lymphocytes persisting in some patients a full decade later.[5] By 2024, the use of this form of immunotherapy is expected to double, driven in part by its expansion into additional cancer subtypes and into earlier lines of therapy.[6–8] Recent studies have shown that cardiovascular (CV) events after CAR-T can occur in up to one in four–five patients, including cardiomyopathy (10%), clinical heart failure (6%), and myocardial infarction (MI) (5%).[9–14] However, it is unknown whether the occurrence of a CV event impacts mortality in patients undergoing CAR-T. Understanding the association between CV events and mortality is important to further advance CV monitoring guidelines in CAR-T recipients.[15] Similarly, prevention and early treatment of cardiotoxicity may further improve survival outcomes in this population. Therefore, we examined a multi-centre registry of CAR-T recipients to ascertain the occurrence of severe CV events (SCE) and to determine whether these events are associated with increased mortality. We hypothesized that SCE after CAR-T would be associated with higher mortality.

# Methods

We created a multi-centre cohort registry of consecutive adult recipients of CD19-targeted CAR-T at the Memorial Sloan Kettering Cancer Center, University of Chicago, University of California Los Angeles, and Massachusetts General Hospital treated between February 2010 and February 2021, whose methodology has been previously described.[9] This retrospective analysis included patients receiving commercially available CAR-T and patients enrolled in two clinical trials: NCT01044069 from 2010 to 2016 and NCT02631044 from 2016 to 2018. The retrospective study was approved by the institutional review board of each institution.

## Covariates

The prevalence of pre-existing CV disease and associated risk factors, including atrial fibrillation, diabetes mellitus, hypertension, smoking, stroke, heart failure, MI, and chronic kidney disease, was extracted by manual chart review (see Supplementary data online, *Table S1*). Biomarkers before and after CAR-T were drawn by each participating institution based on their established protocol. Biomarkers collected before CAR-T infusion included the following: troponin I (troponin), natriuretic peptide, and C-reactive protein (CRP). Inflammatory biomarkers were collected at multiple time points in the first 2 weeks after CAR-T infusion, and peak values were identified for the registry. Biomarkers collected after CAR-T infusion included troponin and natriuretic peptide, as well as inflammatory biomarkers including interleukin-6 (IL-6), tumour necrosis factor alpha (TNF-α), CRP, and ferritin. Additionally, electrocardiographic and echocardiographic variables were recorded, where available. Cardiac testing was performed at the discretion of the treating clinician and was not pre-specified. Cancer-specific covariates of interest included the type of malignancy, previous cancer treatments, and CAR-T product administered. Patients were defined as having a high cancer burden using previously described definitions: >5% blasts on bone marrow aspirate and/or biopsy (in leukaemia) or a lactate dehydrogenase value above the institutional upper limit of normal (ULN) (for lymphoma) prior to initiation of lymphodepleting chemotherapy.[8] Details regarding a subject's CAR-T treatment course, including the incidence and severity of cytokine release syndrome (CRS), as defined by the American Society for Transplantation and Cellular Therapy consensus criteria,[16] and the use of tocilizumab and steroids were collected.

## Cardiovascular event definitions

Severe CV events were defined as a composite of clinical heart failure, cardiogenic shock, and MI. Clinical heart failure was defined as a natriuretic peptide above the ULN for the treating institution and left ventricular ejection fraction (LVEF) of <53% or having either an elevated natriuretic peptide or LVEF < 53% and fulfilling at least one of the following four criteria: (i) heart failure symptoms (shortness of breath, dyspnoea on exertion, orthopnoea, and paroxysmal nocturnal dyspnoea), (ii) physical exam findings consistent with heart failure (pulmonary rales, jugular venous distension, and lower extremity oedema), (iii) imaging findings consistent with heart failure (pulmonary oedema, pleural effusions, and cardiomegaly), or (iv) initiation of new treatment for heart failure [diuretics (excluding hydrochlorothiazide), inotropes, or mechanical support]. Among the patients who met the criteria for clinical heart failure, cardiogenic shock was defined as hypotension requiring milrinone, dobutamine, epinephrine, or norepinephrine, combined with signs of impaired organ perfusion such as reduced mixed venous oxygen or central venous oxygen or an elevated lactate (≥2 mmol/L), liver function tests (≥1.5-fold of ULN), or serum creatinine (≥2 times baseline or need for renal replacement therapy) after ruling out other causes. Myocardial infarction was determined by troponin elevation > 99th percentile of the normal range at each institution along with either ischemic ECG changes or clinical evidence of symptoms of myocardial ischemia (chest, upper extremity, mandibular, or epigastric discomfort) or an ischemic equivalent such as dyspnoea or fatigue. For the first part of our analysis, we treated SCE as an outcome variable to characterize patients who experience SCE. For the remainder of our analysis, we treated SCE as a predictor variable to identify associations with mortality.

## Outcomes

Overall mortality was defined as the time from CAR-T infusion to death from any cause. Deaths were further classified as: (i) non-relapse mortality (NRM) defined as death without recurrence or progression from time of CAR-T infusion or (ii) deaths occurring after cancer recurrence or progression. For NRM, cancer relapse/progression was viewed as a competing risk, while any patient alive at last follow-up and who never experienced relapse/progression before was censored.

Among patients with NRM, we identified death causes via manual chart review of the clinical team's notes or discharge summary, classifying primary aetiology as due to the following: (i) infection (if no other primary cause was attributable), (ii) CAR-T-related non-cardiac toxicity (i.e. severe CRS or immune effector cell-associated neurotoxicity syndrome with no other cause identified), (iii) CV death (i.e. death due to cardiogenic shock, heart failure, or MI, if no other death cause was identified), or (iv) other causes (if none of the preceding categories match).

## Statistical analysis

Continuous variables were presented as mean ± standard deviation or median [interquartile range (IQR)], as appropriate based on normality, and categorical variables were presented as frequencies with percentages. Continuous data were compared using unpaired Student's *t*-test or Wilcoxon rank-sum test, as appropriate. Categorical data were compared using the chi-squared or the Fisher's exact test. Univariate logistic regression was performed to investigate the association between biomarkers and SCE or death. Probabilities of NRM were estimated with the use of the cumulative incidence curve, and Gray's method was used to evaluate the differences between groups. The probabilities of overall mortality were estimated using the Kaplan–Meier (KM) method, and the log-rank test was used to evaluate the differences between groups. The Simon–Makuch-modified KM survival curve was used to plot overall survival stratified by SCE as a time-dependent variable and a *P*-value obtained from a score test provided by a univariable time-dependent Cox model. Cox proportional hazards regression was used to determine associations of characteristics with death following CAR-T infusion, where SCE was treated as a time-dependent variable. For overall mortality, we included ≤10 variables

(108 deaths or one parameter per 10 events) to avoid model overfitting. Variables with $P < 0.10$ on univariate regression were entered into the multivariate Cox proportional hazards regression, while age, pre-existing heart failure, CRS grade ≥ 2, and a diagnosis of acute lymphoblastic leukaemia were included due to their clinical relevance. For NRM, we included a maximum of two variables (22 non-relapse–related deaths or one parameter per 10 events) to avoid model overfitting and adjusted for high cancer burden. Statistical significance was defined as two-tailed $P < 0.05$. Statistical analyses were performed using STATA version 16.0 (StataCorp, College Station, TX) and SAS version 9.4 (SAS Institute, Cary, NC).

# Results

## Baseline characteristics

Among the 202 CAR-T recipients, the median age was 60 (IQR 45–68) years, 26% were female, 79% were White, and 7% were African American (*Table 1*). A smoking history was present in 36%, hypertension in 34%, diabetes in 13%, and pre-existing atrial fibrillation in 8%. A history of MI was noted in 1.5%, stroke in 2%, and prior heart failure in 5.5%. Chimeric antigen receptor T-cell therapy indications included B-cell lymphoma (71%) and acute lymphoblastic leukaemia (ALL, 29%). Investigational CD19 targeting CAR-T were used in 37%, followed by axicabtagene ciloleucel (32%), tisagenlecleucel (17%), and lisocabtagene maraleucel (14%). The majority of patients (87%) were previously treated with anthracycline-based chemotherapy. Before lymphodepletion, 62% had a high cancer burden, including 49% of ALL patients and 68% of lymphoma patients. On the most recent ECG preceding CAR-T [available in 201 (99.5%) of patients], 4% were in atrial fibrillation. On pre-CAR-T echocardiography [available in 188 (93%) of patients], the mean LVEF was 61% ± 8%. Supplementary data online, *Table S2*, lists baseline CV medications prior to CAR-T infusion.

## Characteristics of chimeric antigen receptor T-cell therapy patients who experienced severe cardiovascular events

Thirty-three (16%) patients experienced a SCE at a median of 12 (IQR 7–99) days after CAR-T cell infusion. There were 26 (13%) heart failure events, of which five (2%) developed cardiogenic shock, and there were 11 (5%) patients with MI. Cardiogenic shock was treated with milrinone (1), dobutamine (1), epinephrine (2), and norepinephrine (1). Baseline characteristics of patients who did and did not experience SCE are compared in *Table 1*. Those who experienced SCE had higher burden of pre-existing CV risk factors including hypertension (52% vs. 30%, $P = 0.02$) and prior history of atrial fibrillation (19% vs. 7%, $P = 0.03$) or previous occurrence of heart failure (21% vs. 2%, $P < 0.001$). The KM estimate for SCE at day 100 was higher for those with pre-existing CV risk factors: hypertension {19% [95% confidence interval (CI) 12%–31%] vs. 9% (95% CI 5%–16%), log-rank $P = 0.01$}, atrial fibrillation [24% (95% CI 10%–51%) vs. 12% (95% CI 8%–17%), log-rank $P = 0.01$], and heart failure [67% (95% CI 39%–92%) vs. 10% (95% CI 6%–15%), log-rank $P < 0.0001$]. Pre-CAR-T mean LVEF was lower in patients who developed SCE compared with those who did not (56 ± 10 vs. 62 ± 6%, $P < 0.001$). Those who did and did not experience SCE had similar cancer burden before CAR-T.

Among the 55 (25%) patients with post-CAR-T echocardiograms obtained during index admission for CAR-T infusion, the mean LVEF was lower among those with SCE (45 ± 12 vs. 57 ± 12%, $P = 0.001$; *Table 2*), with a two-fold higher percentage drop in LVEF (−11 ± 12 vs. −5 ± 9%) compared with pre-CAR-T, although this difference was not statistically significant ($P = 0.09$). On follow-up echocardiogram performed in 67 (33%) patients after discharge from index admission for CAR-T infusion, the mean LVEF was lower among those with SCE (51 ± 10 vs. 60 ± 8%, $P = 0.001$).

## Inflammatory and biomarker profile with SCE

Baseline biomarkers prior to CAR-T infusion were available as follows: CRP in 102 (51%), troponin in 57 (28%), and natriuretic peptide in 29 (14%). The median (IQR) time from pre-CAR-T biomarker measurement to CAR-T infusion was CRP [5 (4–6) days], troponin [86 (17–239) days], and natriuretic peptide [195 (24–367) days]. Severe CV events occurred in a higher proportion among patients with a baseline natriuretic peptide level above each institution's ULN (100% vs. 29%, $P = 0.001$), while median baseline troponin and CRP levels were similar among those who did or did not experience subsequent SCE (*Table 1*). Post-CAR-T infusion inflammatory parameters of patients who did and did not experience SCE are compared in *Table 2*. Patients who experienced SCE had an over two-fold higher rate of high-grade (≥2) CRS (70% vs. 33%, $P < 0.001$), as well as higher mean grade of CRS (2.2 ± 0.9 vs. 1.7 ± 0.8, $P = 0.005$), and a nearly three-fold lower rate of not experiencing any CRS (12% vs. 35%, $P = 0.01$). Those who experienced SCE also had higher rates of non-cardiogenic shock (33% vs. 9%, $P < 0.001$) and atrial arrhythmias (36% vs. 15%, $P = 0.003$).

Inflammatory biomarkers were collected multiple times in the first 2 weeks following CAR-T infusion, and peak values were available as follows: CRP in 163 (81%), ferritin in 162 (80%), IL-6 in 61 (30%), and TNF-α in 58 (29%). The median (IQR) time from CAR-T infusion to inflammatory biomarkers was CRP [5 (2–6) days], ferritin [5 (1–7) days], IL-6 [4 (1–5) days], and TNF-α [5 (3–7) days]. Troponin was available in 66 (33%) and natriuretic peptide in 55 (27%). The median (IQR) time from CAR-T infusion to troponin and natriuretic peptide measurement was 10 (6–49) days and 10 (5–119) days, respectively. The median (IQR) change in troponin from pre-CAR-T levels to peak levels after CAR-T was 0.04 (0.004–0.91) ng/mL. Those who experienced SCE had a greater median (IQR) rise in troponin from baseline: 0.51 (0.14–2.8) vs. 0.01 (0.004–0.03) ng/mL ($P = 0.02$). The median (IQR) change in CRP from pre-CAR-T levels to peak levels after CAR-T was [36 (10–112)] mg/dL. The median (IQR) change in CRP was similar among those who did and did not experience SCE: 46 (9–137) vs. 33 (10–117) mg/dL ($P = 0.40$).

Following CAR-T infusion, SCE was associated with higher peak levels of inflammatory and cardiac biomarker levels (*Figure 1A*). This included higher median CRP [48.3 (IQR 18.9–135) vs. 19.9 (IQR 9.3–49.0) mg/dL, $P = 0.004$], higher median ferritin [2905 (IQR 1849–25 134) vs. 1408 (IQR 594–3202) mg/L, $P = 0.003$], and higher median IL-6 levels [7580 (IQR 451–18 479) vs. 63.5 (IQR 16.5–255) pg/mL, $P = 0.002$]. The median TNF-α levels were comparable among patients who did and did not experience SCE {[50 (IQR 13–117) vs. 16 (IQR 11–27) pg/mL, $P = 0.14$}. Severe CV events were also associated with natriuretic peptide levels greater than the institutional ULN [30 (97%) vs. 11 (46%), $P < 0.001$] and a higher median troponin level {[0.9 (IQR 0.1–13.0) vs. 0.05 (IQR 0.03–7.7) ng/mL, $P < 0.001$}. Supplementary data online, *Table S3*, similarly shows the association between SCE and CRP, ferritin, IL-6, and troponin using univariate logistic regression. Tocilizumab was utilized over two-fold more frequently among those with SCE (76% vs. 37%, $P < 0.001$), while we found similar rates of corticosteroid use.

**Table 1 Baseline characteristics, overall, and by SCE occurrence after CAR-T infusion**

| | All patients ($n = 202$) | SCE $n = 33$ | No SCE $n = 169$ | *P*-value |
|---|---|---|---|---|
| Age at time of CAR-T—years | 60 (45–68) | 59 (45–69) | 60 (46–68) | 0.72 |
| Female sex—*n* (%) | 53 (26.2) | 11 (33.3) | 42 (24.9) | 0.31 |
| **Ethnicity** | | | | |
| White | 159 (78.7) | 26 (78.8) | 133 (78.7) | 0.22 |
| Black | 15 (7.4) | 5 (15.2) | 10 (5.9) | |
| Hispanic | 4 (2.0) | 0 (0) | 4 (2.4) | |
| Other | 27 (13.4) | 2 (6.1) | 25 (14.8) | |
| **Pre-CAR-T comorbidities—*n* (%)** | | | | |
| Atrial fibrillation | 17 (8.4) | 6 (18.8) | 11 (6.6) | 0.03 |
| Diabetes mellitus | 26 (12.9) | 4 (12.1) | 22 (13.0) | 0.90 |
| Heart failure | 11 (5.5) | 7 (21.2) | 4 (2.4) | <0.001 |
| Hypertension | 68 (33.7) | 17 (51.5) | 51 (30.2) | 0.02 |
| Smoking | 72 (35.6) | 11 (33.3) | 61 (36.1) | 0.76 |
| Stroke | 4 (2.0) | 1 (3.0) | 3 (1.8) | 0.64 |
| Myocardial infarction | 3 (1.5) | 1 (3.0) | 2 (1.2) | 0.42 |
| eGFR—mL/min | 77.7 ± 24.4 | 78.7 ± 27.4 | 77.4 ± 23.6 | 0.81 |
| Body mass index—kg/m$^2$ | 27.6 ± 6.8 | 26.3 ± 4.6 | 27.9 ± 7.3 | 0.30 |
| **Electrocardiographic parameters** | *n* = 201 | *n* = 33 | *n* = 168 | |
| Sinus rhythm, *n* (%) | 193 (95.5) | 31 (93.9) | 162 (95.9) | 0.63 |
| Atrial fibrillation, *n* (%) | 8 (4.0) | 2 (6.1) | 6 (3.6) | 0.50 |
| PR interval, ms | 151 ± 25 | 146 ± 19 | 152 ± 26 | 0.23 |
| QRS interval, ms | 92 ± 17 | 87 ± 10 | 93 ± 18 | 0.08 |
| QTc interval, ms | 438 ± 33 | 438 ± 30 | 438 ± 33 | 0.93 |
| **Echocardiography parameters** | *n* = 188 | *n* = 32 | *n* = 156 | |
| Ejection fraction, % | 61 ± 8 | 56 ± 10 | 62 ± 6 | <0.001 |
| Days before CAR-T infusion | 40 (20–61) | 28 (11–52) | 42 (24–63) | 0.06 |
| **Biomarkers prior to CAR-T** | | | | |
| B-type natriuretic peptide > ULN, *n*(%) | 14 (48.3) *n* = 29 | 8 (100) *n* = 8 | 6 (28.6) *n* = 21 | 0.001 |
| Troponin, ng/mL | 0.04 (0.01–0.05) *n* = 57 | 0.05 (0.03–0.84) *n* = 11 | 0.04 (0.01–0.05) *n* = 46 | 0.09 |
| CRP, mg/dL | 5.0 (3.0–21.6) *n* = 102 | 7.0 (3.0–44.0) *n* = 25 | 4.0 (3.0–15.5) *n* = 77 | 0.26 |
| **Pre-CAR-T cancer details** | | | | |
| Prior anthracycline—*n* (%) | 176 (87.1) | 32 (97.0) | 144 (85.2) | 0.07 |
| **ALL** | 59 (29.2) | 9 (27.3) | 50 (29.6) | 0.79 |
| Elevated blasts (>5%), *n* (%) | 29 (49.2) | 5 (55.6) | 24 (48.0) | 0.72 |
| Blasts % | 28.3 ± 35.1 | 23.9 ± 24.8 | 29.1 ± 36.8 | 0.69 |
| **Lymphoma** | 143 (70.8) | 24 (72.7) | 119 (70.4) | 0.79 |
| Elevated LDH (>ULN), *n* (%) | 97 (67.8) | 18 (75.0) | 79 (66.4) | 0.41 |
| LDH | 461.1 ± 753.5 | 469.4 ± 393.8 | 459.3 ± 810.4 | 0.95 |
| **High cancer burden**[a] | 126 (62.4) | 23 (69.7) | 103 (61.0) | 0.34 |
| **CD19 CAR-T product, *n* (%)** | | | | |

*Continued*

**Table 1** *Continued*

| | All patients ($n = 202$) | SCE $n = 33$ | No SCE $n = 169$ | *P*-value |
|---|---|---|---|---|
| Axicabtagene ciloleucel | 64 (31.7) | 16 (48.5) | 48 (28.4) | 0.009 |
| Tisagenlecleucel | 34 (16.8) | 8 (24.2) | 26 (15.4) | |
| Lisocabtagene maraleucel | 29 (14.4) | 0 (0) | 29 (17.2) | |
| Investigational | 75 (37.1) | 9 (27.3) | 66 (39.1) | |

SCE, severe cardiovascular events; ALL, acute lymphoblastic leukaemia; CRP, C-reactive protein; LDH, lactate dehydrogenase; ULN, upper limit of normal.
[a]High cancer burden = blasts > 5% (leukaemia) or LDH > ULN at each institution (lymphoma).

**Table 2 Events, overall and by SCE occurrence following CAR-T infusion**

| | All patients ($n = 202$) | SCE ($n = 33$) | No SCE ($n = 169$) | *P*-value |
|---|---|---|---|---|
| No CRS | 63 (31.2) | 4 (12.1) | 59 (34.9) | 0.01 |
| CRS grade[a] | 1.8 ± 0.9 | 2.2 ± 0.9 | 1.7 ± 0.8 | 0.005 |
| CRS ≥ 2 grade | 79 (39.1) | 23 (69.7) | 56 (33.1) | <0.001 |
| **Other events** | | | | |
| Non-cardiogenic shock | 26 (12.9) | 11 (33.3) | 15 (8.9) | <0.001 |
| Atrial arrhythmia | 37 (18.3) | 12 (36.4) | 25 (14.8) | 0.003 |
| **Anti-inflammatory agents** | | | | |
| Tocilizumab | 87 (43.1) | 25 (75.8) | 62 (36.7) | <0.001 |
| Time to tocilizumab, days | | | | |
| From CRS onset | 1 (0–2) | 1 (1–2) | 1 (0–4) | 0.74 |
| From CAR-T infusion | 5 (3–7) | 5 (3–7) | 5 (3–8) | 0.42 |
| Steroids | 51 (25.2) | 15 (45.5) | 36 (21.3) | 0.20 |
| Time to steroids, days | | | | |
| From CRS onset | 3 (2–6) | 5 (3–7) | 3 (1–5) | 0.13 |
| From CAR-T infusion | 7 (5–10) | 7 (5–9) | 8 (5–10) | 0.76 |
| **Electrocardiographic parameters, ms** | $n = 82$ | $n = 20$ | $n = 62$ | |
| PR interval | 145 ± 37 | 154 ± 61 | 142 ± 24 | 0.22 |
| QRS interval | 92 ± 31 | 91 ± 27 | 93 ± 32 | 0.71 |
| QTc interval | 449 ± 39 | 451 ± 47 | 449 ± 36 | 0.77 |
| **Echocardiography parameters (during CAR-T admission)** | $n = 51$ | $n = 19$ | $n = 32$ | |
| Time to echocardiogram, days | | | | |
| From CRS onset | 6 (3–12) | 4 (3–7) | 12 (4–16) | 0.06 |
| From CAR-T infusion | 9 (5–22) | 7 (4–11) | 13 (6–25) | 0.16 |
| Ejection fraction, % | 53 ± 13 | 45 ± 12 | 57 ± 12 | 0.001 |
| Δ ejection fraction, % | −7 ± −10 | −11 ± −12 | −5 ± −9 | 0.09 |
| **Echocardiography parameters (post-discharge)** | $n = 67$ | $n = 13$ | $n = 54$ | |
| Ejection fraction, % | 58 ± 9 | 51 ± 10 | 60 ± 8 | 0.001 |
| Time to echocardiogram, days[+] | 146 (49–371) | 97 (29–377) | 216 (63–371) | 0.23 |

SCE, severe cardiovascular events; CRS, cytokine release syndrome.
[a]Excluded patients who did not have CRS.
[+]From CAR-T infusion.

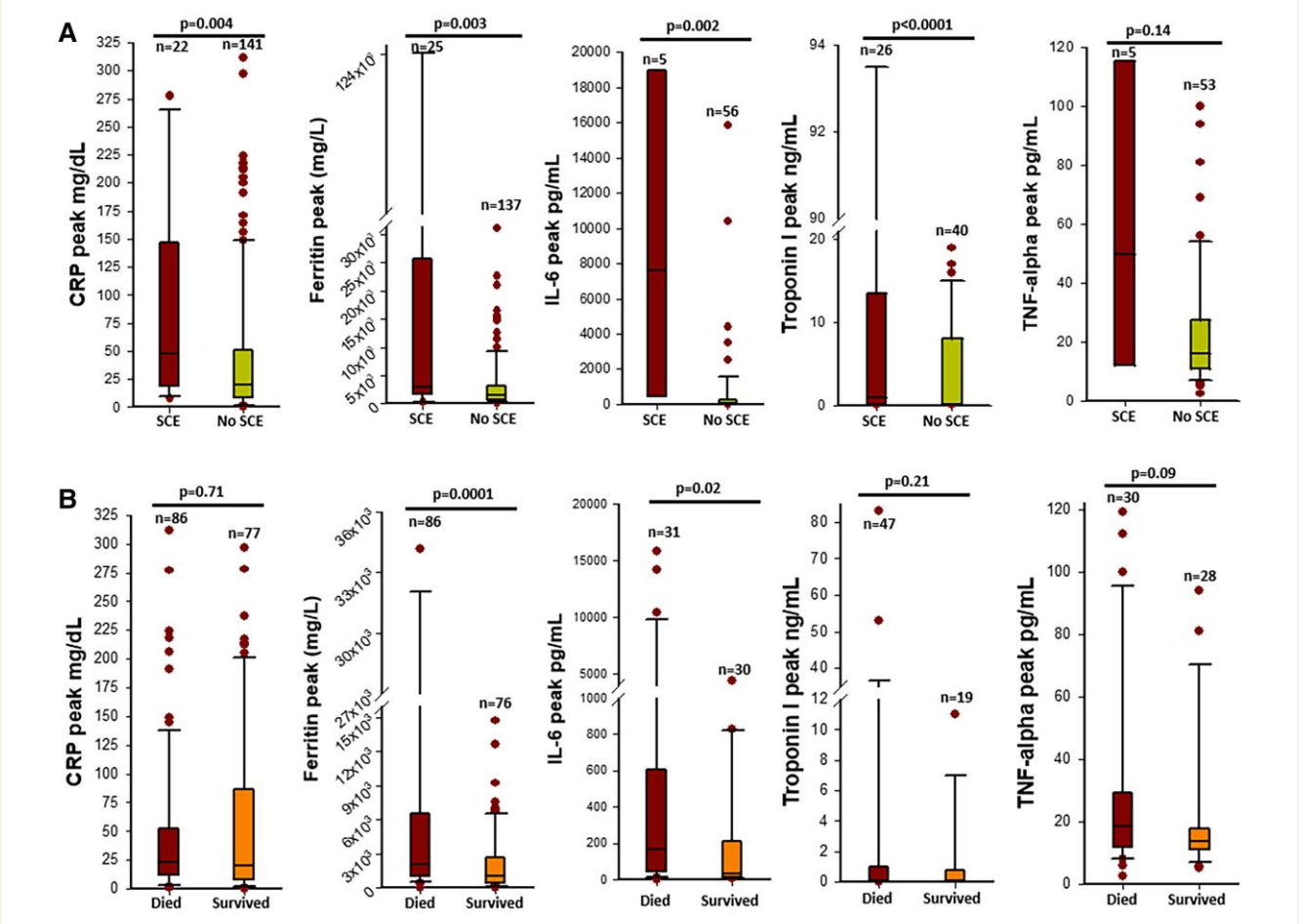



**Figure 1** Boxplots for peak biomarker levels after CAR-T infusion stratified by (*A*) SCE and (*B*) overall mortality. SCE, severe cardiovascular events; CRP, C-reactive protein; IL-6, interleukin-6; TNF-α, tumour necrosis factor alpha.

## Causes of death

Over a median of 297 (IQR 104–647) days follow-up, 108 patients (53%) died including 86 deaths after cancer recurrence or progression and 22 NRMs. The Kaplan–Meier estimate for overall mortality at day 100 was 18% (95% CI 13%–24%) and that at 1 year was 43% (95% CI 36%–50%). The non-relapse mortality cumulative incidence rate at day 100 was 3.5% (95% CI 3.1%–3.9%) and that at 1 year was 6.7% (95% CI 6.1%–7.2%). The causes of NRM included infection [9 (4.5%)], CAR-T-related non-cardiac toxicity (i.e. CRS or immune effector cell-associated neurotoxicity syndrome) in three patients (1%), CV death in one patient (0.5%), and other causes (9 [4.5%]).

## Characteristics of chimeric antigen receptor T-cell therapy patients who died

A comparison of variables between those who did and did not die is shown in *Table 3*. Death was associated with higher cancer burden prior to lymphodepletion (42% vs. 17%, $P < 0.001$) and a diagnosis of ALL (36% vs. 21%, $P = 0.02$). No difference was seen based on CAR-T product administered or prior anthracycline exposure. More patients had hypertension (42% vs. 25%, $P = 0.01$) among those who died. While death was lower among African American patients (4% vs. 12%, $P = 0.03$), overall, there was no difference in ethnicity between those who did and did not die. Additionally, between those who did and did not die, there were no differences in pre-existing heart failure, baseline LVEF, and ECG characteristics (rhythm and PR, QRS, and QTc intervals). The KM day-100 survival estimate was lower for patients with the following risk factors: high cancer burden [74% (95% CI 66%–81%) vs. 94% (95% CI 86%–98%), log-rank $P < 0.0001$], hypertension [78% (95% CI 66%–86%) vs. 84% (95% CI 77%–90%), log-rank $P = 0.006$], and similar for those with and without ALL [84% (95% CI 72%–92%) vs. 81% (95% CI 73%–87%), log-rank $P = 0.52$].

## Inflammatory and biomarker profile of those who died

Pre-CAR-T median levels of troponin and CRP, as well as natriuretic peptide > ULN, were comparable between those who did and did not die (*Table 3*). Post-CAR-T infusion inflammatory parameters of patients who did and did not die are compared in *Table 4*. Patients who died had comparable rates of high-grade (≥2) CRS, mean grade of CRS, and rates and timing of tocilizumab and corticosteroid use. Those who died also had nearly a two-fold higher rate of non-cardiogenic shock (17% vs. 9%), but this trend was not statistically significant ($P = 0.08$). Following CAR-T infusion, there was no significant difference in median (IQR) troponin change from pre-CAR-T levels between those who did and did not die: 0.04 (0.003–0.51) vs. 0.47

**Table 3 Description of patients treated with CAR-T by overall mortality**

| | Died $n = 108$ | Survived $n = 94$ | *P*-value |
|---|---|---|---|
| Age at time of CAR-T—years | 59 (45–67) | 61 (46–69) | 0.59 |
| Female sex—*n* (%) | 30 (27. 8) | 23 (24.5) | 0.59 |
| **Ethnicity** | | | |
| White | 89 (82.4) | 70 (74.5) | 0.13 |
| Black | 4 (3.7) | 11 (11.7) | |
| Hispanic | 1 (0.9) | 3 (3.2) | |
| Other | 15 (13. 9) | 12 (12.8) | |
| **Pre-CAR-T comorbidities, *n* (%)** | | | |
| Atrial fibrillation | 12 (11.1) | 5 (5.3) | 0.14 |
| Diabetes mellitus | 15 (13. 9) | 11 (11.7) | 0.64 |
| Hypertension | 45 (41.7) | 23 (24.5) | 0.01 |
| Smoking | 35 (32.4) | 37 (39.4) | 0.30 |
| Stroke | 2 (1.9) | 2 (2.1) | 0.89 |
| Heart failure | 7 (6.5) | 4 (4.3) | 0.49 |
| Myocardial infarction | 1 (0.9) | 2 (2.1) | 0.48 |
| Body mass index—kg/m$^2$ | 27.1 ± 6.4 | 28.1 ± 7.2 | 0.44 |
| **Echocardiography parameters** | $n = 97$ | $n = 87$ | |
| Ejection fraction, % | 60 ± 8 | 62 ± 7 | 0.27 |
| Days before CAR-T infusion | 40 (19–63) | 41 (20–59) | 0.81 |
| **Electrocardiographic parameters** | $n = 107$ | $n = 94$ | |
| Sinus rhythm, *n* (%) | 101 (93.5) | 92 (97.9) | 0.14 |
| Atrial fibrillation, *n* (%) | 6 (5.6) | 2 (2.1) | 0.21 |
| PR interval, ms | 149 ± 23 | 154 ± 27 | 0.21 |
| QRS interval, ms | 91 ± 18 | 92 ± 15 | 0.79 |
| QTc interval, ms | 440 ± 35 | 435 ± 30 | 0.32 |
| **Biomarkers prior to CAR-T** | | | |
| B-type natriuretic peptide > ULN, *n* (%) | 11 (61.1) $n = 18$ | 3 (27.3) $n = 11$ | 0.08 |
| Troponin, ng/mL | 0.04 (0.01–0.05) $n = 31$ | 0.05 (0.01–0.12) $n = 26$ | 0.45 |
| CRP, mg/dL | 7.0 (2.99–25.6) $n = 55$ | 3.1 (2.56–21.6) $n = 47$ | 0.21 |
| **Pre-CAR-T cancer details** | | | |
| Prior anthracycline | 98 (90.7) | 78 (83.0) | 0.10 |
| **ALL** | 39 (36.1) | 20 (21.3) | 0.02 |
| Elevated blasts (>5%), *n* (%) | 22 (56.4) | 7 (35.0) | 0.16 |
| Blasts, % | 29.6 ± 35.5 | 25.4 ± 35.0 | 0.67 |
| **B-cell lymphoma** | 69 (63.9) | 74 (78.7) | 0.02 |
| Elevated LDH (>ULN), *n* (%) | 23 (33.3) | 9 (12.2) | 0.002 |
| LDH | 611.2 ± 1023.3 | 315.3 ± 258.2 | 0.02 |
| **High cancer burden**[a] | 45 (41. 7) | 16 (17.0) | <0.001 |
| **CD19 CAR-T product, *n* (%)** | | | |
| Axicabtagene ciloleucel | 37 (34.3) | 27 (28.7) | 0.24 |

*Continued*

**Table 3** ***Continued***

| | Died $n = 108$ | Survived $n = 94$ | *P*-value |
|---|---|---|---|
| Tisagenlecleucel | 14 (13.0) | 20 (21.3) | |
| Lisocabtagene maraleucel | 13 (12.0) | 16 (17.0) | |
| Investigational | 44 (40.7) | 31(33.0) | |

ALL, acute lymphoblastic leukaemia; CRP, C-reactive protein; LDH, lactate dehydrogenase; ULN, upper limit of normal.
[a]High cancer burden = blasts > 5% (leukaemia) or LDH > ULN at each institution (lymphoma).

(0.01–1.86) ng/mL ($P = 0.96$). Similarly, there was no difference in median (IQR) CRP change among those who did and did not die: 21 (10–100) vs. 40 (11–137) mg/dL ($P = 0.20$).

Biomarkers after CAR-T infusion were compared between those who did and did not die in *Figure 1B*. Those who died had higher median levels of peak IL-6 [163 (IQR 47–604) vs. 34 (IQR 11–176) pg/mL, $P = 0.02$] and peak ferritin [2057 (IQR 1010–6480) vs. 996 (IQR 396–2622) mg/L, $P = 0.0001$]. Supplementary data online, *Table S4*, similarly shows the association between death and IL-6 or ferritin using univariate logistic regression. Among those who died, there was a non-significant trend towards higher peak TNF-α [18.5 (IQR 12–29) vs. 13.5 (IQR 11–17.5) pg/mL, $P = 0.09$] and similar peak CRP [22.7 (IQR 12.8–52) vs. 21 (IQR 8–85) mg/dL, $P = 0.71$]. The median peak troponin level [0.08 (IQR 0.05–0.98) vs. 0.05 (IQR 0.02–0.76) ng/mL, $P = 0.21$] and the proportions with an elevated natriuretic peptide level above the ULN (81% vs. 63%, $P = 0.16$) were similar between those who did and did not die.

## Cardiovascular events among chimeric antigen receptor T-cell therapy patients who died

Cardiovascular events after CAR-T infusion were compared between those who did and did not die in *Table 4*. Severe CV events were more common among those who died (23% vs. 9%, $P = 0.005$), including a higher incidence of MI (9% vs. 1%, $P = 0.01$) and cardiogenic shock (5% vs. 0%, $P = 0.04$), as well as a non-significant trend towards a higher rate of clinical heart failure (17% vs. 9%; $P = 0.08$). There was no difference in time to SCE between those who did and did not die. Death after SCE occurred at a median (IQR) of 20 (1–34) days. Atrial arrythmias, which were not included in our definition of SCE, occurred at a similar rate between those who did and did not die. Among those who underwent cardiac testing after CAR-T, the LVEF and ECG parameters (PR, QRS, and QTc intervals) were comparable between those who did and did not die.

## Variables associated with mortality

The death rate was higher among those who did experience SCE: 25 (76%) vs. 83 (49%), $P = 0.005$. *Figure 2A* shows overall survival from time of CAR-T infusion plotted as the Simon–Makuch curve stratified by time-dependent variable SCE ($P = 0.0001$). The variables associated with overall mortality on univariate Cox proportional hazards regression were SCE, high cancer burden, hypertension, and prior anthracycline use (*Figure 3*). For the multivariate model, the occurrence of SCE following CAR-T was independently associated with an increased risk of overall mortality [adjusted HR (aHR) 2.8, 95% CI 1.6–4.7]. Similarly, a high cancer burden prior to CAR-T (aHR 2.9, 95% CI 1.8–4.7) and pre-existing hypertension (aHR 1.8, 95% CI 1.2–2.7) were also independently associated with overall mortality. *Figure 2B* shows NRM cumulative incidence curves from time of CAR-T infusion stratified by SCE (Gray's test $P = 0.01$). In the multivariate model adjusted for high cancer burden, SCE following CAR-T was independently associated with an increased risk of NRM (aHR 3.5, 95% CI 1.4–8.8; Supplementary data online, *Table S5*).

# Discussion

We present the first analysis demonstrating that SCE (heart failure, cardiogenic shock, and MI) after CD19 targeting CAR-T independently confers an increased risk of not only overall mortality but also NRM. This association remained even after adjusting for cancer burden prior to CAR-T, the presence of pre-existing CV risk factors, and previous cardiotoxic anthracycline use. We also show that SCE was associated with higher peak levels of IL-6, CRP, ferritin, and troponin (Structured Graphical Abstract). Our findings are important given the frequent occurrence of SCE after CD19 CAR-T—an oncological therapy undergoing rapid expansion in approved indications and utilization.[6,8] Advances in our understanding of the biomarker profile of those at risk for SCE and early treatment of SCE may lead to further improvements in survival for CAR-T recipients.

Our observations suggest that cardiac toxicities following CAR-T are poorly tolerated and may be associated with reduced survival and that close CV monitoring may be necessary to follow the inflammatory and CV sequelae of CAR-T. The association between SCE and worse mortality has also been well documented for other cancer therapies. In a prior publication by our group on myocarditis after immune checkpoint inhibitor (ICI) cancer therapy, we showed a higher mortality among patients who experienced cardiogenic shock and other CV events.[17] Decline in LVEF has also been shown to be an independent predictor of short- and long-term mortality in anthracycline-treated patients.[18,19] Additionally, we show higher NRM among patients who experience SCE, which is likely driven by the SCE's sequalae of renal failure and marked functional decline that portends higher susceptibility to future infections and also limits further therapeutic options. This may explain why SCE is associated with increased NRM driven by infection and less so by direct CV mortality.

Our observation of the high rate of SCE after CAR-T is similar to recent publications demonstrating heart failure in 6%–15% of CAR-T recipients.[9,11] Among patients receiving CAR-T who developed new or worsening cardiomyopathy, half did not experience normalization of systolic function.[10] In our study, we also found that 5% of CAR-T patients experienced an MI, a finding that builds on our prior work demonstrating that an elevated troponin was associated with CV events in CAR-T patients.[9] An elevated troponin has been similarly associated with adverse events following a number of other cancer therapies, including anthracyclines and HER2 targeting therapy.[20,21] A major cause

**Table 4 Events following CAR-T infusion by overall mortality**

| | Died $n = 108$ | Survived $n = 94$ | *P*-value |
|---|---|---|---|
| Days to first SCE event | 12 (7–99) | 13 (6–256) | 0.93 |
| **SCE events** | | | |
| Any SCE | 25 (23.2) | 8 (8.5) | 0.005 |
| Myocardial infarction | 10 (9.3) | 1 (1.1) | 0.01 |
| Cardiogenic shock | 5 (4.6) | 0 (0) | 0.04 |
| Heart failure | 18 (16.7) | 8 (8.5) | 0.08 |
| **Other events** | | | |
| Atrial arrhythmia | 21 (19.4) | 16 (17.0) | 0.66 |
| Distributive shock | 18 (16.7) | 8 (8.5) | 0.08 |
| No CRS, *n* (%) | 28 (25.9) | 35 (37.2) | 0.08 |
| CRS ≥ 2 grade, *n* (%) | 46 (42.6) | 33 (35.1) | 0.28 |
| CRS grade[a] | 1.8 ± 0.9 | 1.8 ± 0.9 | 0.83 |
| **Anti-inflammatory agents** | | | |
| Tocilizumab | 51 (47.2) | 36 (38.3) | 0.16 |
| Time to tocilizumab, days | | | |
| From CRS onset | 1 (1–2) | 1 (0–3) | 0.76 |
| From CAR-T infusion | 5 (3–8) | 5 (2–7) | 0.16 |
| Steroids | 28 (25.9) | 23 (24.5) | 0.74 |
| Time to steroids, days | | | |
| From CRS onset | 5 (2–7) | 3 (2–5) | 0.14 |
| From CAR-T infusion | 8 (6–10) | 7 (4–9) | 0.07 |
| **ICANS** | 52 (48.2) | 37 (39.4) | 0.21 |
| **Electrocardiographic parameters** | $n = 49$ | $n = 33$ | |
| PR interval, ms | 144 ± 43 | 145 ± 25 | 0.92 |
| QRS interval, ms | 90 ± 23 | 96 ± 39 | 0.30 |
| QTc interval, ms | 453 ± 43 | 444 ± 34 | 0.24 |
| **Echocardiography parameters (during admission)** | $n = 34$ | $n = 17$ | |
| Ejection fraction, % | 52 ± 13 | 55 ± 13 | 0.47 |
| Δ ejection fraction, % | −8 ± −10 | −6 ± −11 | 0.49 |
| Time to echocardiogram, days | | | |
| From CRS onset | 8 (3–15) | 4 (3–6) | 0.42 |
| From CAR-T infusion | 10 (6–25) | 7 (3–15) | 0.09 |
| **Echocardiography parameters (post-discharge)** | $n = 39$ | $n = 28$ | |
| Ejection fraction, % | 57.7 ± 9.8 | 59.2 ± 8.2 | 0.52 |

SCE, severe cardiovascular events; CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.
[a]Excluded patients who did not have CRS.

of MI in CAR-T patients is likely due to the imbalance in myocardial oxygen supply/demand (i.e. type 2 MI) in the setting of high-grade CRS. CAR-T-related CRS is a pro-inflammatory state with marked serum cytokine elevation that induces hypotension, myocardial oedema, and contractile dysfunction which places patients at risk for myocardial injury.[22] Similarly, septic shock—which shares physiological features with high-grade CRS[22]—is the most common primary hospital diagnosis associated with type 2 MIs in the general population.[23] We did not include atrial arrythmias in our definition of SCE as these have not been associated with mortality after CAR-T.[13]

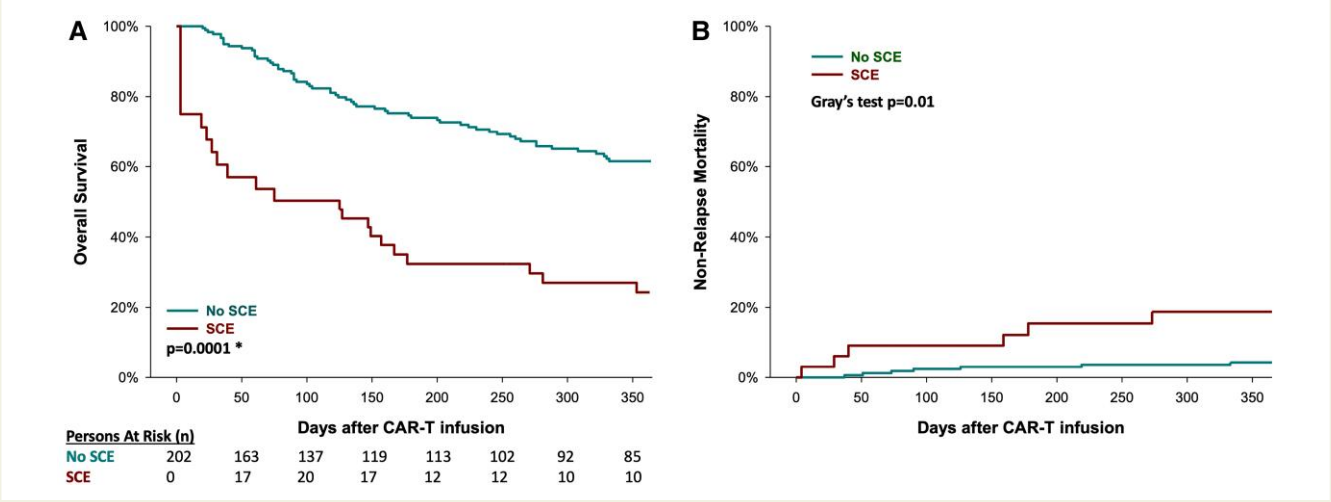



**Figure 2** (*A*) Simon–Makuch curve plotting overall survival and (*B*) cumulative incidence of non-relapse mortality, from time of CAR-T infusion as stratified by SCE. SCE, severe cardiovascular events. **P*-value is from the score test provided by an univariable time-dependent Cox model.

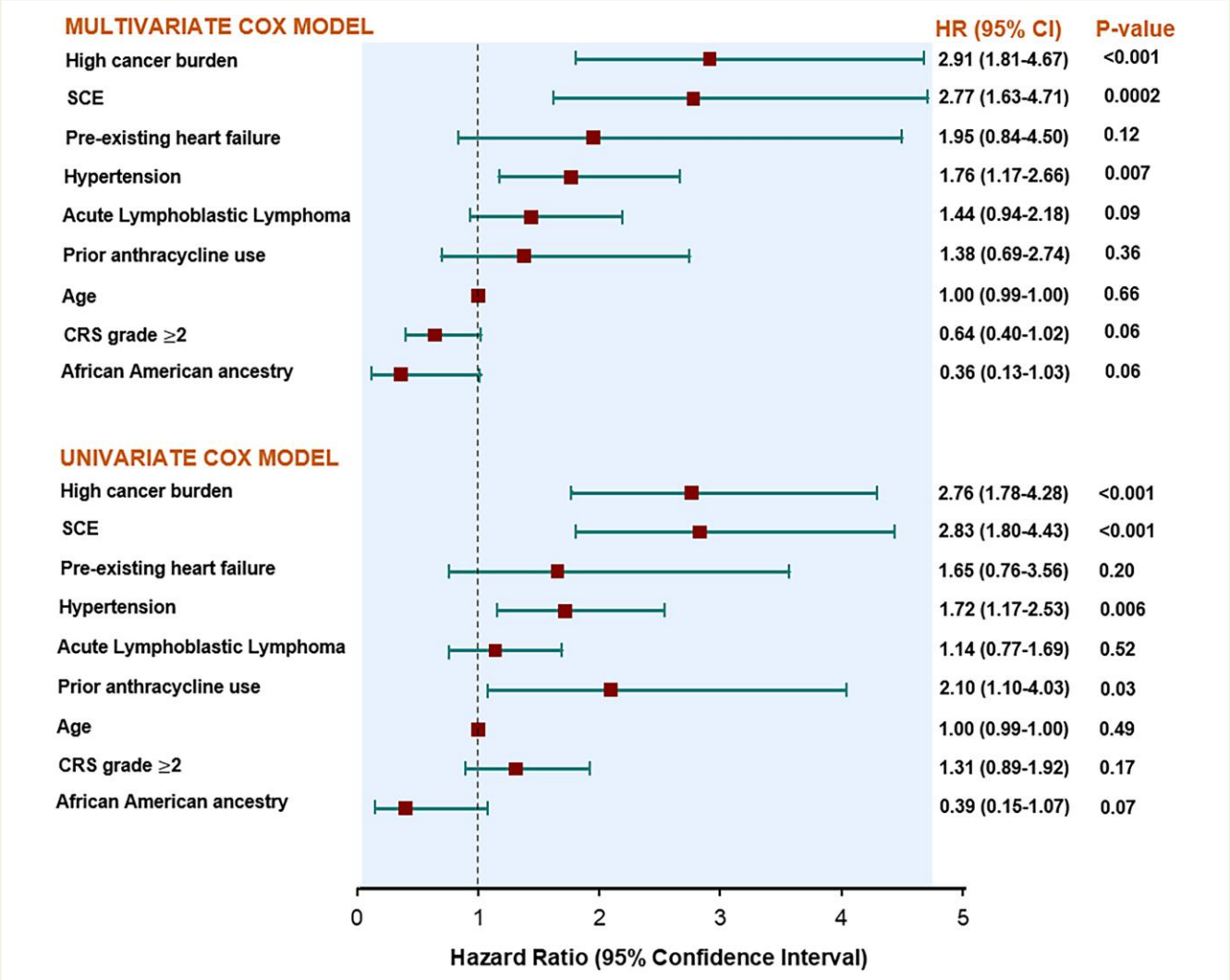



**Figure 3** Association with overall mortality determined using multi-variate Cox proportional hazards regression analysis. SCE, severe cardiovascular events; CRS, cytokine release syndrome; HR, hazard ratio; CI, confidence interval.

We also show the inflammatory cytokine profile of patients experiencing SCE. Changes in IL-6, CRP, and ferritin are associated with CRS,[4,24] while we have previously shown that high-grade CRS is itself associated with SCE.[9] Our current findings of elevated IL-6, CRP, and ferritin in SCE patients further provide insight into the biology of SCE after CAR-T cell therapy—specifically the cardiotoxic role of severe inflammation. Furthermore, the finding of higher peak IL-6 levels in SCE patients has potential therapeutic relevance as IL-6 is the cytokine most strongly associated with severe inflammation,[24] and early use of IL-6 receptor antagonists (e.g. tocilizumab) may mitigate SCE occurrence.[9]

Our study is limited by its retrospective design, including retrospective adjudication of SCE that was partly dependent on cardiac testing performed at the discretion of the treatment team. Similarly, not all patients had cardiac and inflammatory biomarkers measured as this testing was based on each participating site's institutional guidelines. Our study predominantly included adults with B-cell lymphoma and specifically excluded recipients of non-CD19–directed CAR-T. Our patient cohort included subjects treated at large academic medical centres with experience managing CAR-T-related toxicities, and therefore, this may affect the generalizability of our findings.

In conclusion, SCEs (composite of clinical heart failure, cardiogenic shock, and MI) after CD19-targeted CAR-T were independently associated with a higher risk of overall mortality as well as NRM. Severe CV events were associated with higher peak levels of IL-6, CRP, ferritin, and troponin. Understanding the association between severe cardiotoxicity, inflammation, and survival for other cancer therapies (such as ICIs and anthracyclines) has resulted in the development of standardized CV surveillance protocols for early cardiotoxicity detection, including serial echocardiograms, baseline biomarkers, and ECG.[25–28] The optimal CV surveillance strategy following CAR-T is unclear. Future research efforts may include further investigating inflammatory biomarkers as possible predictors of severe cardiotoxicity. Future studies will also need to investigate treatment options to mitigate CAR-T cardiotoxicity such as the early use of tocilizumab to mitigate high-grade CRS and possibly CV events.[9] It is also unknown whether traditional cardioprotective therapies (e.g. statins, beta blockers, and angiotensin pathway inhibitors) may diminish CV risk.

## Author contributions

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# Supplementary data

Supplementary data is available at *European Heart Journal* online.

# Data availability

The data underlying this article will be shared on reasonable request to the corresponding author and in concordance with the requirements of the institutional research board.

# Conflict of interest

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