Predictors and implications of renal injury after CD19 chimeric antigen receptor T-cell therapy

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Abstract

Chimeric antigen receptor (CAR) T cells targeting CD19 induce durable remissions in patients with relapsed or refractory non-Hodgkin lymphoma (NHL), but many patients experience treatment-related toxicity. Cytokine release syndrome and immune effector cell-associated neurologic syndrome are extensively characterized. However, limited data exist on the burden, predictors, and implications of acute kidney injury (AKI) after CAR T-cell therapy. On initial screening of the Food and Drug Administration adverse event reporting system, we identified a disproportionately high rate of renal adverse events among nearly 6,000 CAR T adverse event reports, suggesting it is clinically important in this patient population. In a subsequent single-center analysis of 399 NHL patients treated with CD19 CAR T cells, we found a substantial burden of AKI after CAR T infusion (10% and 5% of any grade and grade ≥2 AKI) with pre-renal causes being predominant (72%). Evolution to chronic kidney disease was rare, however, three patients required hemodialysis. Importantly, patients experiencing cytokine release syndrome and/or neurotoxicity as well as those with low serum albumin and high inflammatory cytokines, including IL-6 and TNF-α, were more likely to develop AKI. While pre-CAR T renal dysfunction was not associated with adverse outcomes, patients developing post-CAR T AKI had lower overall survival compared to their counterparts. Our findings indicate that renal dysfunction is a common toxicity of CAR T-cell therapy with meaningful prognostic impact. Notably, the link between systemic inflammation and renal dysfunction, suggests that readily available biomarkers may inform on renal injury risk after CAR T-cell therapy.

Introduction

Chimeric antigen receptor (CAR) T cells targeting CD19 induce durable remissions in patients with relapsed or refractory non-Hodgkin lymphoma (NHL), including large B cell lymphoma (LBCL) and mantle cell lymphoma (MCL).[1-15] Following a series of pivotal phase I-II multicenter clinical trials, four CD19 CAR T-cell products, axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), lisocabtagene maraleucel (liso-cel), and brexucabtagene autoleucel

(brexu-cel), received Food and Drug Adminstration (FDA) approval for NHL in the third-line setting or later,[1-10] paving the way for follow-up studies in the second-line.[11-14] Three phase III randomized controlled trials separately compared CD19 CAR T-cell therapy to prior standard of care high dose chemotherapy with autologous stem cell transplant (auto-HCT) in LBCL patients with relapsed or refractory disease less than 12 months after completion of first-line chemoimmunotherapy.[11-13,15] Among these, the ZUMA-7 and TRANSFORM studies demonstrated improved median event-free survival in the CAR T-cell arm relative to auto-HCT, leading to FDA approval of axi-cel and liso-cel in this setting.[16-17] Indications for CAR T-cell therapy in lymphoma were further extended after the phase II PILOT study showed impressive efficacy of liso-cel in LBCL patients with significant medical comorbidities including chronic kidney disease (CKD), leading to its expanded approval as second-line therapy for transplant-ineligible patients.[14]

Despite these major therapeutic advances, many patients experience treatment-related toxicity.[1-14] Cytokine release syndrome (CRS), immune effector cell-associated neurologic syndrome (ICANS), and immune effector cell-associated hematologic toxicity are extensively characterized.[18-21] However, limited data exist on the burden, predictors, and implications of acute kidney injury (AKI) after CAR T-cell therapy. Among the seminal trials investigating the use of CD19 CAR T-cell therapy in lymphoma patients who relapse after two or more lines of therapy, only the TRANSCEND study extended eligibility to patients with CKD grade 3.[2-5] Thus, our understanding of lymphoma outcomes and toxicities in patients with pre-existing kidney disease is otherwise limited to small retrospective studies.[22-24]

Here we describe a global pharmacovigilance analysis of nearly 6,000 CD19 CAR T-cell recipients in addition to the largest single retrospective analysis to date of 399 NHL patients with normal and reduced baseline renal function who received CD19 CAR T-cell therapy at our institution. We evaluated AKI incidence, etiologies, and clinical consequences in addition to CAR T-cell-related outcomes and toxicities. Additionally, we analyzed pre-lymphodepletion, pre-infusion, and post-infusion laboratory values to determine predictors of AKI within 100 days after CAR T-cell infusion.

Methods

Food and Drug Administration adverse event reporting system analysis

To further assess the association between CD19 CAR T-cell therapy and AKI we queried the FDA adverse event reporting system (FAERS), a global post-marketing surveillance program, which includes voluntary and mandatory safety reports submitted by healthcare professionals, consumers, and manufacturers. The database was screened for reports of commercial CD19 CAR T-cell products (axi-cel, tisa-cel, liso-cel, and brexu-cel) as the primary etiology of a given AE between January 1, 2017, and September 30, 2022. Patients under 18 years old were excluded. We applied an algorithm to eliminate suspected duplicate reports of the same drug-AE pair with different case numbers by screening for identical values in four key fields: age, sex, event date, and country of occurrence. AKI outcome definition included the ”Preferred Terms” in the “Acute renal failure” Standardized MedDRA Query (version 25.1) with manual validation by the authors.[25]

We performed a disproportionality analysis to compare the reporting of AKI events following CD19 CAR T-cell therapy with all other oncological patients from the database. The age-and-sex-adjusted reporting odds ratio (adj.ROR) and the lower bound of the information component 95% credibility interval (IC_{025}) were used to detect significant disproportionate reporting. A lower bound of the adj.ROR 95% confidence interval (CI) greater than one and a positive IC_{025} value were used as thresholds for signal detection. To mitigate indication and reporting biases, we conducted sensitivity analyses using different comparator groups, including the full database, hemato-oncological patients, and patients with lymphoid malignancies.[26-27]

Memorial Sloan Kettering Cancer Center cohort population

We performed a single-center real-world retrospective study to analyze baseline and dynamic changes in renal function in adult patients with relapsed or refractory NHL treated with CD19 CAR T cells at Memorial Sloan Kettering Cancer Center (MSK) between April 28, 2016 and December 31, 2023. Axi-cel, tisa-cel, liso-cel, and brexu-cel were given mostly as standard therapy. Additionally, some patients received liso-cel under the TRANSCEND NHL 001 study (*clinicaltrials gov. Identifier: NCT02631044*). Our cohort did not include patients on hemodialysis or renal transplant recipients. Patient data were entered and stored in a REDCap database.[28] This research was approved by the Institutional Review Board committee and conducted in accordance with the Declaration of Helsinki.

Definitions

Estimated glomerular filtration rate (eGFR) was calculated via the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Creatinine Equation[29] and was based on serum creatinine just prior to lymphodepletion. Chronic kidney disease grading was tiered by the Kidney Disease Improving Global Outcomes (KDIGO) definitions. AKI was defined by serum creatinine between day 0 and day 100 using KDIGO criteria (see the *Online Supplementary Appendix*). For AKI assessment, disease relapse or progression, anti-cancer treatment after CAR T cells, and death were considered competing events. EMR charts of all cases of AKI were individually reviewed by a board-certified nephrologist

to adjudicate each cause of AKI. Renal recovery was defined as a return in creatinine to baseline range within 90 days. Otherwise, patients were considered as having progressed to CKD. CRS and ICANS were graded according to ASTCT guidelines.[30] Detailed statistical methods and formulas are described in *Online Supplementary Appendix*.

Table 1. Characteristics of CD19 chimeric antigen receptor T reports in the Food and Drug Administration adverse event reporting system by acute kidney injury reporting status.

	AKI N=211	Other CAR T reports N=5,701	*P*
Reporting region[1]			
Americas	149/200 (74.50)	4,010/5,433 (73.81)	0.464
Europe	39/200 (19.50)	1,140/5,433 (20.98)	
Asia	10/200 (5.00)	179/5,433 (3.29)	
Australia	2/200 (1.00)	104/5,433 (1.91)	
Reporter			
Health professional	185/199 (92.96)	4,936/5,379 (91.76)	0.635
Consumer/ lawyer	14/199 (7.04)	443/5,379 (8.24)	
Event year			
2017-2018	33/175 (18.86)	675/3,441 (19.62)	0.538
2019-2020	74/175 (42.29)	1,569/3,441 (45.60)	
2021-2022[2]	68/175 (38.86)	1,197/3,441 (34.79)	
Age in years, median (IQR)	62 (54-70)	62 (51-69)	0.439
Sex			
Female	66/190 (34.74)	1,686/4,510 (37.38)	0.508
Male	124/190 (65.26)	2,824/4,510 (62.62)	
Product			
Axi-cel	116/211 (54.98)	3,410/5,701 (59.81)	0.577
Tisa-cel	71/211 (33.65)	1,709/5,701 (29.98)	
Brexu-cel	17/211 (8.06)	411/5,701 (7.21)	
Liso-cel	7/211 (3.32)	171/5,701 (3.00)	
Indication			
NHL	179/197 (90.86)	3,948/4,499 (87.75)	0.215
ALL	16/197 (8.12)	520/4,499 (11.56)	
Other	2/197 (1.02)	31/4,499 (0.69)	
Concurrent CRS	136/211 (64.45)	2,838/5,701 (49.78)	<0.001
Time in days to AE onset, median (IQR)	2.5 (1.0-8.0)	4.0 (1.0-10.0)	0.009
Outcome			
Hospitalization[3]	104/211 (49.29)	1,959/5,369 (36.49)	<0.001
Life-threatening	48/211 (22.75)	427/5,369 (7.95)	<0.001
Death	104/211 (49.29)	1,250/5,369 (23.28)	<0.001

[1]Among CD19 CAR T recipients from the Americas, 4,095 were from the USA (AKI, N143; non-AKI, N=3,952). [2]Only cases reported before September 30, 2022, were included. [3]Denotes that the adverse event was the cause of inpatient admission or, if it occurred during hospitalization, was the cause of delayed discharge. All values are N/N (%) unless otherwise indicated. *P* values were calculated with the Bonferroni correction for multiple comparisons. AKI: acute kidney injury; CAR T: chimeric antigen receptor T cell; Axi-cel: axicabtagene ciloleucel; Tisa-cel: tisagenlecleucel; Brexu-cel: brexucabtagene autoleucel; Liso-cel: lisocabtagene maraleucel; NHL: non-Hodgkin lymphoma; ALL: acute lymphoblastic leukemia; CRS: cytokine release syndrome; IQR: Interquartile range; AE: adverse events.

Results

Global pharmacovigilance analysis

To evaluate the extent to which renal injury impacts patients with lymphoid malignancies who are treated with CD19 CAR T-cell therapy, we interrogated the FAERS database containing more than 7,000,000 cases: 5,912 patients received CD19 CAR T cells, including 3,526 axi-cel, 1,780 tisa-cel, 178 liso-cel, and 428 brexu-cel (Table 1; Figure 1A). CD19 CAR T-cell recipients were a median age of 62 (interquartile range [IQR], 51-69). The main indications for treatment were NHL (N=4,127 [88%]) and ALL (N=536 [11%]). Reports mostly originated from the Americas (74%).

We identified 211 (3.6%) reports of AKI for which CD19 CAR T-cell therapy was considered the primary etiology. AKI cases were mostly reported in NHL patients (N=179 [91%]). Age, sex, event year, CD19 CAR T type, and indication did not differ significantly between AKI and other CD19 CAR T-cell safety events. Concurrent CRS was reported more frequently by patients who developed AKI relative to those who did not (N=136 [64%] *vs.* N=2,838 [50%], respectively; *P*<0.001). AKI events occurred at a median time of 2.5 (IQR, 1-8) days post-infusion. Patients who developed AKI following treatment had a higher reported fatality rate compared to other CD19 CAR T safety events (N=104 [49%] *vs.* N=1,250 [23%]; *P*<0.001) (Table 1).

Importantly, AKI reporting was significantly higher in patients treated with CD19 CAR T cells compared to all other cancer patients in the FAERS database (adj.ROR= 1.72 [IQR, 1.34–2.20], IC_{025}=0.19). To mitigate indication and reporting biases, we conducted sensitivity analyses by using different comparator groups. The association between CD19 CAR T-cell treatment and increased reporting of AKI remained significant when compared to the entire FAERS database (adj.ROR= 2.40 [IQR, 1.87–3.07], IC_{025}=0.47), patients with hematologic malignancies (adj.ROR=1.44 [IQR, 1.20–1.73], IC_{025}=0.27), and patients with lymphoid malignancies (adj. ROR= 1.39 [IQR, 1.16–1.67], IC_{025}=0.24) (Figure 1B).

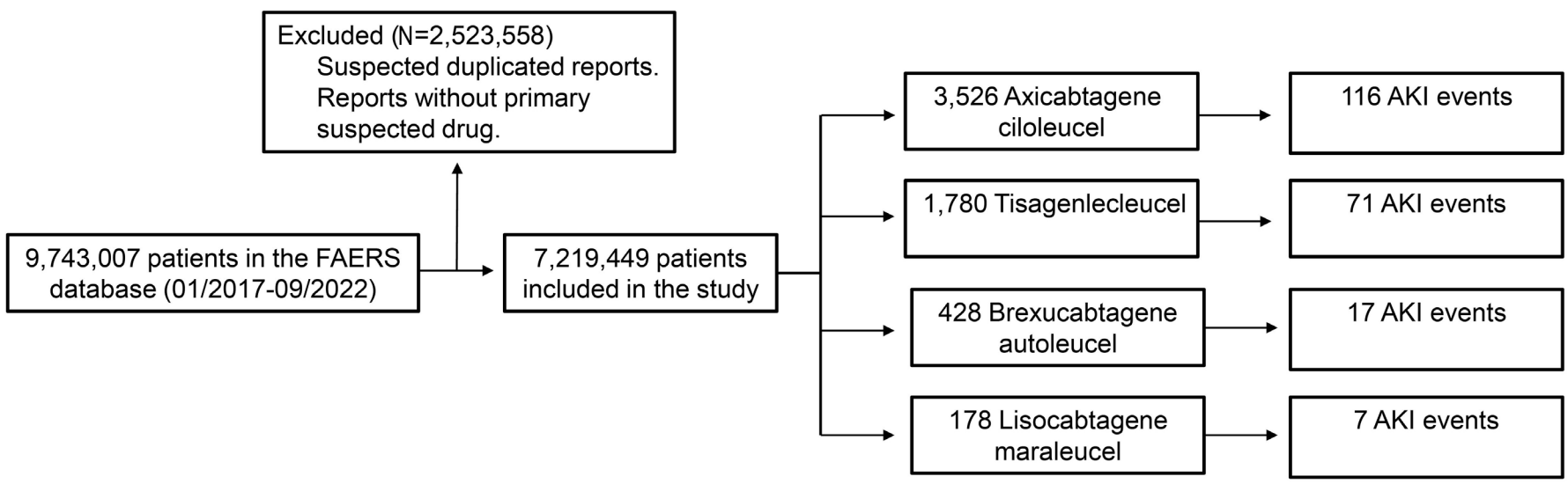
Overall, this pharmacovigilance analysis highlights AKI as a frequently reported AE among patients receiving CD19 CAR T-cell therapy. However, limitations inherent to pharmacovigilance data prevent a precise determination of true incidence and risk factors of AKI.

Memorial Sloan Kettering Cancer Center cohort baseline characteristics

To gain insight into the prevalence, etiology, and implications of AKI, we studied 399 patients (Table 2) diagnosed with NHL (84% LBCL, 11% MCL, and 5% non-LBCL) who underwent CAR T-cell therapy at our institution. Among these patients, the median age was 66 years and CAR T-cell products included 46% axi-cel, 20% tisa-cel, 29% liso-cel, and 5% brexu-cel.

Before lymphodepleting chemotherapy, typically initiated five days prior to CAR T-cell infusion, patients exhibited

A



B

	Total reports N	AKI reports N (%)	adj.ROR (95% CI)	IC_{025}
CAR−T	5,912	211 (3.57)		
Comparator group				
Entire FAERS database	7,214,143	161,717 (2.24)	2.40 (1.87−3.07)	0.47
Cancer patients	1,358,051	36,786 (2.71)	1.72 (1.34−2.20)	0.19
Hemato−oncological patients	424,746	10,860 (2.56)	1.44 (1.20−1.73)	0.27
Lymphoid malignancies patients	354,820	9,236 (2.60)	1.39 (1.16−1.67)	0.24

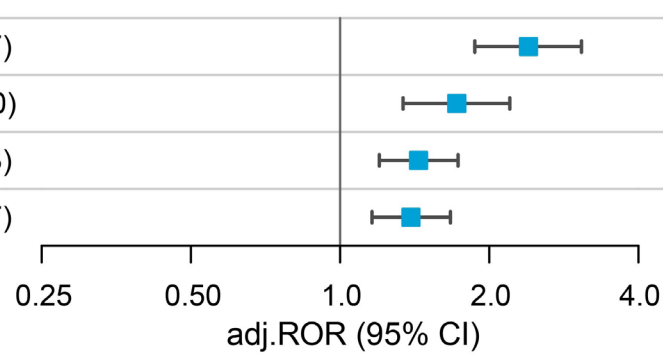


Figure 1. Study flowchart and disproportionality analysis of CAR T-related adverse events. (A) Flowchart of the Food and Drug Adminstration adverse event reporting system (FAERS) data retrieval process. Reports without a defined primary suspected drug for a given adverse event (AE) and suspected duplicated reports were excluded. (B) Disproportionality analysis of CD19 chimeric antigen receptor (CAR) T-related acute kidney injury (AKI) events compared to the full FAERS database, cancer patients, hemato-oncological patients, and patients with lymphoid malignancies. A positive lower bound of the information component 95% credibility interval (IC_{025}>0) and a lower limit of the reporting odds ratio (ROR) 95% confidence interval (CI) above 1 are the conventional thresholds for significant signal detection. NHL: non-Hodgkin lymphoma; adj.ROR: age and sex-adjusted ROR.

a median eGFR of 94 mL/min (IQR, 75-101). Most patients (55%) had a normal eGFR (≥90 mL/min; grade 0-1 CKD), followed by 35% with grade 2 CKD (eGFR 60-89 mL/min) and 10% with grade 3 CKD (eGFR 30-59 mL/min). Older age was associated with baseline CKD grade 2-3 relative to normal eGFR (*P*<0.001). Pre-CAR T cell Karnofsky Performance Scale, number of pre-apheresis treatment lines, and prior hematopoietic stem cell transplantation did not significantly differ across CKD groups (Table 2).

Given that suboptimal lymphodepletion chemotherapy dosing has been associated with differences in outcomes and toxicities in CD19 CAR T-cell-treated patients,[31-32] we calculated total fludarabine dosing. Patients with decreased renal function received lower doses of fludarabine (*P*=<0.001), ranging from a median total dose of 72 mg/m^2 (IQR, 60-76) in stage 3 CKD to 88 mg/m^2 (IQR, 80-91) in patients with normal eGFR. We also used an established pharmacokinetic (PK) model to measure fludarabine exposure, using total fludarabine dose and serum creatinine, age, and weight on the first day of lymphodepletion.[32-33] Among 330 patients (143 axi-cel, 18 brexu-cel, 101 liso-cel, 68 tisa-cel) who received fludarabine as part of lymphodepletion, exposure by area under the curve (AUC) was higher on average in patients with lower eGFR (*P* value inevaluable since eGFR is a variable in the PK calculation model; Table 2).

Memorial Sloan Kettering Cancer Center cohort clinical and toxicity outcomes

At a median follow-up time of 24 months, patients in the cohort experienced a median progression-free survival (PFS) of 12 months (95% confidence interval [CI]: 8.6-18 months) and a median overall (OS) of 36 months (95% CI: 23 months - not reached) (*Online Supplentary Figure S1*). CAR T-cell-related adverse effects occurred at a similar frequency to previously published seminal clinical trials.[1-14] Grade 0-1 CRS occurred in 243 (61%) patients *versus* 156 (39%) who experienced grade ≥2 CRS. The median duration of CRS was 5 days, and 192 (48%) patients required To-

Table 2. Memorail Sloan Kettering Cancer Center cohort patient characteristics by baseline renal function.

Characteristic	Overall N=399[1]	eGFR ≥90 mL/min N=220[1]	eGFR 60-89 mL/min N=140[1]	eGFR <60 mL/min N=39[1]	*P*[2]
Pre-CAR T age in years	66 (56-73)	61 (51-68)	70 (63-77)	72 (65-76)	<0.001
Sex					0.075
Male	260 (65)	153 (70)	81 (58)	26 (67)	
Female	139 (35)	67 (30)	59 (42)	13 (33)	
Pre-CAR T KPS					0.11
>=90	124 (31)	77 (35)	39 (28)	8 (21)	
<90	274 (69)	142 (65)	101 (72)	31 (79)	
Unknown	1	1	0	0	
Ethnicity					0.4
Hispanic or Latino	26 (6.8)	12 (5.7)	10 (7.5)	4 (11)	
Not Hispanic or Latino	354 (93)	197 (94)	123 (92)	34 (89)	
Unknown	19	11	7	1	
Race					0.089
Asian	35 (9.1)	26 (12)	7 (5.3)	2 (5.3)	
Black or African American	16 (4.2)	6 (2.8)	8 (6.0)	2 (5.3)	
Other	16 (4.2)	10 (4.7)	3 (2.3)	3 (7.9)	
White	316 (83)	170 (80)	115 (86)	31 (82)	
Unknown	16	8	7	1	
NHL broad classification					0.6
LBCL	335 (84)	186 (85)	119 (85)	30 (77)	
Mantle cell lymphoma	44 (11)	22 (10)	15 (11)	7 (18)	
Non-LBCL	20 (5.0)	12 (5.5)	6 (4.3)	2 (5.1)	
NHL transformation origin					0.42
de novo LBCL	210 (53)	124 (57)	68 (49)	18 (46)	
transformed tFL	77 (19)	39 (18)	32 (23)	6 (15)	
Other primary	42 (11)	21 (9.6)	15 (11)	6 (15)	
Unknown/not applicable	70	36	25	9	
Double or triple hit					0.057
Not double or triple hit	258 (70)	142 (70)	86 (68)	30 (77)	
Double or triple hit	47 (13)	27 (13)	20 (16)	0 (0)	
Unknown/ not applicable	94	51	34	9	
Cell of origin					0.6
GCB	165 (43)	94 (45)	59 (43)	12 (32)	
non-GCB	157 (41)	83 (39)	57 (42)	17 (45)	
Unknown/not applicable	77	43	24	10	
Prior treatment lines	3 (2-4)	3 (2-4)	3 (2-4)	3 (2-4)	0.5
Unknown	6	4	2	0	
Prior treatment lines (category)					0.5
<=3 lines	256 (65)	146 (68)	88 (64)	22 (56)	
4-5 lines	89 (23)	48 (22)	31 (22)	10 (26)	
6+ lines	48 (12)	22 (10)	19 (14)	7 (18)	
Unknown	6	4	2	0	
Previous auto-HCT	77 (19)	45 (21)	22 (16)	10 (26)	0.3
Previous allo-HCT	19 (4.8)	11 (5.0)	4 (2.9)	4 (10)	0.14
Primary refractory disease	146 (37)	89 (40)	47 (34)	10 (26)	0.2
Unknown	3	0	3	0	
Bridging type					0.5
no bridging	86 (22)	44 (20)	35 (25)	7 (18)	
non-systemic bridging	65 (16)	40 (18)	17 (12)	8 (21)	
systemic bridging	248 (62)	136 (62)	88 (63)	24 (62)	

Continued on following page.

Characteristic	Overall N=399[1]	eGFR ≥90 mL/min N=220[1]	eGFR 60-89 mL/min N=140[1]	eGFR <60 mL/min N=39[1]	*P*[2]
CAR T product					0.006
Axi-cel	183 (46)	117 (53)	54 (39)	12 (31)	
Brexu-cel	23 (5.8)	11 (5.0)	7 (5.0)	5 (13)	
Liso-cel	115 (29)	58 (26)	48 (34)	9 (23)	
Tisa-cel	78 (20)	34 (15)	31 (22)	13 (33)	
CAR T co-stimulatory domain					0.015
CD28	206 (52)	128 (58)	61 (44)	17 (44)	
41BB	193 (48)	92 (42)	79 (56)	22 (56)	
Lymphodepletion					0.6
Flu/Cy	343 (86)	192 (87)	117 (84)	34 (87)	
Bendamustine	56 (14)	28 (13)	23 (16)	5 (13)	
Total fludarabine dose mg/m²	86 (74-90)	88 (80-91)	79 (72-89)	72 (60-76)	<0.001
Unknown	57	29	23	5	
Predicted fludarabine AUC mgh/L	15.75 (13.95-17.51)	14.71 (13.30-16.35)	17.03 (15.0718.88)	17.72 (15.5820.29)	N/A
Unknown	69	36	28	5	
Predicted fludarabine AUC mgh/L category					N/A
0- 18	266 (81)	179 (97)	69 (62)	18 (53)	
18-25	64 (19)	5 (2.7)	43 (38)	16 (47)	
Unknown	69	36	28	5	
Pre-CAR T disease response					0.6
CR	40 (10)	21 (9.5)	15 (11)	4 (10)	
PR	130 (33)	79 (36)	41 (29)	10 (26)	
SD/PD	229 (57)	120 (55)	84 (60)	25 (64)	
LDH range pre-LD					0.4
normal	242 (61)	134 (61)	81 (58)	27 (69)	
elevated	157 (39)	86 (39)	59 (42)	12 (31)	
CRP pre-LD	0.6 (0.4-2.7)	0.7 (0.3-3.4)	0.6 (0.4-1.8)	0.6 (0.3-1.9)	0.4
Unknown	71	41	27	3	
Ferritin pre-LD	196 (71-525)	181 (71-550)	187 (69-465)	302 (97-576)	0.2
Unknown	73	42	28	3	

[1]Median (interquartile range [IQR] Q1-Q3); N (%). [2]Kruskal-Wallis rank sum test; Pearson's $\chi 2$ test; Fisher's exact test. CAR T: chimeric antigen receptor T cell; KPS: Karnofsky Performance Scale; NHL: non-Hodgkin lymphoma; LBCL: large B-cell lymphoma; tFL: transformed follicular lymphoma; GCB: germinal center B cell; Axi-cel: axicabtagene ciloleucel; Tisa-cel: tisagenlecleucel; Brexu-cel: brexucabtagene autoleucel; Liso-cel: lisocabtagene maraleucel; Flu/Cy: fludarabine and cyclophosphamide; auto-HCT: autologous stem cell transplant; allo-HCT: allogeneic stem cell transplant; CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; AUC: area under the curve (for drug exposure over time); pre-LD: pre-lymphodepletion; LDH: lactate dehydrogenase; CRP: C reactive protein. N/A (not applicable) indicates that we are unable to obtain *P* value since estimated glomerular filtration rate (eGFR) is in the pharmokinetic (PK) calculation model.

cilizumab infusion. Grade 0-1 ICANS occurred in 322 (81%) patients relative to 77 (19%) with grade ≥2 symptoms. The median duration of ICANS was 5 days, and 150 (38%) patients required steroids. Overall, 62 (16%) patients were admitted to the intensive care unt after CAR T-cell infusion. Significant hematologic toxicity was also observed in the cohort with 287 (74%) patients experiencing severe neutropenia (absolute neutrophil count <500) with a median duration of 10 days and 95 (25%) patients with severe thrombocytopenia (platelets <20x10^9/L) with a median duration of 21 days (*Online Supplementary Table S1*).

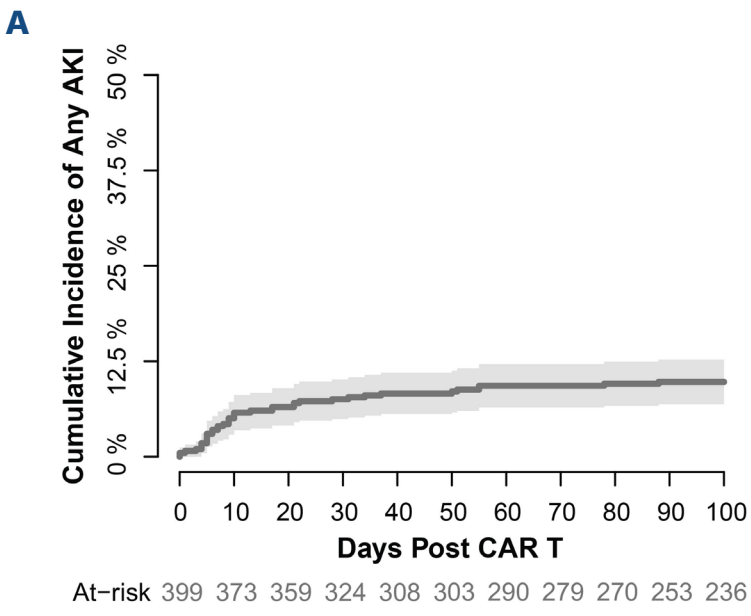
In a cause-specific Cox regression model, surrogates for disease burden,[34] including elevated pre-lymphodepletion lactate dehydrogenase (LDH) and the need for systemic bridging therapy (treatment given between apheresis and infusion), were associated with OS and PFS. Pre-lymphodepletion eGFR, however, was not associated with OS, PFS, CRS grade ≥2, ICANS grade ≥2, or neutropenia (*Online Supplementary Tables S2-S6*). Thus, baseline renal function was not significantly associated with efficacy or toxicity endpoints.

Clinical burden of acute kidney injury after CD19 CAR T-cell therapy

Between CAR T-cell infusion (day 0) and day 100, excluding patients who experienced disease relapse and/or received additional anti-cancer treatment, the cumulative incidence of any AKI and grade ≥2 AKI were 10% (39 patients) and 4.8% (19 patients), respectively (Figure 2A, B). The median

time to any AKI was 9 days, whereas the median time to grade 2+ AKI was 7 days. The trajectory of creatinine and eGFR for all patients over 12 months following CAR T-cell infusion is depicted (*Online Supplementary Figure S2A, B*). Of the 39 patients who experienced an AKI, 28 (71.8%) were attributed to pre-renal factors, including 14 cases that occurred concurrently with CRS. Eight (20.5%) AKI events were considered intra-renal etiology, including five cases occurring with CRS-induced hemodynamic compromise, one case occurring with TLS, and two cases associated with acute tubular necrosis. Three (7.7%) cases of AKI were linked to hydronephrosis (Figure 2C). Continuous renal replacement therapy (CRRT) was initiated in three patients for AKI due to hemodynamic instability stemming from CRS. Three patients (7.7%) died of CRS-induced shock in the intensive care unit and 20 (51.2%) patients died from complications of lymphoma progression after resolution of AKI. Other causes of death included progression of lung cancer (2.6%), COVID and a pulmonary embolism (2.6%), acute myocardial infarction (2.6%), and unknown (5.1%). Eight (20.5%) patients are alive as of August 2024. Among evaluable AKI patients, one patient progressed to CKD with serum creatinine remaining over 1.5-fold higher than baseline at the end of follow-up.

The potential contribution of medications to renal injury was also considered. Among the 39 patients who experienced AKI, 31 (79.5%) received potentially nephrotoxic drugs within 1 week prior to onset of AKI (*Online Supplementary Table S7*). Furosemide administration within 7 days of AKI onset was observed in 12 (30.8%) patients of which nine AKI events were pre-renal etiology, five of which occurred in the setting of CRS. The most frequent exposure was vancomycin in 19 patients (48.7%), though serum troughs exceeded the maximum therapeutic range (20 mg/L) in only six patients (serum concentrations of 25, 45, 21.4, 24.6, 21.6, 40 mg/L), among which two patients had post-renal AKI cause and three patients had concurrent CRS, including one patient who experienced resolution of AKI with fluid resuscitation. Among the ten patients (25.6%) who received vancomycin concurrently with piperacillin-tazobactam, a combination that has been associated with increased risk of renal injury,[35] only one patient experienced an intra-renal AKI event, suggesting that antibiotic exposure was not a significant cause of renal injury in our cohort.



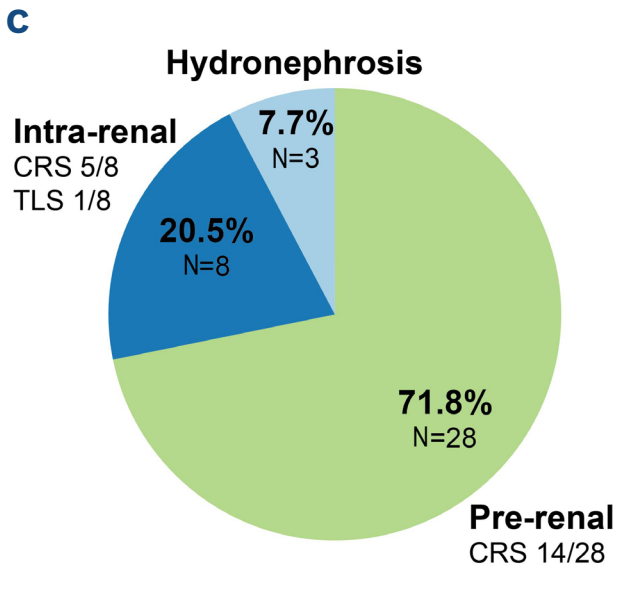


Figure 2. Cumulative incidence and etiologies of acute kidney injury. The cumulative incidence of acute kidney injury (AKI) at any grade (A) and grade ≥2 AKI (B) up to day 100 are shown. Shaded regions correspond to 95% confidence intervals. Disease relapse or progression, change in treatment, and death were considered competing events. Causes of AKI in the MSK cohort are displayed according to category as adjudicated by a nephrologist (C). Cases of cytokine release syndrome (CRS) and tumor lysis syndrome (TLS) that occurred during the time of AKI are also listed. CAR T: chimeric antigen receptor T cell.

Table 3. Cox regression analysis for pre-lymphodepletion predictors of acute kidney injury.

Characteristics[1]	Univariable			Multivariable		
	HR[1]	95% CI[1]	*P*[1]	HR[1]	95% CI[1]	*P*[1]
Pre-CAR T age	1.01	0.99-1.04	0.3	-	-	-
Pre-CAR T KPS			0.2			-
>=90	-	-		-	-	
<90	1.56	0.74-3.29		-	-	
Baseline eGFR			0.063			-
eGFR >=90	-	-		-	-	
eGFR 60-89	0.48	0.23-1.02		-	-	
eGFR <60	0.37	0.09, 1.54		-	-	
Bridging type			0.3			-
no bridging	-	-		-	-	
non-systemic bridging	1.84	0.58-5.78		-	-	
systemic bridging	2.05	0.79-5.31		-	-	
Platinum exposure			0.5			-
not exposed	-	-		-	-	
exposed	1.35	0.60-3.06		-	-	
Predicted fludarabine AUC mgh/L	0.90	0.78-1.03	0.11	-	-	-
Predicted fludarabine AUC mgh/L category			0.1			-
0-18	-	-		-	-	
18-25	0.42	0.13-1.37		-	-	
CAR T product			0.2			-
Axi-cel	-	-		-	-	
Brexu-cel	1.80	0.61-5.31		-	-	
Liso-cel	0.60	0.25-1.44		-	-	
Tisa-cel	1.41	0.65-3.05		-	-	
Hgb	0.76	0.64-0.90	0.001	1.05	0.84-1.31	0.7
LDH	2.00	1.41-2.83	<0.001	1.58	0.92-2.73	0.11
Albumin	0.15	0.08-0.26	<0.001	0.15	0.07-0.32	<0.001
CRP	1.08	1.02-1.14	0.024	0.96	0.8-1.04	0.3
Ferritin	1.39	1.09-1.78	0.008	-	-	-

[1]Lactate dehydrogenase (LDH) and ferritin were log transformed. HR: hazard ratio; CI: confidence interval; CAR T: chimeric antigen receptor T cell; KPS: Karnofsky Performance Scale; Axi-cel: axicabtagene ciloleucel; Tisa-cel: tisagenlecleucel; Brexu-cel: brexucabtagene autoleucel; Liso-cel: lisocabtagene maraleucel; eGFR: estimated glomerular filtration rate; Flu/Cy: fludarabine and cyclophosphamide; pre-LD: pre-lymphodepletion; Hgb: hemoglobin; CRP: C reactive protein; AUC: area under the curve (for drug exposure over time); pre-lymphodepletion indicates laboratory value obtained prior to initiating lymphodepleting chemotherapy, in most cases 5 days prior to CAR T-cell infusion.

Risk factors for acute kidney injury

We first evaluated biomarkers predictive of renal injury prior to administration of lymphodepleting chemotherapy, occurring about 5 days prior to CAR T-cell infusion. Clinical characteristics of event-free AKI *versus* non-AKI patients are shown (*Online Supplementary Table S8*). In a univariable cause-specific Cox regression, baseline lower hemoglobin and albumin levels and higher log transformed ferritin, CRP, and log transformed LDH levels were associated with developing any AKI (Table 3). Incidence of AKI stratified by high *versus* low pre-lymphodepletion laboratory values, including LDH, albumin, ferritin, and hemoglobin is shown (Figure 3A-D). Importantly, no association was detected between baseline eGFR and developing renal injury, consistent with a prior study.[24] Furthermore, neither the use of systemic bridging therapy nor specifically bridging platinum therapy were significantly associated with developing any AKI. In a multivariable model, using stepwise regression of significant covariates, serum albumin level prior to lymphodepletion remained a significant risk factor for AKI (hazard ratio [HR]=0.15 [95% CI: 0.07-0.32]; *P*<0.001; Table 3).

Since fludarabine-based conditioning regimens were previously shown to be a risk factor for AKI after allo-HCT,[36] we used the fludarabine PK model to further investigate the potential impact of disparate fludarabine exposures across patients in our cohort. Fludarabine exposure by AUC, either as a continuous or categorical variable (high 18-25 *vs*. low 0-18 mgh/L), was not significantly associated with developing any grade AKI in a cause specific regression model (Table 3).

Since systemic inflammation has been linked to adverse CAR T-cell outcomes,[37] we evaluated biomarkers of inflammation just prior to CAR T-cell infusion (day 0). At this time

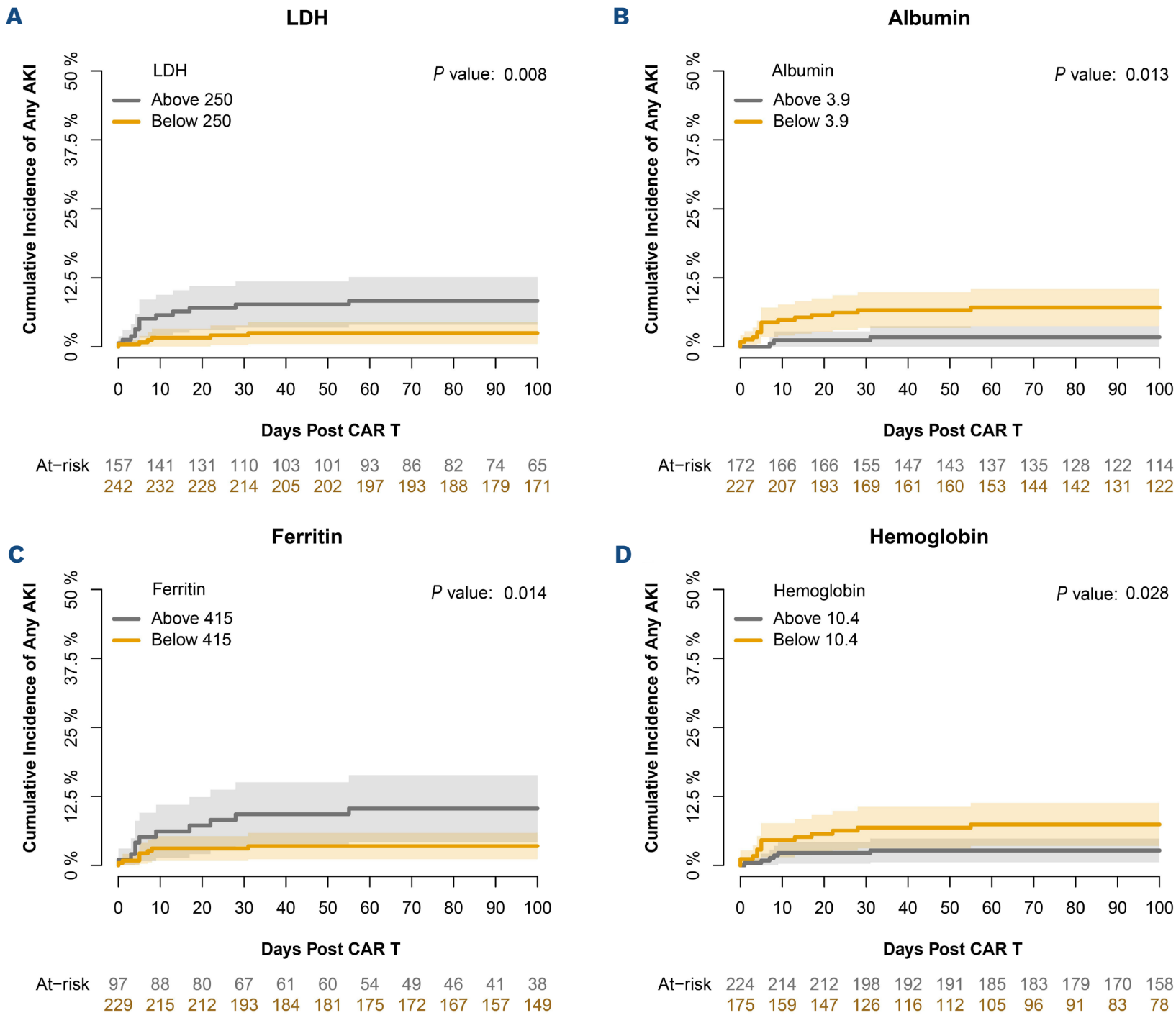


Figure 3. Incidence of any acute kidney injury by pre-lymphodepletion laboratory values. Cumulative incidence of acute kidney injury (AKI) was stratified according to pre-lymphodepletion lacate dehydrogenase (LDH) (A) above the upper limit of normal 250 U/L (grey) *versus* below 250 U/L (orange), albumin (B) above the upper limit of normal 3.9 g/L (grey) *versus* ≤3.9 g/L (orange), log-transformed ferritin (C) above the upper limit of normal 415 ng/mL (grey) *versus* ≤415 ng/mL (orange), and hemoglobin above 10.4 g/dL (grey) are compared to patients with hemoglobin ≤10.4 g/dL (orange). Shaded regions represent 95% confidence intervals. CAR T: chimeric antigen receptor T cell; U/L: units per liter.

point, higher serum CRP, TNF-α, and log-transformed IL-6 and IL-10 were significantly associated with developing AKI. Serum log transformed IL-6 (HR=1.74 [95% CI: 1.18-2.56]; *P*=0.008) and TNF-α (HR=2.23 [95% CI: 1.54-3.23]; *P*=<0.001) on day 0 remained significant in a multivariable model with stepwise addition of inflammatory biomarker covariates (Table 4). Thus, elevations of pre-infusion cytokines IL-6 and TNF-α are significant risk factors for AKI. Since inflammatory markers are dynamic, we modeled them longitudinally between days 0 to 30 using GEE models adjusting for time from CAR T infusion. When modeling markers individually, while adjusting for time, age, and co-stimulatory domain, elevations in log-transformed serum ferritin, CRP, TNF-α, and IL-10, but not LDH, were individually associated with decreased eGFR on average (Figure 4A). Serum log-transformed TNF-α remained significant on multivariate analysis (estimate -6.98 [95% CI: -10.29 to -3.67]; *P*<0.001; Figure 4B). Trends in post-infusion eGFR stratified by categorized TNF-α serum levels over time is shown (*Online Supplementary Figure S3*).

We also considered the potential impact of infectious complications on renal injury between day 0 and day 100. Among patients who did not experience a disease-related event, bacteremia occurred in six (15%) patients prior to the AKI event relative to 18 (7.3%) patients without AKI. As a time-dependent covariate, bacteremia was significantly associated with AKI (HR=2.78 [95% CI: 1.07-7.23]; *P*=0.036). Viral infections were also associated with AKI (20.5% *vs.*

Table 4. Cox-regression analysis for pre-infusion predictors of acute kidney injury.

Characteristic[1]	Univariable			Multivariable		
	HR[1]	95% CI[1]	*P*[1]	HR[1]	95% CI[1]	*P*[1]
Hgb	0.68	0.55-0.84	<0.001	-	-	-
LDH	2.54	1.76-3.66	<0.001	-	-	-
Albumin	0.19	0.11-0.34	<0.001	-	-	-
CRP	1.09	1.05-1.14	<0.001	-	-	-
Ferritin	1.00	1.00-1.00	0.015	1.00	1.00-1.00	0.8
Fibrinogen	0.54	0.17-1.70	0.3	-	-	-
TNF-α	2.75	1.98-3.83	<0.001	2.23	1.54-3.23	<0.001
IL-10	1.82	1.39-2.38	<0.001	-	-	-
IL-6	1.89	1.43-2.50	<0.001	1.74	1.18-2.56	0.008

[1]Lactate dehydrogenase (LDH), ferritin, tumor necrosis factor-alpha (TNF-α), and interleukin (IL)-6 were log-transformed. Pre-infusion indicates day 0 laboratory value just prior to chimeric antigen receptor (CAR) T-cell infusion. HR: hazard ratio; CI: confidence interval; Hgb: hemoglobin; CRP: C reactive protein.

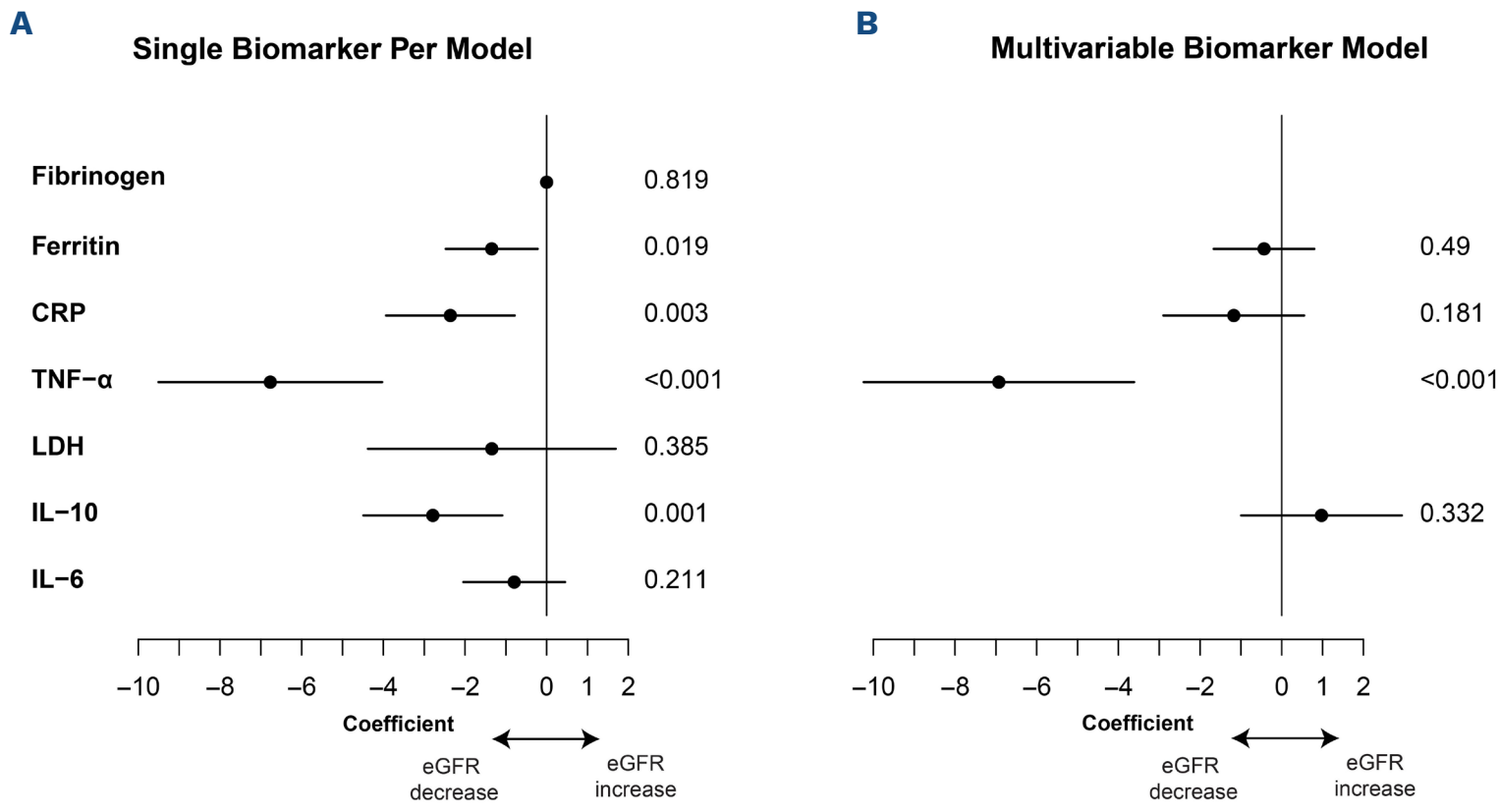


Figure 4. Generalized estimating equation model for longitudinal association of post-infusion predictors of estimated glomerular filtration rate. All generalized estimating equation (GEE) models are adjusted for age at infusion, co-stimulatory domain of the chimeric antigen receptor (CAR) product, and the time from CAR T-cell infusion using a linear and quadratic term. Associations of various biomarkers on estimated glomerular filtration rate(eGFR) (log-transformed) were analyzed from the time of CAR T-cell infusion to day +30. Single biomarker per model (A) and multivariable biomarker (B) analyses of the indicated laboratory parameters are shown. Ferritin, C recative protein (CRP), TNF-α, lactate dehydrogenase (LDH), interleukin (IL)-10, and IL-6 were log-transformed.

14%; HR=4.52 [95% CI:1.93-10.6]; *P*<0.001; *Online Supplementary Table S9*).

Finally, since systemic inflammation, CRS, and ICANS are potentially linked,[37] we studied the impact of CRS and ICANS, as time-dependent covariates, on AKI. Any grade CRS (HR=2.59 [95% CI: 1.13-5.97]; *P*=0.025) and any grade ICANS (HR=3.07 [95% CI: 1.53-6.16]; *P*=0.002) were significantly associated with AKI. Tocilizumab administration was also associated with increased AKI risk (HR=4.05 [95% CI: 1.94-8.46]; *P*=<0.001). Overall, our findings suggest that systemic inflammation is a prominent risk factor for AKI in patients receiving CAR T-cell therapy.

Implications of acute kidney injury

To compare disease-related outcomes of patients in the cohort, we calculated PFS and OS in patients who developed AKI compared to those who did not. Univariable Cox regression analysis using AKI as a time-dependent covariate demonstrated that patients who developed any AKI through day 100 experienced significantly lower PFS (HR=2.63 [95% CI: 1.79-3.87]; *P*<0.001) and OS (HR=3.36 [95% CI: 2.25-5.00]; *P*<0.001). Among patients who developed grade ≥2 AKI, there was also significantly lower PFS (HR=3.14 [95% CI: 1.89-5.24]; *P*<0.001) and OS (HR=4.18 [95% CI: 2.49-7.02]; *P*<0.001). To further investigate this difference, we analyzed

AKI as a time-dependent covariate in a cox regression model for neutropenia and did not find a significant association (*Online Supplemenatry Table S6*). Thus, lymphoma patients who experience renal injury after CD19 CAR T-cell therapy have inferior survival, which is not driven by neutropenia.

Discussion

Renal injury, while recognized as a complication of cancer treatments, remains underexplored in the context of CAR T-cell therapy, a transformative approach in oncology. Addressing this gap, our study harnesses both global and institutional data sources to shed light on kidney dysfunction following CAR T-cell therapy. Through a detailed pharmacovigilance analysis of nearly 6,000 adverse event reports from the FDA's database for patients treated with CAR T, we uncovered a disproportionately high incidence of AKI in comparison to other treatments. Our examination of a cohort of 399 lymphoma patients, the largest group studied to date, revealed that AKI is a prevalent issue, affecting 10% of patients. Significantly, our analysis pinpointed cytokines associated with systemic inflammation as key contributors to the development of AKI. The observation that patients with post-infusion renal injury faced reduced overall survival highlights the importance of preemptive strategies to mitigate this risk, emphasizing the importance of understanding and addressing renal toxicity in the era of CAR T-cell therapy.

Consistent with our previously published retrospective series of 46 adult patients with NHL treated with CD19 CAR T cells,[22] we find that most AKI events after CAR T-cell infusion are grade 1 and that most patients recover from these events within 3 months. Median time to any AKI was 9 days in our cohort, relative to 2.5 days in our pharmacovigilance analysis, likely reflecting heterogenous AKI definitions in the FAERS database. In contrast to a recently published analysis,[24] we include LBCL patients treated with liso-cel, which is crucial due to the expanded use of this product in patients with baseline renal dysfunction. Our large and diverse patient cohort includes patients with other lymphoma subtypes including MCL, which historically necessitates aggressive upfront platinum-containing chemotherapy regimens followed by auto-HCT in a subset of patients. The study shows that baseline renal dysfunction leading into CAR T-cell therapy is not associated with differences in survival or toxicity outcomes, though this may reflect the small number of patients with stage 3 CKD in our cohort.

Our analysis demonstrates that readily available biomarkers reflecting physiological reserve, disease burden, and systemic inflammation may inform on renal injury risk. Intriguingly, we are the first to determine that hypoalbuminemia is strongly associated with risk of AKI after CAR T-cell therapy. Low serum albumin is frequently seen in patients with critical illness and is considered a negative acute phase reactant.[38] In the setting of elevated serum cytokines, increased albumin clearance due to higher capillary permeability and decreased albumin production at the transcriptional level can occur.[38] Thus, baseline systemic inflammation as reflected by decreased albumin and increased CRP, ferritin, TNF-α, and/or IL-6 may predispose to increased renal toxicity after CAR T-cell infusion. Our observation that post-infusion serum TNF-α levels, but not LDH levels, are associated with AKI suggests that inflammatory cytokines, rather than the direct impact of tumor lysis, are important in developing nephrotoxicity. Our finding that TLS was observed in only one patient is consistent with this. We also find that patients who develop any grade CRS or ICANS, including those expereiencing or being treated for high grade toxicity, are at increased risk for AKI. Therefore, inflammation prior to and after CAR T-cell infusion are important predictors of renal injury. Bacteremia occurred in 15% of patients prior to AKI, though nearly half of AKI events occurred in the setting of CRS, suggesting stronger contribution of CAR T cells relative to sepsis-induced cytokine release.

Weaknesses of the study include the retrospective nature of the analysis and inability to profile all medication exposures across the cohort. Since drug-induced renal injury typically occurs just prior to AKI, broad comparison of nephrotoxin exposures between AKI and non-AKI patients is likely to enrich for non-culprit drugs that may not be temporally linked to renal injury. Furthermore, non-AKI patients lack a clear reference point for this comparison. Administration of nephrotoxic drugs within 7 days prior to AKI was observed in patients, though pre-renal causes were the most frequent mechanism of injury in this group, suggesting a contribution of transient hypoperfusion rather than drug-induced pathogenesis. Additionally, PK modeling was used to address the potential impact of fludarabine exposure differences across patients in the cohort, and we did not find an association with AKI.

The association between renal injury and subsequent mortality suggests that AKI is a clinically and prognostically significant complication that is worthy of prospective analysis in future cellular therapy trials. Our finding that patients with baseline renal dysfunction have similar disease outcome and toxicity supports broadening CAR T-cell patient eligibility to include patients with lower baseline eGFR. In fact, one group recently published on the successful and safe administration of lymphodepleting chemotherapy and CD19 CAR T cells in lymphoma patients with pre-existing ESRD.[39] With the recent approval of liso-cel in transplant-ineligible patients, CAR T-cell therapy is now being considered feasible in patients with significant medical comorbidities.[14] We anticipate that a growing number of patients with CKD will undergo CAR T-cell therapy, therefore, our understanding of therapy-associated risks in this population is crucial.

Significant challenges remain in predicting and preventing CAR T-cell therapy-associated toxicities, yet our study supports the use of readily measured and potentially clinically actionable inflammatory biomarkers to inform on renal injury risk after CAR T-cell infusion. The use of steroids has been shown to decrease serum cytokines in older patients prior to the initiation of chemotherapy,[40] thus patients with baseline hypoalbuminemia and elevated serum cytokine levels may benefit from additional therapy prior to CAR T-cell infusion to optimize renal injury risk. Although risk mitigation strategies will require further validation, we advocate for adequate hydration and appropriate avoidance of nephrotoxic agents as able in CAR T-cell recipients, especially those with AKI risk factors.

Disclosures

AB has received compensation for participating in consulting activities with Bristol Myers Squibb. MS served as a paid consultant for McKinsey & Company, Angiocrine Bioscience, Inc., and Omeros Corporation; received research funding from Angiocrine Bioscience, Inc., Omeros Corporation, and Amgen, Inc.; served on ad hoc advisory boards for Kite - a Gilead Company; and received honoraria from i3Health, Medscape, CancerNetwork for CME-related activity and honoraria from IDEOlogy. SG receives research funding from Miltenyi Biotec, Takeda Pharmaceutical Co., Celgene Corp., Amgen Inc., Sanofi, Johnson and Johnson, Inc., Actinium Pharmaceuticals, Inc., and is on the advisory boards for: Kite Pharmaceuticals, Inc., Celgene Corp., Sanofi, Novartis, Johnson and Johnson, Inc., Amgen Inc., Takeda Pharmaceutical Co., Jazz Pharmaceuticals, Inc., Actinium Pharmaceuticals, Inc.. MLP has received compensation for participating in consulting activities with Bristol Myers Squibb, Novartis, Cellectar, and Synthekines. GS received financial compensation for participating in advisory boards at Abbvie, Beigene, BMS, Genentech/Roche, Genmab, Janssen, Kite/Gilead, Loxo/Lilly, Merck, Novartis, and Nurix; he has received financial compensation for consulting from Abbvie, Atbtherapeutics, Beigene, BMS, Debiopharm, Genentech/Roche, Genmab, Innate Pharma, Incyte, Ipsen, Kite/Gilead, Modex, Molecular Partners, Nordic Nanovector, Orna Therapeutics, and Treeline; he received research support from Abbvie, Genentech, Genmab Janssen, Ipsen, and Nurix, which was managed by his institution; he is also a shareholder of Owkin. JHP received consulting fees from Affyimmune Therapeutics, Amgen, Autolus, Be Biopharma, Beigene, Bright Pharmaceutical Services, Inc., Caribou Biosciences, Curocell, Galapagos, In8Bio, Kite, Medpace, Minerva Biotechnologies, Pfizer, Servier, Sobi, and Takeda; he received honoraria from OncLive, Physician Education Resource, and MJH Life Sciences; he serves on scientific advisory board of Allogene Therapeutics, Artiva Biotherapeutics and Green Cross Biopharma; and he received institutional research funding from Autolus, Genentech, Fate Therapeutics, InCyte, Servier, and Takeda. GS has as research funding to the institution from Janssen, Amgen, BMS, Beyond Spring, and GPCR, and is on the DSMB for ArcellX. M-AP reports honoraria from Adicet, Allogene, Allovir, Caribou Biosciences, Celgene, Bristol-Myers Squibb, Equilium, Exevir, ImmPACT Bio, Incyte, Karyopharm, Kite/Gilead, Merck, Miltenyi Biotec, MorphoSys, Nektar Therapeutics, Novartis, Omeros, OrcaBio, Sanofi, Syncopation, VectivBio AG, and Vor Biopharma; he serves on DSMB for Cidara Therapeutics and Sellas Life Sciences, and the scientific advisory board of NexImmune; he has ownership interests in NexImmune, Omeros and OrcaBio; he has received institutional research support for clinical trials from Allogene, Incyte, Kite/Gilead, Miltenyi Biotec, Nektar Therapeutics, and Novartis.

Contributions

AB, VG, IJ and RS designed the study concept, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. AB, VG, JF, SD, IJ and RS contributed to the acquisition, analysis or interpretation of the data. AB, AG and RS drafted the manuscript. AB, RS, AG, JF and SD handled the statistical analysis. IJ and RS were involved insupervision. All authors critically reviewed the manuscript.

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Data-sharing statement

All summary statistics are included in the paper. Data are available upon request form the corresponding author and approval of the IRB.

References

1. Schuster SJ, Svoboda J, Chong EA, et al. Chimeric antigen receptor T cells in refractory B-cell lymphomas. N Engl J Med. 2017;377(26):2545-2554.
2. Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene ciloleucel CAR T-cell therapy in refractory large B-cell lymphoma. N Engl J Med. 2017;377(26):2531-2544.
3. Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in adult relapsed or refractory diffuse large B-cell lymphoma. N Engl J Med. 2019;380(1):45-56.
4. Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019;20(1):31-42.
5. Abramson JS, Palomba ML, Gordon LI, et al. Lisocabtagene maraleucel for patients with relapsed or refractory large B-cell lymphomas (TRANSCEND NHL 001): a multicentre seamless design study. Lancet. 2020;396(10254):839-852.
6. Neelapu SS, Jacobson CA, Oluwole OO, et al. Outcomes of older patients in ZUMA-1, a pivotal study of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2020;135(23):2106-2109.
7. Schuster SJ, Tam CS, Borchmann P, et al. Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. Lancet Oncol. 2021;22(10):1403-1415.
8. Neelapu SS, Jacobson CA, Ghobadi A, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2023;141(19):2307-2315.
9. Wang M, Munoz J, Goy A, et al. KTE-X19 CAR T-cell therapy in relapsed or refractory mantle-cell lymphoma. N Engl J Med. 2020;382(14):1331-1342.
10. Wang M, Munoz J, Goy A, et al. Three-year follow-up of KTE-X19 in patients with relapsed/refractory mantle cell lymphoma, including high-risk subgroups, in the ZUMA-2 study. J Clin Oncol. 2023;41(3):555-567.
11. Locke FL, Miklos DB, Jacobson CA, et al. Axicabtagene ciloleucel as second-line therapy for large B-cell lymphoma. N Engl J Med. 2022;386(7):640-654.
12. Bishop MR, Dickinson M, Purtill D, et al. Second-line tisagenlecleucel or standard care in aggressive B-cell lymphoma. N Engl J Med. 2022;386(7):629-639.
13. Abramson JS, Solomon SR, Arnason J, et al. Lisocabtagene maraleucel as second-line therapy for large B-cell lymphoma: primary analysis of the phase 3 TRANSFORM study. Blood. 2023;141(14):1675-1684.
14. Sehgal A, Hoda D, Riedell PA, et al. Lisocabtagene maraleucel as second-line therapy in adults with relapsed or refractory large B-cell lymphoma who were not intended for haematopoietic stem cell transplantation (PILOT): an open-label, phase 2 study. Lancet Oncol. 2022;23(8):1066-1077.
15. Westin JR, Oluwole OO, Kersten MJ, et al. Survival with axicabtagene ciloleucel in large B-cell lymphoma. N Engl J Med. 2023;389(2):148-157.
16. Perales MA, Anderson LD Jr, Jain T, et al. Role of CD19 chimeric antigen receptor T cells in second-line large B cell lymphoma: lessons from phase 3 trials. An expert panel opinion from the American Society for Transplantation and Cellular Therapy. Transplant Cell Ther. 2022;28(9):546-559.
17. Kanate AS, Majhail N, DeFilipp Z, et al. Updated indications for immune effector cell therapy: 2023 guidelines from the American Society for Transplantation and Cellular Therapy. Transplant Cell Ther. 2023;29(10):594-597.
18. Locke FL, Rossi JM, Neelapu SS, et al. Tumor burden, inflammation, and product attributes determine outcomes of axicabtagene ciloleucel in large B-cell lymphoma. Blood Adv. 2020;4(19):4898-4911.
19. Wudhikarn K, Pennisi M, Garcia-Recio M, et al. DLBCL patients treated with CD19 CAR T cells experience a high burden of organ toxicities but low nonrelapse mortality. Blood Adv. 2020;4(13):3024-3033.
20. Jacobson CA, Hunter BD, Redd R, et al. Axicabtagene ciloleucel in the non-trial setting: outcomes and correlates of response, resistance, and toxicity. J Clin Oncol. 2020;38(27):3095-3106.
21. Rejeski K, Perez A, Sesques P, et al. CAR-HEMATOTOX: a model for CAR T-cell-related hematologic toxicity in relapsed/refractory large B-cell lymphoma. Blood. 2021;138(24):2499-2513.
22. Gutgarts V, Jain T, Zheng J, et al. Acute kidney injury after CAR-T cell therapy: low incidence and rapid recovery. Biol Blood Marrow Transplant. 2020;26(6):1071-1076.
23. Kanduri SR, Cheungpasitporn W, Thongprayoon C, et al. Systematic review of risk factors and incidence of acute kidney injury among patients treated with CAR-T cell therapies. Kidney Int Rep. 2021;6(5):1416-1422.
24. Wood AC, Perez AP, Arciola B, et al. Outcomes of CD19-targeted chimeric antigen receptor T cell therapy for patients with reduced renal function including dialysis. Transplant Cell Ther. 2022;28(12):829.e1-829.e8.
25. Mozzicato P. Standardised MedDRA queries: their role in signal detection. Drug Saf. 2007;30(7):617-619.
26. Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf. 2009;18(6):427-436.
27. Norén GN, Hopstadius J, Bate A. Shrinkage observed-to-expected ratios for robust and transparent large-scale pattern discovery. Stat Methods Med Res. 2013;22(1):57-69.
28. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. J Biomed Inform. 2019;95:103208.
29. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C-based equations to estimate GFR without race. N Engl J Med. 2021;385(19):1737-1749.
30. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant. 2019;25(4):625-638.
31. Fabrizio VA, Boelens JJ, Mauguen A, et al. Optimal fludarabine lymphodepletion is associated with improved outcomes after CAR T-cell therapy. [Erratum in Blood Adv. 2023 Jun 27;7(12):2924]. Blood Adv. 2022;6(7):1961-1968.
32. Scordo M, Flynn JR, Gonen M, et al. Identifying an optimal fludarabine exposure for improved outcomes after axi-cel therapy for aggressive B-cell non-Hodgkin lymphoma. Blood Adv. 2023;7(18):5579-5585.
33. Langenhorst JB, Dorlo TPC, van Maarseveen EM, et al. Population pharmacokinetics of fludarabine in children and adults during conditioning prior to allogeneic hematopoietic cell transplantation. Clin Pharmacokinet. 2019;58(5):627-637.
34. International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's

lymphoma. N Engl J Med. 1993;329(14):987-994.
35. Hammond DA, Smith MN, Li C, Hayes SM, Lusardi K, Bookstaver PB. Systematic review and meta-analysis of acute kidney injury associated with concomitant vancomycin and piperacillin/tazobactam. Clin Infect Dis. 2017;64(5):666-674.
36. Andronesi A, Sorohan B, Burcea A, et al. Incidence and risk factors for acute kidney injury after allogeneic stem cell transplantation: a prospective study. Biomedicines. 2022;10(2):262.
37. Faramand RG, Lee SB, Jain MD, et al. Baseline serum inflammatory proteins predict poor CAR T outcomes in diffuse large B-cell lymphoma. Blood Cancer Discov. 2024;5(2):106-113.
38. Levitt DG, Levitt MD. Human serum albumin homeostasis: a new look at the roles of synthesis, catabolism, renal and gastrointestinal excretion, and the clinical value of serum albumin measurements. Int J Gen Med. 2016;9:229-255.
39. Hunter BD, Hoda D, Nguyen A, et al. Successful administration of chimeric antigen receptor (CAR) T-cell therapy in patients requiring hemodialysis. Exp Hematol Oncol. 2022;11(1):10.
40. Lin RJ, Owens CN, Drill E, et al. Prephase rituximab/prednisone therapy and aging-related, proinflammatory cytokine milieu in older, vulnerable patients with newly diagnosed diffuse large B-cell lymphoma. Haematologica. 2022;107(5):1144-1152.