Incidence and Risk Factors for Acute Kidney Injury After Chimeric Antigen Receptor T-Cell Therapy

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Abstract

Objective: To evaluate the association of baseline and postinfusion patient characteristics with acute kidney injury (AKI) in the month after chimeric antigen receptor T-cell (CAR-T) therapy.

Methods: We retrospectively reviewed records of 83 patients with non-Hodgkin lymphoma undergoing CAR-T therapy (axicabtagene ciloleucel) between June 2016 and November 2020. Patients were followed up to 1 month after treatment. Post-CAR-T AKI was defined as a more than 1.5-fold increase in serum creatinine concentration from baseline (on the day of CAR-T infusion) at any time up to 1 month after CAR-T therapy.

Results: Of 83 patients, 14 (17%) developed AKI during follow-up. At 1 month after CAR-T infusion, 10 of 14 (71%) AKI events had resolved. Lower baseline estimated glomerular filtration rate, use of intravenous contrast material, tumor lysis prophylaxis, higher peak uric acid and creatine kinase levels during follow-up, and change in lactate dehydrogenase from baseline to peak level within 1 month after initiation of CAR-T therapy were significantly associated with AKI incidence during follow-up. Incidence of AKI was also higher in patients who received higher doses of corticosteroids and tocilizumab.

Conclusion: Acute kidney injury occurred in approximately 1 in 6 patients who received axicabtagene ciloleucel for non-Hodgkin lymphoma. Patients with high tumor burden receiving higher total doses of corticosteroids or tocilizumab should be closely monitored for development of AKI. Lower baseline kidney function at CAR-T initiation, exposure to contrast material, and progressive increase in levels of tumor lysis markers (uric acid, lactate dehydrogenase, creatine kinase) after CAR-T infusion may predict risk of AKI during the 1 month after infusion.

C himeric antigen receptor T-cell (CAR-T) therapy is a promising new immunotherapy for refractory and relapsed malignant neoplasms, such as certain non-Hodgkin lymphomas (NHLs), acute lymphoblastic leukemias, and multiple myeloma. This therapy involves the reprogramming of T cells in vitro to direct them against specific antigens on neoplastic cells, such as CD19 in the case of aggressive B-cell lymphomas and B-cell maturation antigen in multiple myeloma. As this breakthrough therapy has achieved success with the potential to induce long-lasting remissions, the number of indications for its use will continue to expand.

Despite the significant therapeutic potential of CAR-T therapy for inducing remissions in hematologic malignant neoplasms, high rates of treatment-related toxicity,
such as cytokine release syndrome (CRS), immune effector cell–associated neurotoxicity syndrome (ICANS), cytopenias, and electrolyte abnormalities, have been reported in these patients. Previous studies also have found CAR-T infusion to be associated with renal toxicity, particularly acute kidney injury (AKI). Kidney injury, especially in conjunction with CRS, may lead to the need for renal replacement therapy (RRT) and culminate in death.

Identifying risk factors for AKI in CAR-T recipients could enable preemptive management to help reduce the incidence of AKI and its subsequent adverse outcomes. Prior studies evaluating AKI in patients with NHL who received CAR-T therapy have not defined AKI clearly or have had only small numbers of patients. There also are insufficient data from larger cohorts of patients with NHL receiving anti-CD19 CAR-T therapy on risk factors or biomarkers that may predict AKI. The aim of our study therefore was to investigate the associations of demographic and clinical parameters, comorbidities, levels of blood biomarkers, and development of AKI during the first month after CAR-T therapy in patients with refractory NHL. We also assessed the differences in adverse effects and medication use by AKI status.

METHODS

Study Participants
In this single-center, retrospective, observational study, we manually chart reviewed and abstracted the electronic health records of all patients who had received anti-CD19 CAR-T therapy (axicabtagene ciloleucel) for aggressive NHL from June 2016 to November 2020 at Mayo Clinic in Rochester, Minnesota. Patients who were younger than 18 years, did not provide research authorization, or were experiencing an unresolved episode of AKI at the initiation of CAR-T infusion were excluded from the cohort. This study was approved by Mayo Clinic Institutional Review Board.

Data Collection
Demographic and clinical characteristics, comorbidities, medication use, and laboratory measurements were abstracted from patients’ electronic medical records by a trained team of nephrology fellows and research trainees (J.P.T.-G., J.M., and N.F.) who were overseen by the study physician (S.M.H.). Outcome measures were abstracted from the immune effector cell compliance program database. Baseline data were collected at the time of CAR-T therapy initiation, and follow-up data were collected up to 31 days after initiation of CAR-T therapy (the mandatory follow-up period per CAR-T protocol). Laboratory data before chemotherapy were collected if tests were performed within 6 months before administration of lymphodepleting chemotherapy, which is given 5 to 7 days before CAR-T infusion per protocol.

Demographic and clinical characteristics collected at baseline included age, sex, race, ethnicity, body mass index, and estimated glomerular filtration rate (eGFR) calculated by the Chronic Kidney Disease Epidemiology Collaboration equation. Medication data obtained consisted of allopurinol or rasburicase prophylaxis at baseline and type of nephrotoxin (eg, antibiotics, nonsteroidal anti-inflammatory drugs, intravenous [IV] contrast medium), if administered. Preexisting comorbidities collected included stage of chronic kidney disease (CKD; per clinic records, defined as meeting criteria for CKD stage 3a or higher according to the Kidney Disease Outcomes Quality Initiative guidelines for at least 3 months before CAR-T therapy), type 2 diabetes mellitus, hypertension, coronary artery disease, and heart failure. Baseline as well as clinically relevant peak or nadir levels during follow-up after CAR-T infusion were collected for serum creatinine (SCr), sodium, potassium, phosphorus, magnesium, bicarbonate, and other biomarkers, such as serum ferritin, creatine kinase (CK), C-reactive protein (CRP), and lactate dehydrogenase (LDH). The details
Incident AKI was defined as a 1.5-fold increase in SCr concentration from baseline value (on the day of CAR-T infusion) during the follow-up period. Severity of AKI was graded according to the Kidney Disease: Improving Global Outcomes guidelines (ie, stage 1: increase in SCr of 1.5- to 1.9-fold from baseline; stage 2: increase in SCr of 2.0- to 2.9-fold from baseline; and stage 3: increase in SCr ≥3.0-fold from baseline, or requiring RRT, or SCr concentration ≥4.0 mg/dL [to convert to μmol/L, multiply by 88.4]). We further classified the AKI event as prerenal (resolved with improved fluid intake or IV fluid support within 72 hours of onset), renal (persisted for >72 hours or not responsive to IV or oral fluids), or postrenal (evidence of radiologic obstruction along the urinary tract, with AKI resolving after removal of the obstruction). The resolution of an AKI episode was defined as a return of the SCr concentration to within 25% of the baseline value. Urinalysis data from 1 week before and up to 1-month follow-up from initiation of the CAR-T therapy period were abstracted for all patients who developed AKI.

Adverse events collected during follow-up included CRS, neurotoxicity (grading criteria for both mentioned in Supplemental material), and need for intensive care unit (ICU) admission. Administration and doses of corticosteroids and tocilizumab for the management of CRS during the 1 month of follow-up were also recorded. Doses of either dexamethasone or methylprednisolone were converted to cumulative oral prednisone equivalents (in milligrams). Doses of tocilizumab (anti—interleukin 6 monoclonal antibody) were calculated in standard doses of 8 mg/kg. Dates of admission, discharge, and readmission to the hospital after CAR-T therapy were recorded to compute the durations of hospital admissions. Not all patients initiating CAR-T therapy were admitted to the hospital; however, consistent with CAR-T protocol, every patient was observed daily for at least 1 month at an outpatient station to screen for post-therapy adverse events. Mortality data were collected up to 6 months after CAR-T therapy or before March 2021, whichever came first.

**Statistical Analyses**

Data are presented as mean (standard deviation) for normally distributed or median (interquartile range [IQR]) for nonnormally distributed continuous variables and number (percentage) for categorical variables. *P* values assessing patients’ demographic, clinical, and laboratory differences across AKI status were derived by the 2-sample equal variance *t*-test for normally distributed or Wilcoxon rank sum test for nonnormally distributed continuous variables. The χ² test was used for categorical variables. Both absolute and percentage changes in serum values and inflammatory markers from baseline to peak or nadir were calculated. Acute kidney injury and CRS-free days within the first month were calculated by subtracting the duration of each event within a 31-day follow-up period. If a patient died within the 31-day window, their number of days free of the event was set at 0 to correspond to the worst possible outcome.

The details of the statistical methods used for computing the associations between adverse events, medication use, and incident AKI can be found in the Supplemental material.

**RESULTS**

**Baseline Characteristics**

There were 83 patients meeting inclusion criteria for analysis. None of the patients in this study had ongoing AKI at the time of CAR-T infusion. Baseline demographic and clinical characteristics are reported in Table 1. Patients had a mean (SD) age of 55.2 (12.3) years at initiation of CAR-T therapy, with a majority being White and male (Table 1). Lower eGFR (mean [SD], 80.4 [26.9] mL/min per 1.73 m² in the AKI group vs 93.5 [21.2] mL/min per 1.73 m² in the non-AKI group; *P*=.047), higher rates of
initiation of allopurinol or rasburicase prophylaxis (10 [71.4%] in the AKI group vs 26 [37.7%] in the non-AKI group; \( P = .020 \)), and IV administration of contrast medium in addition to other nephrotoxic medications (9 [64.3%] vs 20 [29.0%] in the AKI vs non-AKI groups; \( P = .012 \)) at the time of CAR-T infusion were significantly associated with increased risk for incident AKI after therapy.

Of the 8 patients with CKD before CAR-T therapy, only 2 patients (25%) went on to develop AKI during follow-up.

### AKI Incidence After CAR-T Therapy

During the course of 31 days after CAR-T initiation, 14 patients (17%) developed an incident AKI event; 11 (78.5%) had stage 1, 1 (7.2%) had stage 2, and 2 (14.3%) had...
stage 3 AKI. AKI was classified as renal intrinsic in 10 patients (71.4%) and prerenal in 2 patients (14.2%), and 2 patients (14.2%) were thought to have obstructive AKI secondary to tumor progression. All patients with stage 2 or stage 3 AKI had episodes lasting more than 72 hours. Two patients required RRT, 1 of whom died within 48 hours of onset of AKI of HLH/MAS in the setting of severe CRS. Median (IQR) time to AKI was 7.5 (6.0 to 15.0) days after initiation of CAR-T therapy, and median (IQR) number of AKI-free days within 1 month after CAR-T therapy was 24 (20 to 26) days. At day 31, 10 of 14 patients (71%) had resolved their AKI events. Urinalysis results for the AKI patients can be found in Supplemental Table 1 (available online at http://www.mayoclinicproceedings.org).

Electrolytes and Biomarkers Before and After CAR-T Therapy
Baseline and follow-up peak and nadir serum electrolyte values and other biomarkers are presented in Table 2. Of the electrolytes, bicarbonate nadir levels were lower in the AKI group compared with the non-AKI group (median [IQR], 19 [18 to 23] mmol/L vs 21 [20 to 22] mmol/L; P=.042). The most encountered electrolyte disturbances in the follow-up period were hyponatremia, hypokalemia, and hypophosphatemia (Supplemental Table 2, available online at http://www.mayoclinicproceedings.org). Of the biomarkers, peak serum uric acid levels during follow-up were found to be higher in patients with AKI (median [IQR], 5.6 [4.9 to 7.1] mg/dL; to convert to mmol/L, multiply by 0.0595) compared with those without AKI (median [IQR], 4.7 [3.8 to 5.5 mg/dL]; P=.015). Higher rates of incident AKI were also associated with higher peak CK levels (median [IQR], 59 [46 to 630] U/L; to convert to μkat/L, multiply by 0.0167) for AKI patients than for non-AKI patients (median [IQR], 43 [29 to 67] U/L; P=.016).

Absolute and percentage changes in serum measurements of uric acid, CK,
LDH, ferritin, and CRP from baseline to peak or nadir are reported in Table 3. Both absolute and percentage changes in LDH levels were higher for AKI patients compared with non-AKI patients (median [IQR] absolute change: 34 [0 to 150] U/L vs 2 [0 to 25] U/L [to convert to μkat/L, multiply by 0.0167]; median [IQR] percentage change: 21.3% [0% to 34.3%] vs 0.9% [0% to 10%]; \( P = .011 \). Results were similar in comparing absolute and percentage changes of LDH levels from before lymphodepleting chemotherapy to peak across AKI status as a sensitivity analysis (data not shown). In AKI patients, the median (IQR) number of days to reach peak LDH levels was 6.0 (0.0 to 21.0) days. The timing of AKI and CRS onset and duration by LDH levels in the 14 patients who developed AKI are shown in Supplemental Figure 1 (available online at http://www.mayoclinicproceedings.org). Only 4 patients who developed AKI did not experience increases in LDH levels from baseline in the 31 days after CAR-T therapy; of these 4 patients, 2 patients (50%) demonstrated increases in LDH levels from before lymphodepleting chemotherapy.

### CRS, Neurotoxicity, Adverse Outcomes, and Medications After CAR-T Therapy

During follow-up, 71 patients (85.5%) developed grade 1 or higher CRS, with grade 1 and grade 2 accounting for most of these cases (Table 4). Whereas the odds of an incident AKI event increased with more severe CRS grades, results did not reach statistical significance. In those with CRS, the median (IQR) onset time of CRS was 3 (1 to 5) days after CAR-T infusion, and the median (IQR) number of CRS-free days within 1 month after CAR-T therapy was 26 (24 to 27) days. In the 12 patients experiencing both an AKI and CRS event, AKI occurred a median (IQR) of 4 (1 to 11.5) days after CRS onset, and 4 patients (33.3%) had an

<table>
<thead>
<tr>
<th>Laboratory measure</th>
<th>No AKI (n=69)</th>
<th>AKI (n=14)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Uric acid (mg/dL)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute change</td>
<td>0.4 (0.0-0.9)</td>
<td>1.0 (0.0-2.2)</td>
<td>.055</td>
</tr>
<tr>
<td>Percentage change</td>
<td>9.2 (0.0-21.1)</td>
<td>14.0 (0.0-66.7)</td>
<td>.15</td>
</tr>
<tr>
<td><strong>Creatine kinase (U/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute change</td>
<td>5.0 (0.0-40)</td>
<td>26 (0.0-3568)</td>
<td>.58</td>
</tr>
<tr>
<td>Percentage change</td>
<td>20.8 (0.0-94.6)</td>
<td>96.3 (0.0-6861)</td>
<td>.47</td>
</tr>
<tr>
<td><strong>LDH (U/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute change</td>
<td>2.0 (0.0-25)</td>
<td>34 (0.0-150)</td>
<td>.011</td>
</tr>
<tr>
<td>Percentage change</td>
<td>0.9 (0.0-10.0)</td>
<td>21.3 (0.0-34.3)</td>
<td>.010</td>
</tr>
<tr>
<td><strong>Ferritin mcg/L</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute change</td>
<td>335 (115-1305)</td>
<td>395 (55-2645)</td>
<td>.93</td>
</tr>
<tr>
<td>Percentage change</td>
<td>63.7 (33.6-155.8)</td>
<td>96.1 (139-221.3)</td>
<td>.98</td>
</tr>
<tr>
<td><strong>CRP (mg/L)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute change</td>
<td>72 (26-133)</td>
<td>45 (9.9-162)</td>
<td>.97</td>
</tr>
<tr>
<td>Percentage change</td>
<td>261.2 (78.7-717.1)</td>
<td>332.7 (44.4-755.6)</td>
<td>.87</td>
</tr>
</tbody>
</table>

*AKI, acute kidney injury; CRP, C-reactive protein; IQR, interquartile range; LDH, lactate dehydrogenase.

*To convert uric acid levels to mmol/L, multiply by 0.0595; to convert creatine kinase and LDH values to μkat/L, multiply by 0.0167; to convert CRP values to nmol/L, multiply by 9.524.

*P values in bold denote statistical significance at the .05 α level. P values were derived using the Wilcoxon rank sum test because of skewedness of the laboratory change measures.

*All serum and inflammatory marker values collected during follow-up are peak values.

*Baseline uric acid level was determined before lymphodepleting chemotherapy because of the effect on serum uric acid levels.
AKI episode that occurred after the resolution of CRS (Supplemental Figure 1). After CAR-T therapy, ICANS (neurotoxicity) was seen in 44 of the patients (53%), with risk of AKI observed to be increased by severity grade, but it was not statistically significant. Higher rates of corticosteroid administration were associated with incident AKI events (9 [64.3%] vs 22 [31.9%] patients with vs without AKI; \( P = .028 \)) as well as with a higher dose of corticosteroids (median [IQR], 1067 [784 to 3950] mg for AKI patients vs 301 [67 to 934] mg for non-AKI patients; \( P = .013 \)). A higher number of tocilizumab doses for adverse event management was also significantly associated with risk of an AKI event in the 31-day follow-up period (\( P = .005 \)). Of the patients who did not develop CRS, none received corticosteroids or tocilizumab. Of the 71 patients with CRS, 31 (43.7%) received corticosteroids, with a median (IQR) dose of 667 (133 to 2050) mg; 28 (39.4%) received tocilizumab. There was also a significant positive association between the CRS maximum grade and number of tocilizumab doses (Spearman rank correlation, 0.59; \( P < .001 \)). Similar findings were seen in comparing medication use in patients with and without neurotoxic effects. See Supplemental Figures 2 and 3 (available online at http://www.mayoclinicproceedings.org) for corticosteroid and number of tocilizumab doses across CRS grade, neurotoxicity grade, and AKI status.

Of the 83 patients, there were 19 deaths during 6 months of follow-up after CAR-T initiation. Causes of death included disease progression, sepsis, and severe adverse events after CAR-T therapy. Estimated survival (95% CI) was 91% (85% to 98%) at 3 months and 75% (66% to 86%) at 6 months (Supplemental Figure 4A, available online at http://www.mayoclinicproceedings.org). Of the 14 patients who experienced an AKI event during 31 days of follow-up after CAR-T initiation, there were 4 deaths during 6 months of follow-up after the AKI event (Supplemental Figure 4B), with estimated survival of 76% (56% to 100%) at 3 months and 67% (44% to 100%) at 6 months.

**DISCUSSION**

As the availability and popularity of CAR-T therapy for cancer treatment increase, it is important to evaluate the incidence rates and risk factors for renal toxicity.\(^1\)\(^-\)\(^3\)\(^,\)\(^4\)\(^-\)\(^5\)\(^,\)\(^8\)\(^-\)\(^9\) The rate of incident AKI at 1 month after CAR-T infusion in our cohort was 17%, with most cases resolving at the end of follow-up. This incidence is comparable to that in previous studies\(^5\)\(^-\)\(^8\) but lower than the incidence of 30% reported by Gutgarts et al.\(^5\) The study design and durations of follow-up were not the same between the 2 studies, however, probably explaining some of the differences in results. Lower eGFR at initiation of CAR-T therapy, use of tumor lysis drug prophylaxis, and exposure to IV contrast medium in patients undergoing CAR-T infusion were significantly associated with the development of AKI in our cohort. Furthermore, CRS and ICANS occurred equally in AKI and non-AKI patients, with no differences in severity of CRS between

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**FIGURE.** Absolute and percentage changes in lactate dehydrogenase (LDH) levels from baseline to peak. The y-axis is displayed on the log scale. Blue points and boxplots denote patients with acute kidney injury (AKI). Green points and boxplots denote patients without AKI. Boxes denote the median and interquartile range of the data. Whiskers denote the range of the data.
the 2 groups. The use of corticosteroids and tocilizumab, however, was associated with more AKI.

In our study, most of the AKI cases were adjudicated to have had initial prerenal insults secondary to inflammatory capillary leak or a combination of fluid loss and insufficient fluid intake. Only 1 patient in the entire cohort developed tumor lysis syndrome–associated AKI and recovered within 1 week of starting supportive care. One other patient developed HLH/MAS and died in association with severe lactic acidemia. Therefore, in most patients developing post–CAR-T AKI, early aggressive management and preemptive measures, such as avoiding fluid depletion and nephrotoxins, may decrease risk of kidney injury.

This study is underpowered to accurately report an association of post–CAR-T AKI with preexisting CKD, but the association of lower baseline eGFR reflects that patients with lower renal reserve, independent of having CKD, are at risk for development of AKI after CAR-T therapy. This is an important finding as candidates for CAR-T therapy presenting with decreased kidney function will need to be closely monitored for incident AKI. Whereas exposure to contrast medium was significantly higher in the AKI group compared with the non-AKI group, it is difficult to comment on the role of other nephrotoxins because their timelines of administration could not be well characterized. As it might not always be feasible to avoid other nephrotoxic medications during CAR-T therapy, IV administration of contrast medium should be avoided if feasible. Our study also found that a higher proportion of patients who developed AKI

### TABLE 4. Adverse Events and Medication Use Within 31 Days After Initiation of CAR-T Therapy, Overall and by AKI Status

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>No AKI (n=69)</th>
<th>AKI (n=14)</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>P&lt;sup&gt;trend&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRS incidence</td>
<td>59 (85.5)</td>
<td>12 (85.7)</td>
<td>1.02 (0.20-5.24)</td>
<td>.98</td>
<td>.29</td>
</tr>
<tr>
<td>CRS maximum grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.22</td>
</tr>
<tr>
<td>None</td>
<td>10 (14.5)</td>
<td>2 (14.3)</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>34 (49.3)</td>
<td>5 (35.7)</td>
<td>0.74 (0.12-4.38)</td>
<td>.21</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>24 (34.8)</td>
<td>6 (42.9)</td>
<td>1.25 (0.22-7.28)</td>
<td>.77</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td></td>
<td>.005</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1 (1.4)</td>
<td>1 (7.1)</td>
<td>5.00 (0.21-118)</td>
<td>.26</td>
<td></td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>36 (52.2)</td>
<td>8 (57.1)</td>
<td>1.22 (0.38-3.90)</td>
<td>.73</td>
<td></td>
</tr>
<tr>
<td>Grade of neurotoxicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.22</td>
</tr>
<tr>
<td>None</td>
<td>33 (47.8)</td>
<td>6 (42.9)</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15 (21.7)</td>
<td>1 (7.1)</td>
<td>0.37 (0.04-3.32)</td>
<td>.17</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>13 (18.8)</td>
<td>3 (21.4)</td>
<td>1.27 (0.28-5.85)</td>
<td>.96</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5 (7.2)</td>
<td>3 (21.4)</td>
<td>3.30 (0.62-17.6)</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3 (4.3)</td>
<td>1 (7.1)</td>
<td>1.83 (0.16-20.7)</td>
<td>.68</td>
<td></td>
</tr>
<tr>
<td>Need for ICU admission</td>
<td>20 (29.0)</td>
<td>6 (42.9)</td>
<td>1.84 (0.57-5.98)</td>
<td>.31</td>
<td></td>
</tr>
<tr>
<td>Receiving corticosteroids (dose &gt;0)</td>
<td>22 (31.9)</td>
<td>9 (64.3)</td>
<td>3.85 (1.15-12.8)</td>
<td>.028</td>
<td></td>
</tr>
<tr>
<td>Total corticosteroid dose (mg)</td>
<td>301 (67-934)</td>
<td>1067 (784-3950)</td>
<td>1.00 (1.00-1.001)</td>
<td>.013</td>
<td></td>
</tr>
<tr>
<td>No. of standard tocilizumab doses (in 8-mg/kg units)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>.005</td>
</tr>
<tr>
<td>None</td>
<td>50 (72.5)</td>
<td>5 (35.7)</td>
<td>Reference</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>16 (23.2)</td>
<td>5 (35.7)</td>
<td>3.13 (0.80-12.2)</td>
<td>.49</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 (2.9)</td>
<td>3 (21.4)</td>
<td>15.0 (2.01-112)</td>
<td>.14</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 (1.4)</td>
<td>1 (7.1)</td>
<td>10.0 (0.54-186)</td>
<td>.49</td>
<td></td>
</tr>
</tbody>
</table>

*AKI*, acute kidney injury; CAR-T, chimeric antigen receptor T cell; CRS, cytokine release syndrome; ICU, intensive care unit; OR, odds ratio.

*Categorical variables are presented as number (percentage). Continuous variables are presented as median (interquartile range). P values in bold denote statistical significance at the .05 level. P values were derived using logistic regression.

Overall P values for CRS maximum grade, neurotoxicity grade, and tocilizumab dose were assessed by trend tests.
had received tumor lysis prophylaxis before CAR-T therapy. This is an interesting finding as the initiation of prophylaxis was based on the clinical assessment of tumor burden before CAR-T infusion. It therefore would be prudent to specifically watch such patients for subsequent kidney injury. Higher peak CK levels in the follow-up period and higher peak uric acid levels after lymphodepleting chemotherapy similarly were also associated with incident AKI. These findings reinforce the preceding findings that greater tumor burden with high cell turnover may increase the risks of renal adverse events after CAR-T therapy.21,22 Similar to what has been reported in previous studies, we did not find significant associations between serum ferritin or CRP levels and incidence of AKI.4,5 The rates of hypophosphatemia were higher in patients with AKI than in those without AKI, but results were nonsignificant. Larger studies would be needed to investigate whether electrolyte changes during follow-up can be predictive of post–CAR-T AKI.

Patients in the AKI cohort additionally had a higher magnitude of change in LDH levels from baseline compared with those who did not develop AKI. As LDH is an injury biomarker, increased levels of LDH after CAR-T therapy could be a function of several mechanisms, such as severity of CRS affecting different organs systems including kidneys, HLH/MAS, tumor lysis and lymphoma aggressiveness, concomitant infection, and decrease in renal clearance. The median time to LDH peak for AKI patients was 6 days; therefore, a sharp increase in serum LDH concentration during the first week after initiation of CAR-T therapy should raise clinician awareness to a patient’s increased risk of AKI. Future prospective studies involving serial collections of laboratory measures after initiation of CAR-T therapy are needed to validate these findings.

In a systematic review, Kanduri et al6 found that higher grades of CRS were significantly associated with AKI after CAR-T infusion. Whereas our study found higher odds of incident AKI with increasing CRS grades, the results were not significant. This could be due in part to our low rate of CRS events grade 3 or higher, which is considerably lower than the estimates of 13% reported in previous publications.4,5 This discrepancy in CRS profiles may be partially explained by the evolving practice in the management of CRS and changes in grading.23 Close monitoring of serum biomarkers, fluid support, and early initiation of corticosteroids or tocilizumab during CRS episodes can be useful to reduce the incidence of AKI. In AKI patients without a CRS event, AKI was due to significant volume depletion secondary to diuretics and suspected obstructive uropathy. Thus, for a subset of patients, the cause of kidney injury after CAR-T infusion may not necessarily be severe capillary leak secondary to immune response, and management would need to be individualized in such cases.

An intriguing finding in our study was the significant association between incident AKI and administration of higher doses of tocilizumab and corticosteroids for adverse event management after CAR-T. A higher total dose of corticosteroids and the number of tocilizumab doses in the AKI group by the treating physician could be surrogate markers for the clinical severity of CRS and neurotoxicity after CAR-T therapy that is not completely captured by the current adverse event grading. Although this association is not consistent with our findings as we could not find an association between AKI and CRS, it may reflect recognition by the treating hematologist of factors that were not captured with this retrospective study. The previous study by Gutgarts et al5 did not find an association between incident AKI and follow-up peak interleukin 6 values. However, their cohort was smaller and levels of inflammatory cytokines were not measured at the time of AKI development.

Last, contrary to previous findings, the lack of association of AKI incidence with ICU admissions could be due to Mayo Clinic’s CAR-T service structure, which uses a hospital-based outpatient follow-up system. This service structure results in earlier interventions in response to

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suspected CRS and AKI episodes, which could translate into fewer ICU admissions. The 3-month and 6-month survival estimates after an AKI event were similar to the rates after initiation of CAR-T therapy, and we would need larger cohorts in the future to confirm our findings.

This is the largest study, to our knowledge, to investigate the association between serum laboratory markers and incidence of AKI after initiation of CAR-T therapy in patients with NHL. It corroborates some findings from previous studies and adds to the knowledge of predictors for AKI in the setting of CAR-T therapy. However, our study has limitations. Our patient cohort reflects the midwestern, largely White population; therefore we cannot generalize these findings to other populations of patients. Because of the retrospective nature of our study, data including laboratory measures were limited by availability. Our sample size did not allow multivariable adjusted analyses. Larger cohort studies are needed to develop multivariable risk prediction models for incident AKI.

CONCLUSION
Approximately 1 in 6 patients who receive CAR-T therapy for resistant NHL develop AKI in the first month after infusion. Patients with high tumor burden receiving larger doses of corticosteroids or tocilizumab should be closely monitored for development of AKI. Baseline eGFR, IV administration of contrast medium, follow-up uric acid and CK levels, and changes in LDH levels may be useful markers to identify patients at increased risk of AKI and may guide early initiation of supportive measures in patients after CAR-T therapy.

POTENTIAL COMPETING INTERESTS
Yi Lin serves as a consultant for the pharmaceutical companies Kite/Gilead, Celgene/BMS, Juno/BMS, BlueBird Bio, Janssen, Legend Biotech, Merck, Takeda, Boston Scientific. All funds and compensation are paid to Mayo Clinic; there is no personal compensation. Funders did not have any role in study design, data collection, analysis, reporting, or the decision to submit for publication. N. Nora Bennani serves on the advisory board of Daichii, Sankyo, Kyowa Kirin, Vividion, and Kymera. She does not receive any personal honoraria. The companies did not have any role in study design, data collection, analysis, reporting, or the decision to submit for publication. All other authors have no conflicts of interest.

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SUPPLEMENTAL ONLINE MATERIAL
Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: AKI, acute kidney injury; CAR-T, chimeric antigen receptor T cell; CK, creatine kinase; CKD, chronic kidney disease; CRP, C-reactive protein; CRS, cytokine release syndrome; eGFR, estimated glomerular filtration rate; HLH/MAS, hemophagocytic lymphohistiocytosis/macrophage activation syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; ICU, intensive care unit; IQR, interquartile range; IV, intravenous; LDH, lactate dehydrogenase; NHL, non-Hodgkin lymphoma; RRT, renal replacement therapy; SCr, serum creatinine

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