


Chimeric Antigen Receptor T-Cell Therapy: Potentially Nephrotoxic?


Daniela Alferes ^{1*}


Inês Coelho ²

Hugo Ferreira ²

Teresa Chuva ²

Ana Paiva ²

Sérgio Chacim ³

José Mário Mariz ³

José Maximino Costa ²

1. Division of Nephrology, Department of Medicine, Centro Hospitalar Vila Nova de Gaia/Espinho, Vila Nova de Gaia, Portugal

2. Division of Nephrology, Department of Medicine, Instituto Português de Oncologia do Porto, Porto, Portugal

3. Division of Hematology, Department of Medicine, Instituto Português de Oncologia do Porto, Porto, Portugal

<https://doi.org/>

Abstract

Introduction: Chimeric antigen receptor (CAR) T-cell therapy is an effective new treatment for hematologic malignancies. In this study, we aimed to characterize the acute kidney injury (AKI) and electrolyte disorders among adults with refractory and relapsed haematological malignancies treated with CAR-T therapy and explore clinical outcomes.

Methods: A retrospective, observational study was performed. Adult patients who received anti-CD19 CAR-T therapy between January 2019 and July 2022 were screened for inclusion.

Results: Among 41 patients receiving CAR T-cell therapy, cytokine release syndrome and neurotoxicity rates occurred in 65.9% and 19.5%, respectively. AKI occurred in 6 patients (14.6%): 4 had stage 1 AKI and 2 developed stage 2 AKI, all related to decreased kidney perfusion. Electrolyte abnormalities occurred in 65.9% and most of them were clinically mild.

Conclusion: In this study, the incidence of AKI was low, with a complete resolution in most cases by the end of follow-up. Electrolyte abnormalities were common among recipients of CAR-T, although of low severity.

Keywords: Acute Kidney Injury/chemically induced; Acute Kidney Injury/etiology; Receptors, Antigen, T-Cell/therapeutic use; Receptors, Chimeric Antigen

INTRODUCTION

The use of immunotherapy in the treatment of solid organ and haematological malignancies has increased dramatically. Adoptive cell transfer methods and chimeric antigen receptor T-cell (CAR-T) therapies have both evolved as a result of a greater understanding of T-cell pathways.^{1,2} CAR-T cells are biologically designed cells with a CAR receptor that identifies and binds to a particular protein: a tumor antigen.³⁻⁵

Despite the significant therapeutic potential of CAR-T therapy for inducing remissions in refractory and relapsed malignant neoplasms,^{5,6} high rates of treatment-related toxicity have been reported, in contrast to those seen with conventional chemotherapies, monoclonal antibodies, and small-molecule targeted therapies.^{3,4,7} The toxic effects that

are reported with CAR-T cells are frequently on-target effects. Their spectrum depends on the specificity of antibody single-chain variable fragments and T-cell activation. Thus, when the target cell is eliminated or the CAR-T cell engraftment is terminated, these toxic effects are reversible. This reversibility stands in contrast to many of the toxic effects of cytotoxic chemotherapy, which can cause permanent genetic modifications of stem cells as well as other cells and are off-target effects. These permanent changes may have clinically significant long-term effects.³

Most observed toxicities are associated with cytokine release syndrome (CRS), characterized by high fever, hypotension, hypoxia, and/or multiorgan toxicity; and neurotoxicity, known as CAR-T-cell-related encephalopathy

Received: 18/09/2023 Accepted: 28/11/2023 Published Online: 03/01/2024 Published: 11/03/2024

* Corresponding Author: Daniela Patrícia Gomes Alferes | alferesdaniela@gmail.com | Rua Conceição Fernandes, 4434-502 Vila Nova de Gaia, Portugal | ORCID iD: 0000-0002-6442-1686

© Author(s) (or their employer(s)) 2024. Re-use permitted under CC BY-NC 4.0. No commercial re-use. Published by PKJ

syndrome (CRES). The latter, is typically characterized by a toxic encephalopathic state with symptoms of confusion, delirium, occasional seizures and cerebral edema.^{3,7,8} Rare cases of fulminant haemophagocytic lymphohistiocytosis (HLH), also known as macrophage-activation syndrome (MAS), which is characterized by severe immune activation, lymphohistiocytic tissue infiltration, and immune-mediated multiorgan failure, have also been reported.⁷⁻⁹ Systemic toxicities associated with CAR-T cells can potentially lead to acute kidney injury (AKI). The incidence of AKI reported in literature varies from 5% to 33%.² Typically, the rise in serum creatinine is noted within 7 to 10 days after infusion and renal replacement therapy is rarely required.⁸ In previous studies using CAR-T cells, electrolyte disorders were also reported.^{4,9} The most common was hypokalaemia, followed by hypophosphatemia and finally, hyponatremia. It is unclear if this is directly related to CAR-T cell therapy or a consequence of CRS.⁸

Given the increased interest in these therapies; it is important for nephrologists to understand their potential kidney effects. We present a series of adults with refractory and relapsed haematological malignancies treated with CAR-T therapy. We aimed to characterize the AKI and electrolyte abnormalities that occurred in these patients, examining the relationship between these findings and clinical outcomes.

MATERIAL AND METHODS

We performed a retrospective, observational study that included adult patients with refractory and relapsed haematological malignancies who received anti-CD19 CAR-T therapy between 2019 and July 2022 in Portuguese Oncology Institute of Porto. Patients who were younger than 18 years old or were experiencing an unresolved episode of AKI at the initiation of CAR-T infusion were excluded from the cohort. Patients were followed until August 2022 or time of death.

Study Approval Statement

The study protocol is according to the Declaration of Helsinki and was approved by the Ethics Committee of the Portuguese Oncology Institute of Porto.

Consent to Participate Statement

Given its retrospective and non-interventional nature, we did not obtain patients' informed consent.

Data Collection

All clinical data were elicited from the electronic clinical records and included demographic, comorbidities, and medication data at the time of CAR-T therapy initiation. Laboratory data, including levels of serum creatinine, serum electrolytes, and lactate dehydrogenase were obtained within 7 days prior and first 30 days after CAR-T administration. Post-infusion treatment complications occurring in the

first 30 days after CAR-T administration were reported and included CRS, CRES, AKI and electrolyte disorders.

Baseline and post-infusion glomerular filtration rate (GFR) were calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. Baseline chronic kidney disease (CKD) was defined as GFR < 60 mL/min/1.73 m² for 90 or more days before CAR-T therapy according to the kidney disease: Improving Global Outcomes guidelines (KDIGO). AKI was defined as a 1.5-fold increase in serum creatinine concentration from baseline value (on the 7 days prior to CAR-T infusion) during the follow-up period. Severity of AKI was graded according to the KDIGO. The resolution of an AKI episode was defined as a return of the serum creatinine concentration to within 25% of the baseline value.

The grades of CRS and CRES were based on regular clinical assessments by the primary oncology team during the hospitalization and were graded according to American Society for Transplantation and Cellular Therapy (ASTCT). Administration and doses of corticosteroids and tocilizumab for the management of systemic toxicities during the first month of follow-up were also recorded.

Electrolyte disorders were defined using Common Terminology Criteria for Adverse Events (CTCAE).

Statistical Analysis

Categorical variables were presented as number (percentage). Continuous variables were presented as mean (standard deviation) or median (interquartile range). *P* values assessing patients demographics, clinical, and laboratory differences across AKI status were derived by Wilcoxon rank sum test for non-normally distributed continuous variables. Fisher's exact test was used for categorical variables. A *p* < 0.05 was considered significant. The small sample size and low incidence of events limited our ability to perform an association analysis on the risk of AKI.

RESULTS

A total of 41 patients were treated during this period. Median follow-up was 289 days (range 6-994 days). Baseline characteristics are described in Table 1.

Median age of patients was 46 years (range 18-66 years). The majority were male (58.5%). Most patients had B-cell non-Hodgkin lymphomas (95.1%) and received 2 lines of treatment and some of the patients underwent hematopoietic cell transplantation (29.3%) prior to CAR-T cell therapy. Lymphodepletion regimen consisted in cyclophosphamide and fludarabine in nearly all patients (97.6%). Most patients received axicabtagene ciloleucel (51.2%), 43.9% received tisagenlecleucel and one patient received brexucabtagene autoleucel. Baseline comorbidities included hypertension (24.4%) and diabetes mellitus (7.3%). No patient had a history of heart disease, cirrhosis, and chronic kidney disease (CKD). The median baseline creatinine prior to the start of lymphodepletion was 0.6

(range 0.5 – 1.2) mg/dL, and median GFR was 109 mL/min/1.73 m².

Table 1. Baseline characteristics at initiation of CAR-T therapy, by AKI status.

	Overall (n=41)	AKI	
		No (n=35)	Yes (n=6)
Age (years) Median [Min, Max]	46.0 [18.0, 66.0]	47.0 [18.0, 66.0]	38.0 [26.0, 64.0]
Sex			
Female	17 (41.5%)	15 (42.9%)	2 (33.3%)
Male	24 (58.5%)	20 (57.1%)	4 (66.7%)
CAR-T type			
Axicabtagene ciloleucl	21 (51.2%)	17 (48.6%)	
Tisagenlecleucl	18 (43.9%)	16 (45.7%)	4 (66.7%)
Brexucabtagene autoleucl	2 (4.9%)	2 (5.7%)	
Indication of CAR-T therapy			
ALL	2 (4.9%)	1 (2.9%)	1 (16.7%)
NHL	39 (95.1%)	34 (97.1%)	
HCT prior to CAR-T therapy	12 (29.3%)	10 (28.6%)	2 (33.3%)
Lymphodepletion regimen			
Cyclophosphamide/Fludarabine	40 (97.6%)	34 (97.1%)	6 (100%)
None	1 (2.4%)	1 (2.9%)	
Diabetes	3 (7.3%)	2 (5.7%)	1 (16.7%)
Hypertension	10 (24.4%)	9 (25.7%)	1 (16.7%)
Serum creatinine baseline (mg/dL) Median [Min, Max]	0.600 [0.500, 1.20]	0.600 [0.500, 1.20]	0.600 [0.600, 0.900]
GFR baseline (CKD-EPI) (mL/min/1.73 m ²) Median [Min, Max]	109 [64.6, 144]	109 [64.6, 144]	111 [90.0, 129]
Prelymphodepletion LDH (U/L) Median [Min, Max]	257 [147, 1510]	256 [147, 823]	302 [162, 1510]

AKI – acute kidney injury; CART – chimeric antigen receptor; ALL – acute lymphoblastic leukemia; NHL – B-cell non-Hodgkin lymphomas; HCT – hematopoietic cell transplantation; GFR – glomerular filtration rate; LDH – lactate dehydrogenase.

Post CAR-T Cell Complications

Post CAR-T cell complications were recorded in 32 patients (Table 2).

CRS occurred in 27 (65.9%) patients and CRES was seen in 8 patients (19.5%). Six patients experienced both complications. MAS/HLN was noticed in 1 patient. Six patients developed an incident AKI event (14.6%) and 27 had electrolyte abnormalities (65.9%).

Four patients (66.7%) had stage 1 AKI and 2 patients had stage 2 AKI. Median time of AKI after initiation of CAR-T therapy was 6.5 days (range 5.0 to 9.0). There was no administration of nephrotoxins at the time of kidney injury, and obstruction the urinary tract was excluded in all cases of AKI. Median uric acid level of patients with AKI was 3.7 (range 2.5-5) mg/dL. No patient had substantial elevations in uric acid levels after CAR-T therapy. All AKI episodes reversed with improved fluid intake or intravenous fluid support.

Grade 1 hypokalaemia was the most prevalent abnormality, observed in 20 patients (48.8%). Hyponatremia occurred in 18 patients (43.9%), with 2 patients experiencing grade 2 hyponatremia. Eight patients (19.5%) developed hypophosphatemia: grade 1 in 7 patients and grade 2 in

a single patient. No patient experienced grade 2 or higher hypokalaemia, nor did any have had grade 3-5 hyponatremia or hypophosphatemia. Median time to nadir for electrolyte abnormalities was 5 to 6 days from time of CAR-T administration.

There were significant differences between AKI group and no-AKI group in relation to grade CRS, with larger percentage of grade 2 CRS or higher in the AKI group ($p=0.001$) (Table 3). Although most patients with AKI received axicabtagene ciloleucl (66.7%), there were no significant differences in CART construct administered between groups.

Length of Stay and Mortality During the Follow-up Period

During the follow-up, we registered 12 deaths: 1 from complication of therapy (grade 4 CRES), 1 from infectious complication unrelated with therapy (occurred 159 days after therapy) and 10 associated to progression of the underlying cancer.

As shown in Table 3, among patients with AKI, median length of stay was 20 days and days until death after therapy were 9.5. These results were significantly different from patients who did not have AKI ($p=0.04$).

Table 2. Complications after administration of CAR-T cell therapy.

Complications of CAR-T cell therapy	All patients n=32
CRS	27 (65.9%)
Grade 1	20 (74.1%)
Grade 2	5 (18.5%)
Grade 3 or 4	2 (7.4%)
CRES	8 (19.5%)
Grade 1	3 (37.5%)
Grade 2	4 (50.0%)
Grade 3 or 4	1 (12.5%)
MAS/HLH	1 (3.13%)
Use of IS to treat CRS or CRES	27 (65.9%)
Dexamethasone	27 (100%)
Tocilizumab	13 (48.1%)
Anakinra	4 (14.8%)
AKI	6 (14.6%)
Time to peak (days)	
Median [Min, Max]	6.50 [5.00, 9.00]
Peak creatinine (mg/dL)	
Median [Min, Max]	1.30 [1.10, 1.40]
Hypokalaemia	20 (48.8%)
Grade 1	20 (100%)
Grade 2	0 (0%)
Grade 3-5	0 (0%)
Time to nadir potassium concentration (days)	5.00 [2.00, 18.0]
Hyponatremia	18 (43.9%)
Grade 1	16 (88.9%)
Grade 2	2 (11.1%)
Grade 3-5	0 (0%)
Time to nadir sodium concentration (days)	5.50 [2.00, 9.00]
Hypophosphatemia	8 (19.5%)
Grade 1	7 (87.5%)
Grade 2	1 (12.5%)
Grade 3-5	0 (0%)
Time to nadir phosphorus concentration (days)	5.50 [2.00, 13.0]

CART: chimeric antigen receptor; CRS: cytokine release syndrome; CRES: CAR-T-cell-related encephalopathy syndrome; MAS/HLH: macrophage-activation syndrome/haemophagocytic lymphohistiocytosis; IS: Immunosuppression; AKI: acute kidney injury.

Of the 4 patients who survived during admission for CAR-T, all returned to creatinine level and GFR baselines. At end follow-up, the patients had median creatinine of 0.7 (range 0.6 – 0.8) mg/dL, and median GFR of 106 [(range 106–122.4) mL/min/1.73 m²].

DISCUSSION

CAR-T therapy has been a breakthrough in anticancer therapy. However, it also has a unique toxicity profile and is increasingly becoming recognized as a cause of renal adverse events.

The mechanism of AKI in patients with CAR-T cell therapy is not completely understood. However, it is proposed that the release of high concentrations of cytokines can lead to vasodilation, decreased cardiac output, and intravascular volume depletion due to increased vascular permeability and third spacing of fluids, causing reduced kidney perfusion, and potentially leading to acute tubular injury. In

addition, high fever and nausea/vomiting associated with CRS induce intravascular volume depletion and/or CRS-related cardiomyopathy can also lead to a shock state and acute cardiorenal syndrome with concomitant AKI. Cytokines themselves may potentiate the renal injury due to intrarenal inflammation. Accumulation of fluid in the interstitial space leads to other problems, such as pleural effusions, peripheral, pulmonary and intestinal oedema, ascites, and muscle oedema. Rarely, AKI can result from severe ascites or rhabdomyolysis secondary to compartment syndrome and/or muscle oedema. In patients with large tumour burdens treated with CAR-T cells, tumour lysis syndrome constitutes another potential mechanism for AKI.^{8,9}

We found a low rate of AKI and most patients experienced only mild AKI and all (except those who died during hospitalization) recovered renal function. Our reported incidence of AKI was lower than the 30% found in the study by Gurtgarts *et al*¹⁰; however, it was comparable to results published in previous studies.^{2,11,12} AKI occurred within 5 to 10 days after CAR-T therapy, coinciding with CRS, and based on clinical data, appeared to be secondary to decreased kidney perfusion. In a systematic review, Kanduri *et al*² found that higher grades of CRS were significantly associated with AKI after CAR-T infusion. Despite the small sample of our study, we found significant differences between the group with and without AKI regarding CRS grade, with a larger percentage of grade 2 or higher CRS in the AKI group. Our findings suggest possible association between AKI and CRS severity, though this needs to be validated in a larger study. Our centre's protocol includes close monitoring of serum biomarkers, fluid support, and early initiation of corticosteroids or tocilizumab during episodes of CRS; these attitudes may have contributed to reduce the incidence of severe CRS and consequently of AKI in this series.

The structure of the chimeric antigen receptor may contribute to patterns of toxicity. Most patients (51.2%) described in this series received axicabtagene ciloleucel, a CD19-targeting CAR-T that has a CD28 costimulatory domain and is characterized by rapid T-cell expansion and robust inflammatory cytokine secretion. The remaining patients received tisagenlecleucel CAR construct, which targets the same epitope of CD19 but has a different costimulatory domain (4-1BB) and is associated with a reduced inflammatory profile.¹³ Although not statistically significant, it should be noted that most patients with AKI received axicabtagene ciloleucel. In the group without AKI the percentage of patients who received axicabtagene ciloleucel and tisagenlecleucel was similar.

We also found that electrolyte abnormalities were common among recipients of CAR-T, but rates of clinically relevant hypokalaemia, hyponatremia and hypophosphatemia were low. This may be due to lower rates and grade of CRS and/or close monitoring and management of electrolyte

disturbances, according to protocols established in our institution.

Moreover, our findings indicated that patients who developed AKI experienced higher mortality rates within a shorter timeframe and longer hospitalization durations. Various studies have consistently demonstrated that AKI occurrence during a hospital stay is associated with a higher likelihood of mortality compared to patients without AKI, leading to increased healthcare resource utilization and potentially higher healthcare costs.^{14,15} The severity and duration of AKI episodes often correlate with the increased risk of adverse outcomes, making it an important factor to consider in patient care and management strategies.

Our study is limited by the relatively small cohort size, as well as its observational and retrospective nature, which precludes further hazard risk analysis to identify other modifiable risk factors. As experience with CAR-T cells grows, larger studies are needed to stratify patients according to their risk of toxicity, including kidney injury.

Despite its limitations, this study is first to describe the experience of a Portuguese Center with CAR-T therapy and its effects on renal function and electrolyte disorders. The utility of CAR-T therapies has significantly expanded across various cancer types. Collaboration between nephrologists and cancer specialists is essential to comprehend these innovative treatments and their renal implications. Careful administration of resuscitative crystalloid fluids can stabilize and reverse AKI in patients with mild cytokine release syndrome, while more severe cases might require loop diuretics and dialysis. Recognizing the significance of CAR-T cell therapy and its renal effects is crucial for nephrologists treating cancer patients.

In conclusion, this study observed a low incidence of AKI, mostly resolving by the end of follow-up, and although electrolyte abnormalities were common, they tended to be mild.

Table 3. Baseline and Clinical Outcomes by AKI status.

	Overall (N=41)	AKI		p-value
		No (N=35)	Yes (N=6)	
Age (years)	46.0 [18.0, 66.0]	47.0 [18.0, 66.0]	38.0 [26.0, 64.0]	0.449
Sex				
Female	17 (41.5%)	15 (42.9%)	2 (33.3%)	
Male	24 (58.5%)	20 (57.1%)	4 (66.7%)	
CAR-T type				
Axicabtagene ciloleucl	21 (51.2%)	17 (48.6%)	4 (66.7%)	
Tisagenlecleucl	18 (43.9%)	16 (45.7%)	2 (33.3%)	
Brexucabtagene autoleucl	2 (4.9%)	2 (5.7%)	0 (0%)	
Diabetes	3 (7.3%)	2 (5.7%)	1 (16.7%)	0.386
Prelymphodepletion LDH (U/L)	257 [147, 1510]	256 [147, 823]	302 [162, 1510]	0.483
CRS	27 (65.9%)	21 (60.0%)	6 (100%)	0.079
Grade 1	20 (74.1%)	19 (90.5%)		
Grade 2	5 (18.5%)	2 (9.5%)	1 (16.7%)	0.001
Grade 3 or 4	2 (7.4%)	0 (0%)		
CRES	8 (19.5%)	5 (14.3%)	3 (50.0%)	0.109
Use of IS to treat CRS or CRES	27 (65.9%)	21 (60.0%)	6 (100%)	1.000
Electrolyte abnormalities	27 (65.9%)	22 (62.9%)	5 (83.3%)	0.645
Length of stay (days)				
Median [Min, Max]	16.0 [9.00, 35.0]	16.0 [9.00, 35.0]		
Days until death after therapy				
Median [Min, Max]	146 [6.00, 895]	154 [63.0, 895]		

CAR-T – chimeric antigen receptor; LDH – lactate dehydrogenase; CRS – cytokine release syndrome; CRES – CAR-T-cell-related encephalopathy syndrome; AKI – acute kidney injury.

Acknowledgements

To Pedro Leite Silva, Epidemiology Department of Instituto Português de Oncologia do Porto, for their assistance in conducting the statistical analysis.

Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Protection of Human and Animal Subjects: The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki as revised in 2013).

Provenance and Peer Review: Not commissioned; externally peer reviewed.

Contributorship Statement

DA: Collected, analysed and interpreted the data, and writing original draft – review and editing.

IC: Collected the data, review and editing of the manuscript.

HF, TC, AP, SC: Review of the manuscript.

JMM and JMC: Designed the study, supervision and review of the manuscript.

All authors approved the final version of this manuscript.

REFERENCES

1. Gill S, Maus MV, Porter DL. Chimeric antigen receptor T cell therapy: 25years in the making. *Blood Rev.* 2016; 30: 157–67. doi: 10.1016/j.blre.2015.10.003.
2. Kanduri SR, Cheungpasitporn W, Thongprayoon C, Petnak T, Lin Y, Kovvuru K, 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: 1416–22. doi: 10.1016/j.ekir.2021.02.013.
3. June CH, Sadelain M. Chimeric antigen receptor therapy. *New Engl J Med.* 2018; 379: 64–73. doi: 10.1056/NEJMra1706169.
4. Neelapu SS, Tummala S, Kebriaei P, Wierda W, Gutierrez C, Locke FL, et al. Chimeric antigen receptor T-cell therapy-assessment and management of toxicities. *Nat Rev Clin Oncol.* 2018; 15: 47–62. doi: 10.1038/nrclinonc.2017.148.
5. Zhang X, Zhu L, Zhang H, Chen S, Xiao Y. CAR-T cell therapy in hematological malignancies: current opportunities and challenges. *Front Immunol.* 2022; 13. doi:10.3389/fimmu.2022.927153.
6. Marofi F, Motavalli R, Safonov VA, Thangavelu L, Yumashev AV, Alexander M, et al. CAR T cells in solid tumors: challenges and opportunities. *Stem Cell Res Ther.* 2021; 12. doi:10.1186/s13287-020-02128-1.
7. Brudno JN, Kochenderfer JN. Recent advances in CAR T-cell toxicity: Mechanisms, manifestations and management. *Blood Rev.* 2019; 34: 45–55. doi: 10.1016/j.blre.2018.11.002.
8. Jhaveri KD, Rosner MH. Chimeric antigen receptor T cell therapy and the kidney: What the nephrologist needs to know. *Clin J Am Soc Nephrol.* 2018;13:796-8. doi: 10.2215/CJN.12871117.
9. Perazella MA, Shirali AC. Nephrotoxicity of cancer immunotherapies: past, present and future. *J Am Soc Nephrol.* 2018;29:2039-52. doi: 10.1681/ASN.2018050488.
10. Gutgarts V, Jain T, Zheng J, Maloy MA, Ruiz JD, Pennisi M, et al. Acute kidney injury after CAR-T cell therapy: low incidence and rapid recovery. *Biol Blood Marrow Transplant.* 2020;26:1071-6. doi: 10.1016/j.bbmt.2020.02.012.
11. Gupta S, Seethapathy H, Strohbehn IA, Frigault MJ, O'Donnell EK, Jacobson CA, et al. Acute kidney injury and electrolyte abnormalities after chimeric antigen receptor t-cell (CAR-T) therapy for diffuse large b-cell lymphoma. *Am J Kidney Dis.* 2020;76:63-71. doi: 10.1053/j.ajkd.2019.10.011.
12. Farooqui N, Sy-Go JPT, Miao J, Mehta R, Vaughan LE, Bennani NN, et al. Incidence and risk factors for acute kidney injury after chimeric antigen receptor T-cell therapy. *Mayo Clin Proc.* 2022; 97: 1294–304. doi: 10.1016/j.mayocp.2022.05.018.
13. Ying Z, He T, Wang X, Zheng W, Lin N, Tu M, et al. Parallel comparison of 4-1BB or CD28 co-stimulated CD19-targeted CAR-T cells for b cell non-Hodgkin's lymphoma. *Mol Ther Oncolytics.* 2019;15:60-68. doi: 10.1016/j.omto.2019.08.002.
14. Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term Risk of Mortality and Other Adverse Outcomes After Acute Kidney Injury: A Systematic Review and Meta-analysis. *Am J Kidney Dis.* 2009;53:961-73. doi: 10.1053/j.ajkd.2008.11.034.
15. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol.* 2005;16:3365-70. doi: 10.1681/ASN.2004090740.