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BRIEF REPORT

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CAR T therapy in adult DLBCL patients in Slovenia: Evaluation of predictive scores for outcomes and adverse events

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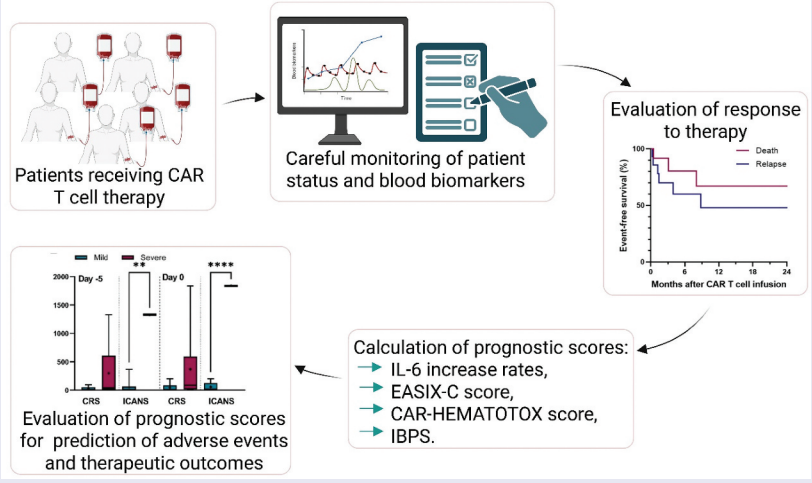
ABSTRACT

CAR T cell therapy is a promising immunotherapy for hematologic malignancies, yet early prediction of outcomes and adverse events remains difficult, especially in small real-world cohorts. We retrospectively analyzed 14 adult patients with diffuse large B-cell lymphoma (DLBCL) treated with CAR T cells in Slovenia, assessing IL-6 increase rates and established predictive metrics including EASIX-C, CAR-HEMATOTOX, and IBPS on Day −5 (pre-lymphodepletion) and Day 0 (infusion). Contrary to our expectation, an inverse correlation was observed between the increase rate of IL-6 and the occurrence of severe cytopenias, indicating higher IL-6 increase rate leads to less severe cytopenias. The EASIX-C score showed higher predictive values when calculated on Day 0, contrary to the CAR-HEMATOTOX score, whose higher predictive values were observed on Day −5. The IBPS predictive values showed mixed results when comparing Day −5 to Day 0. We observed 50% response rate and 29% remission rate. The results highlight the utility of predictive scores, with unexpected findings on IL-6 suggesting further study is necessary.

PLAIN LANGUAGE SUMMARY

CAR T cell therapy is an innovative treatment that uses a patient's own immune cells to fight blood cancer. This study looked at adult patients in Slovenia who received this therapy and evaluated whether certain early warning scores could predict serious side effects and treatment outcomes. Interestingly, we found that faster increases in a protein called IL-6 were linked to fewer issues with low blood counts, which was unexpected. Two scores – EASIX-C and CAR-HEMATOTOX – were found to be helpful in predicting a brain-related side effect called ICANS. Overall, about half of the patients showed improvement, and nearly one-third went into remission. These findings suggest that using these scores before and during treatment could help doctors better manage risks and improve patient care.



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CAR T cell therapy; hematologic malignancies; diffuse large B-cell lymphoma; predictive scores; adverse events; therapeutic outcomes

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Introduction

Chimeric antigen receptor (CAR) T cell therapy is a promising immunotherapy for treating hematologic malignancies, introducing a shift toward more personalized and effective treatment approach. Despite the benefits of this innovative immunotherapy, it is still used for patients who relapsed after at least two previous lines of cancer therapy, or for whom for any reason other therapies can no longer be considered effective.[1] The reason for this lies in the current limitations of the therapy, with a possibility of severe side effects and patient unresponsiveness.[2] Up to 36% of eligible patients undergoing CAR T cell treatment are only later identified as non-responders.[3] The most common side effects of CAR T cell therapy are cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), both of which can lead to multiple organ failure and even death.[4] Up to 46% of patients may develop severe CRS symptoms, and up to 50% may experience severe ICANS symptoms.[5] These serious side effects can result in long-lasting health issues.[6] Numerous attempts have been made to identify effective predictive biomarkers for CAR T cell therapy progression, yet the results have so far shown limited success.

Interleukin-6 (IL-6) is a key mediator of cytokine release syndrome (CRS) and may also influence other treatment-related complications and patient outcomes, making its kinetics a valuable biomarker for both monitoring toxicity and guiding supportive care strategies.[7,8] The Endothelial Activation and Stress Index (EASIX) score, indicative of endothelial injury, has been proposed for its potential to predict CAR T cell therapy-related adverse events.[9] The CAR-HEMATOTOX score, which incorporates baseline cytopenias and inflammatory indicators, is another frequently utilized predictive tool. This score is linked with extended cytopenias after CAR T cell treatment.[10] In parallel, the Inflammation-Based Prognostic Score (IBPS), which evaluates systemic immune inflammation and a prognostic nutritional index, shows promise in predicting outcomes of CAR T cell therapy, though additional validation is necessary.[11]

This retrospective study overviews therapy course, development of adverse events, and treatment outcomes in adult patients treated with CAR T cell therapy at UMC Ljubljana. The aim of this study is to test IL-6 increase rates after infusion and EASIX-C, CAR-HEMATOTOX, and IBPS on Day −5 (pre-lymphodepletion) and Day 0 (infusion) for early prediction of adverse events and therapeutic outcomes. Establishing efficient predictive metrics could significantly improve patient care and the overall success rate of the therapy. This approach aims not only to test predictive scores but also to aid in tailoring treatment strategies and managing side effects more effectively for future patients receiving this innovative therapy.

Materials and methods

Between July 2020 and October 2024 14 patients diagnosed with either DLBCL or PMBCL received CAR T cell treatment at the Department of Hematology at UMC Ljubljana. For this analysis, all patients were classified under the broader DLBCL category, including both traditional DLBCL and PMBCL subtypes. Due to the small cohort size, we combined these subtypes to enhance statistical robustness, while acknowledging potential biological differences. Patients' condition was closely monitored and peripheral blood biomarkers frequently measured. For the purpose of this retrospective study, patient data (age, gender, other treatments, disease burden, etc.) and corresponding laboratory results were systematically retrieved from medical records. All patients received lymphodepleting regimen with fludarabine and cyclophosphamide (Flu-Cy) before CAR T cell infusion. Patients were treated with commercially available anti-CD19 CAR T cells tisagenlecleucel (Kymriah®, Novartis). Therapeutic response was assessed by PET-CT scan and categorized as either a complete response (CR) indicating the total elimination of tumor cells, or progressive disease (PD), signifying the continued presence of tumor cells, over a 3-month period following CAR T cell infusion. Patients were observed for up to 2 years. Therapeutic outcomes were defined as remission, disease progression (presence of the disease within ≤3 months after administration), relapse (presence of the disease after >3 months post-administration), and death. We performed Kaplan-Meier survival analysis to evaluate the 2-year outcomes following CAR T cell therapy. We also tested for correlation between the number of previous

treatments and CAR T cell therapy outcomes. After examining the collected data, the predictive scores and regression analyses were conducted.

IL-6 levels in peripheral blood were measured daily following CAR T cell infusion as a marker for inflammation and a potential early indicator of CRS. Our hypothesis was that an elevated increase rate of IL-6 levels post-infusion would indicate a rapid onset of inflammation, potentially leading to higher incidences of associated side effects, including CRS, and consequently worse therapeutic outcomes. Increase rates were calculated with exponential regression of IL-6 measurements from Day 0 (day of CAR T cell infusion) to the day of IL-6 peak for each patient. IL-6 levels were observed prior to the administration of drugs that could affect its levels. IL-6 increase rates were determined from the calculated equations of exponential regression, as shown in Equation (1), where a is the y-intercept and b is the coefficient that represents the increase rate.[12] IL-6 increase rate calculations for each patient are presented in Figure 1.

$$y = a \times e^{(b \times x)} \tag{1}$$

To evaluate the prognostic potential of EASIX-C score, CAR-HEMATOTOX score, and IBPS in predicting therapeutic outcomes, adverse events, and severe cytopenias associated with CAR T cell therapy, the prognostic assessments were made at two critical time points: before the lymphodepleting regimen (Day −5) and on the day of CAR T cell infusion (Day 0). The EASIX-C, CAR-HEMATOTOX, and IBPS were calculated as previously described.[10,11,13]

Statistical analyses were conducted to assess the predictive values of the scores at both time points (Day −5 and Day 0) and the therapeutic outcomes, adverse events, and severe cytopenias associated with CAR T cell therapy. Therapeutic outcomes were classified as positive (remission) and negative (death, disease progression, or relapse). CRS and ICANS were graded according to the American Society for Transplantation and Cellular Therapy (ASTCT) consensus criteria.[14] CRS and ICANS were categorized as mild (grades 0 and 1) or severe (grades 2–4).[15] Cytopenias were graded according to the Common Terminology Criteria for Adverse Events (CTCAE).[16] Statistical analyses and graphs were generated using GraphPad Prism 9.5.0 software (GraphPad Software Inc., USA). All data were tested for normal distribution with the Shapiro-Wilk or Kolmogorov-Smirnov test. One-way ANOVA was employed to identify significant differences between means across multiple groups, followed by a *post-hoc* Tukey's multiple comparison test for pairwise comparisons. Unpaired t-test was used to compare means of two groups of data. Results were considered statistically significant if $p \leq .05$. These comprehensive methods facilitated a thorough evaluation of prognostic markers and their association with treatment outcomes in CAR T cell therapy, providing valuable insights for optimizing patient selection and treatment strategies.

Results

The first adult patient with DLBCL was treated with CAR T cells at UMC Ljubljana in 2020 and until October 2024 a total of 15 patients were selected for the treatment. Of these, 14 adult patients (93%) received CAR T cell infusion and one patient (7%) was unable to receive the drug due to disease progression. Of the 14 patients that were able to receive therapy, three were females (21%) and 11 were males (79%) with a median age of 35 years for females, 60 years for males, and 58 years for the whole patient group. Patient characteristics, clinical outcomes, duration of response, side effects, and treatments before and after CAR T cell therapy are presented in Table 1. Patients received from two to eight prior treatments before receiving CAR T cell therapy (median value of prior treatments is 4.5). We found no correlation between the number of previous treatments and CAR T cell therapy outcomes.

Three months after CAR T cell infusion, a complete response (CR) to therapy was observed in seven patients (50%), while seven patients (50%) experienced progressive disease (PD). Over a subsequent two-year observation period, three patients (21%) experienced disease relapse, median time to relapse after CAR T cell infusion was 106 days, three patients (21%) died due to disease progression, median time to death after CAR T cell infusion was 95 days, and four patients (29%) achieved durable remission. During the

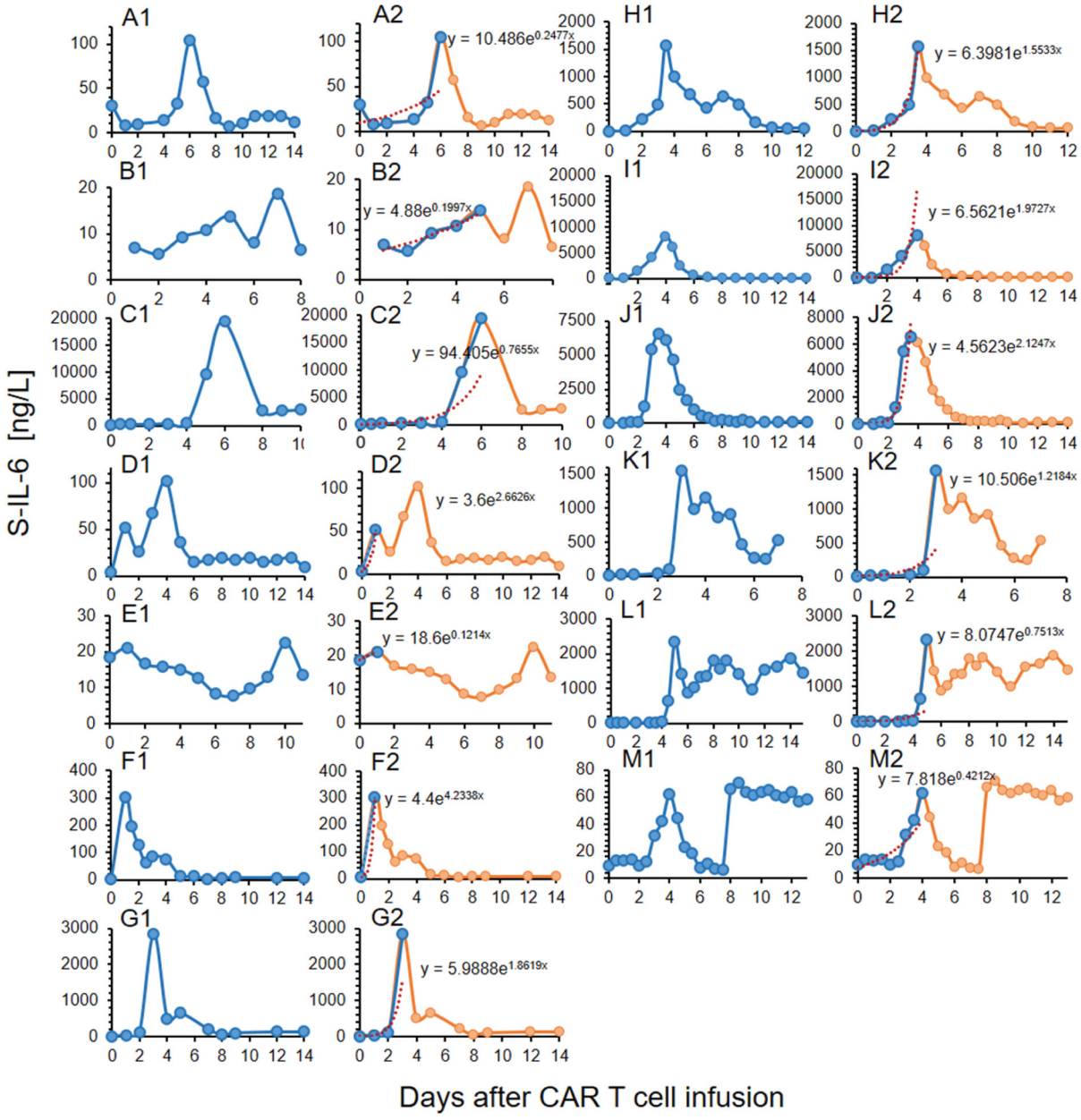

Figure 1. Soluble IL-6 in peripheral blood and the calculation of exponential regression increase rate after CAR T cell infusion for each patient. Graphs marked as one present the peripheral blood soluble IL-6 concentration profiles post-infusion and graphs marked as two display the corresponding exponential regression analyses used to calculate the increase rate of IL-6 for each patient, shown as red dashed lines. Paired graphs represent patient 2 (A), patient 3 (B), patient 4 (C), patient 5 (D), patient 6 (E), patient 7 (F), patient 9 (G), patient 10 (H), patient 11 (I), patient 12 (J), patient 13 (K), patient 14 (L), and patient 15 (M).

course of CAR T cell therapy seven patients (50%) experienced mild CRS (grade 1), four patients (29%) experienced CRS grade 2, two patients (14%) experienced severe CRS (grade 3), one patient (7%) experienced mild ICANS (grade 1) and one patient (7%) experienced severe ICANS (grade 4). Treatment outcomes and adverse events in adult patients with DLBCL undergoing CAR T cell therapy at the UMC Ljubljana are presented in Figure 2. After the treatment, nine patients (64%) experienced various forms of severe blood cytopenias, including neutropenia, anemia, and thrombocytopenia, consistent with outcomes observed in other CAR T cell therapy studies.[5]

Table 1. Patient characteristics, clinical outcomes, side effects, and previous treatments in adult patients treated with CAR T cell therapy in Slovenia.

Pt.	Gender	Diagnosis	Age at infusion	Outcome	Duration of response (days)	CRS grade	ICANS grade	Other side effects	Number of previous treatments	Previous treatments	Treatments after CAR T cell therapy	Alive
1	M	DLBCL	47	Relapse on day 269	269	1	0	Pancytopenia	5	RT, R-CHOP, R-DHAP, IGEV regimen, AuSCT	RPB, CBVPP, RT	No
2	M	DLBCL	71	Remission	Ongoing at last follow-up (730)	1	0	Cytopenias	6	R-CHOP, IC, RT, R-CBVPP, IC, R-GEMOX		Yes
3	M	DLBCL	39	Remission	Ongoing at last follow-up (730)	0	0	Refractory anemia and thrombocytopenia	5	R-CHOP, RT, R-Benda, AuSCT, R-DHAP		Yes
4	M	DLBCL	66	Death on day 14	NA	3	4	Liver failure, cytopenias	4	R-CHOP, R-EPOCH, R-DHAP, RT		No
5	F	PMBCL	35	Disease progression	NA	1	0	Pulmonary infection with Aspergillus	2	R-EPOCH, R-DHAP	CBVPP, AISCT, PBV, BN	Yes
6	M	PMBCL	40	Disease progressionand death on day 95	NA	1	0	Neutropenia	5	R-EPOCH, RT, R-DHAP, AuSCT, IGEV		No
7	F	PMBCL	29	Relapse on day 119	119	1	0		3	R-CHOP, R-DHAP, R-IGEV	RT, RPB, IGEV, AISCT	Yes
8	F	DLBCL	/	Did not receive treatment due to disease progression								Yes
9	F	DLBCL	63	Remission	Ongoing at last follow-up (582)	3	0	Neutropenia, Thrombocytopenia, Pancytopenia	6	R-CHOP, RT, R-DHAP, RPB, RT, R-CBVPP		Yes
10	M	DLBCL	56	Relapse on day 106	106	2	0		2	Ibrutinib, R-EPOCH, Venetoclax	RT, Tafa-Len	Yes
11	M	DLBCL	62	Remission	Ongoing at last follow-up (428)	2	0	Leukopenia and Thrombocytopenia	8	R-CHOP, RT, R-benda, Flu-Cy, RT, R-DHAP, RT, GEMOX		Yes
12	M	DLBCL	60	Disease progression	NA	2	1	Neutropenia	2	R-CHOP, RPB	RT, Glo	Yes
13	M	PMBCL	30	Disease progression and death on day 244	NA	1	0	Neutropenia and Thrombocytopenia	3	R-EPOCH, RT, R-DHAP, R-IGEV	RT, BN, VIPOR	No
14	M	DLBCL	71	Disease progression	NA	2	0		6	CP, COP, CHOP, FC, RPB, RT		Yes
15	M	DLBCL	66	Dissease progression	NA	1	0	Anemia, Neutropenia, Pancytopenia	4	Me, R-CHOP, R-DHAP, IGEV	Glo	Yes

Pt: Patient; **DLBCL**: Diffuse Large B-Cell Lymphoma; **PMBCL**: Primary Mediastinal Large B-Cell Lymphoma; **CRS**: Cytokine Release Syndrome; **ICANS**: Immune Effector Cell-Associated Neurotoxicity Syndrome; **M**: Male; **F**: Female; **NA**: not applicable; **RT**: Radiation Therapy; **Glo**: Glofitamab; **CHOP**: Cyclophosphamide, Doxorubicin, Vincristine, Prednisone; **R-CHOP**: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone; **COP**: Cyclophosphamide, Vincristine, Prednisone; **Me**: Methylprednisolone; **R-DHAP**: Rituximab, Dexamethasone, Cytarabine, Cisplatin; **IGEV regimen**: Ifosfamide, Gemcitabine, Etoposide, Vinorelbine; **AuSCT**: Autologous Hematopoietic Stem Cell Transplantation; **AISCT**: Allogeneic Hematopoietic Stem Cell Transplantation; **IC**: Intrathecal Chemotherapy; **R-Benda**: Rituximab and Bendamustine; **GEMOX**: Gemcitabine, Oxaliplatin; **R-GEMOX**: Rituximab, Gemcitabine, Oxaliplatin; **R-EPOCH**: Rituximab, Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin; **R-CBVPP**: Rituximab, Cyclophosphamide, Carmustine, Etoposide, Procarbazine, Prednisone; **CBVPP**: Cyclophosphamide, Carmustine, Etoposide, Procarbazine, Prednisone**; R-IGEV**: Rituximab, Ifosfamide, Gemcitabine, Etoposide, Vinorelbine; **RPB**: Rituximab, Polatuzumab, Bendamustine; **PBV**: Polatuzumab, Bendamustine, Venetoclax; **VIPOR**: Venetoclax, Ibrutinib, Prednisone, Obinutuzumab, and Lenalidomide; **BN**: Brentuksimab, Nivolumab; **CP**: Chlorambucil, Prednisone; **Tafa-Len**: Tafasitimab, Lenalidomide; **FC**: Fludarabine, Cyclophosphamide.

The Kaplan-Meier survival analysis, shown in Figure 3, shows the 2-year outcome following CAR T cell therapy. The outcomes of interest were event-free survival, with events categorized as either death or relapse.

In the analysis of IL-6 increase rate as a potential predictor for the development of severe side effects, no statistically significant differences were observed among patient groups classified with mild or severe CRS/ICANS ($p > .05$). Consequently, the IL-6 increase rate did not substantiate our hypothesis as a determinant for the severity of adverse events. Similarly, when evaluating the prognostic value of IL-6 increase rate for therapeutic outcomes, the results did not indicate statistical significance ($p > .05$), suggesting that the IL-6 increase rate lacks predictive value for these clinical endpoints in our study. Surprisingly, a notable trend was observed regarding the development of severe cytopenias. Contrary to our initial hypothesis, a statistically significant inverse correlation was found ($p = .037$), indicating that a higher IL-6 increase rate, anticipated to correlate with a faster onset and increased severity of side effects, was associated with the presence of only mild-to-none cytopenias. Conversely, a lower IL-6 increase rate was associated with the development of severe cytopenias following CAR T cell therapy. This unexpected finding underscores the potential complexity in the relationship between IL-6 dynamics and hematologic toxicity, warranting further investigation. The results for IL-6 increase rates are presented in Figure 4(D,H,L). Patient-level data for IL-6 increase rates and cytopenia severity are provided in Supplementary Table S1 for clarity.

In the analysis of EASIX-C score as a potential predictor for adverse events, statistically significant differences between means were observed for mild/severe ICANS on both Day 0 ($p < .0001$) and Day −5 ($p = .0032$), with Day 0 showing a higher difference between means, indicating a higher predictive value. Conversely, for mild/severe CRS on both Day 0 and Day −5, the differences between means were not statistically significant ($p = .4793$ and $p = .6884$, respectively). Notably, Day 0 exhibited a higher difference between means in the mild/severe CRS comparison, suggesting superior predictive value compared to the EASIX-C score calculated on Day −5. In predicting therapeutic outcomes with the EASIX-C score, Tukey multiple comparisons revealed no statistically significant differences between means for positive and negative outcomes on both Day 0 ($p = .9709$) and Day −5 ($p = .9978$). However, the difference between the EASIX-C score group means was slightly greater when the score was calculated on Day 0 compared to Day −5, suggesting that measurements obtained at the time of CAR T cell infusion may provide improved discrimination between outcome groups when considering mean differences alone. For predicting cytopenias, both Day 0 ($p = .8776$) and Day −5 ($p = .9891$) EASIX-C values showed no statistically significant differences between means. However, the differences between means on Day 0 were higher than those on

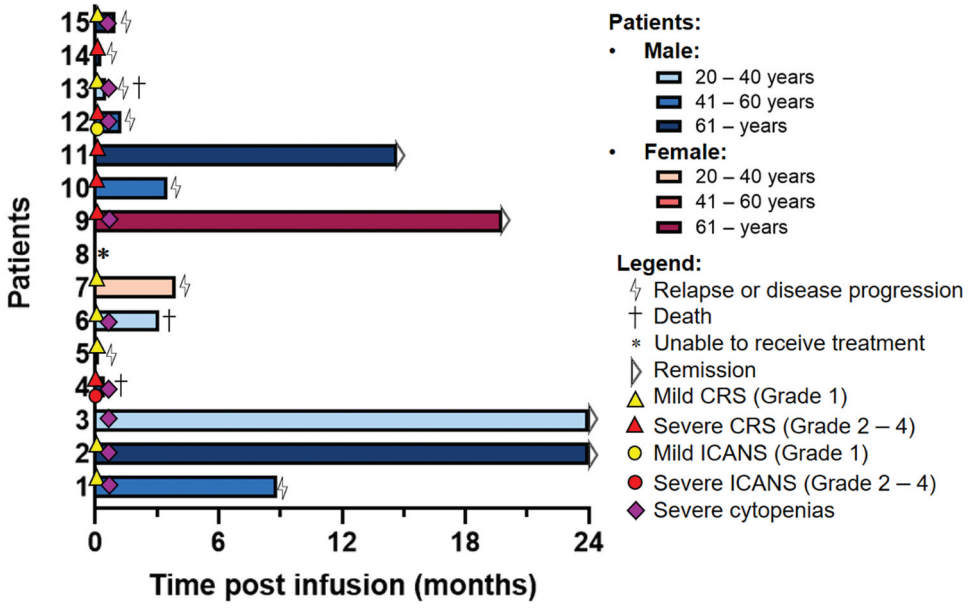

Figure 2. Two-year treatment outcomes and adverse events in adult patients with diffuse large B-cell lymphoma (DLBCL) undergoing CAR T cell therapy at the University Medical Centre Ljubljana (UMC Ljubljana).

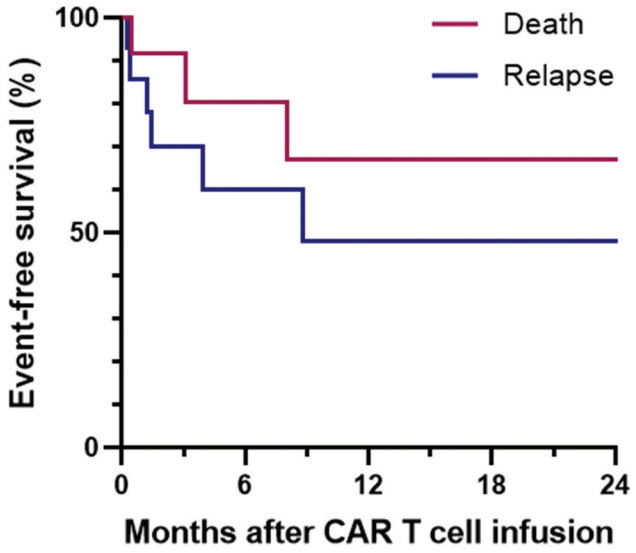

Figure 3. Kaplan-Meier curves for 2-year outcomes after CAR T cell infusion. Curves represent the percentages of patients experiencing event-free survival, with events defined as either death (red line) or relapse (blue line), where relapse is defined as disease relapse or progression.

Day −5, suggesting that the use of EASIX-C score for predicting severe cytopenias associated with CAR T cell therapy based solely on mean differences would be more accurate on Day 0. The results for the EASIX-C scores are presented in Figure 4(A,E,I).

In the analysis of the CAR-HEMATOTOX score for the prediction of mild/severe CRS and ICANS, no statistically significant differences were observed for CRS on both Day 0 and Day −5 ($p > .9999$). The differences between means for mild/severe ICANS were more pronounced, with Day 0 exhibiting a lower difference ($p = .1338$) compared to Day −5, which was statistically significant ($p = .0457$), contrasting with the results obtained for the EASIX-C score, indicating that higher predictive value is obtained when the score is calculated on Day −5. No statistically significant differences were observed between means of positive/negative therapeutic outcome groups on Day −5 ($p = .9549$) and Day 0 ($p > .9999$). No statistically significant differences were observed for cytopenias, but slightly higher differences were noted on Day 0 ($p = .8998$) compared to Day −5 ($p = .9821$). These findings suggest that the CAR-HEMATOTOX score demonstrates a higher predictive value for calculations of adverse events and therapeutic outcomes conducted on Day −5 compared to those on Day 0. The results for the CAR-HEMATOTOX scores are presented in Figure 4(B,F,J).

For the IBPS score, results regarding differences between means of groups for mild/severe CRS and ICANS revealed no statistically significant differences. However, when comparing mean differences, predictive value for CRS was higher when calculations were made on Day 0 ($p = .3305$) compared to Day −5 ($p > .999$), while for ICANS, the predictive value was higher on Day −5 ($p = .5823$) than on Day 0 ($p = .9025$). For the prediction of therapeutic outcomes no statistically significant differences were noted in IBPS scores, however, higher mean differences were observed on Day 0 ($p = .9968$) compared to Day −5 ($p = .9757$). For severe cytopenias associated with CAR T cell therapy, higher differences in IBPS score were observed on Day 0 ($p = .4197$) compared to Day −5 ($p = .5438$). The IBPS score exhibited mixed differences in predictive values when calculated on Day −5 and on Day 0. The results for the IBPS scores are presented in Figure 4(C,G,K).

Discussion

Our study provides real-world data on adult patients with DLBCL treated with CAR T cell therapy in Slovenia and evaluates the performance of established predictive scores at two early time points. A major limitation of this analysis is the small cohort size, which limits statistical power and precludes drawing firm conclusions regarding the predictive performance of individual biomarkers and scores. Accordingly, the

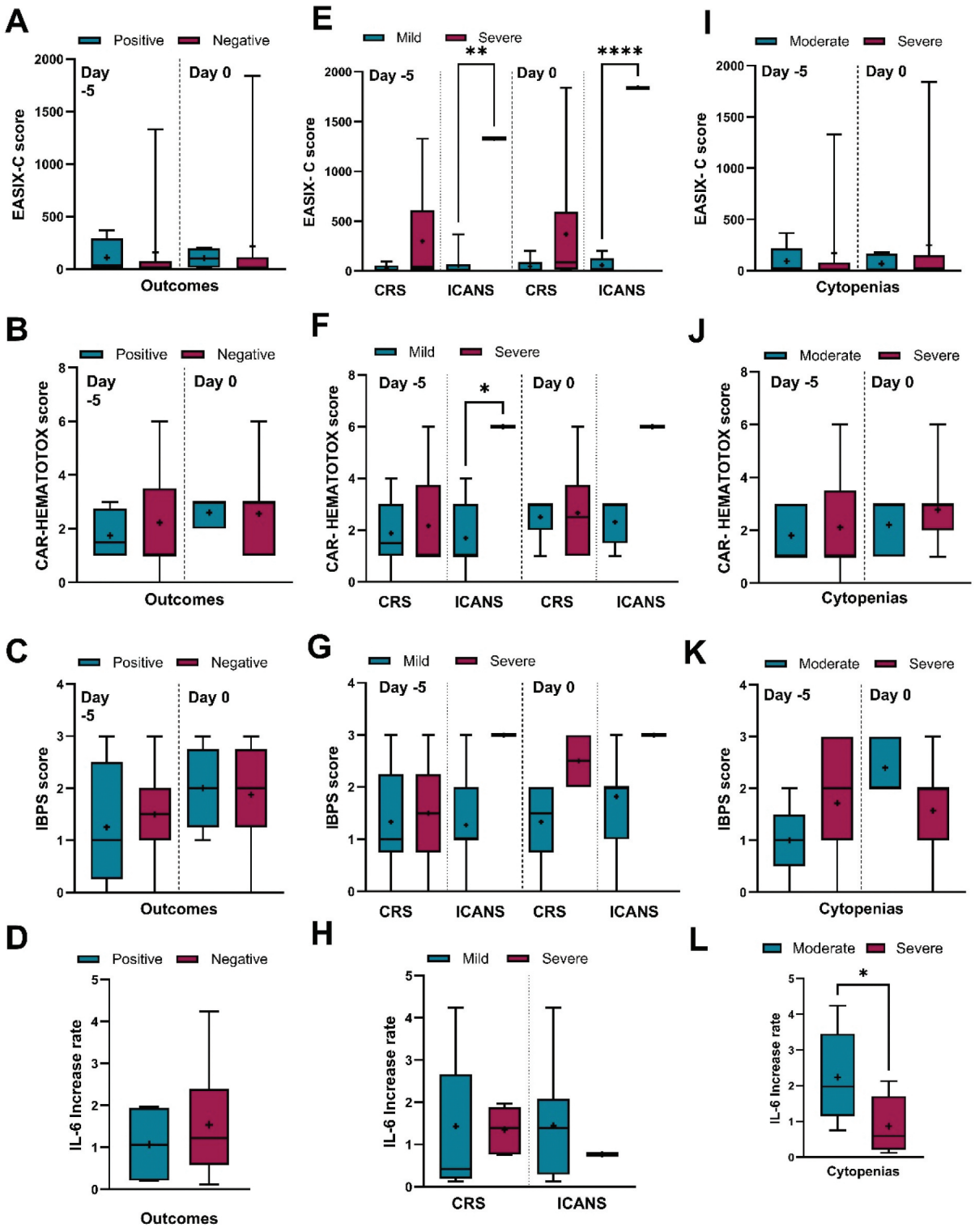

Figure 4. Comparative analysis of predictive scores and IL-6 increase rates in CAR T cell therapy for prediction of therapeutic outcomes, severity levels of CRS and ICANS, and severe cytopenias associated with CAR T cell therapy. The first column shows comparative analyses for positive/negative therapeutic outcomes for the EASIX-C score (A), the CAR-HEMATOTOX score (B), the IBPS score (C), and IL-6 increase rate (D), the second column shows comparative analyses for mild/severe CRS and ICANS on Day −5 and Day 0 for the EASIX-C score (E), the CAR-HEMATOTOX score (F), the IBPS score (G), and IL-6 increase rate (H), while the third column shows comparative analyses for moderate/severe cytopenias associated with CAR T cell therapy both on Day −5 and Day 0 for the EASIX-C score (I), the CAR-HEMATOTOX score (J), the IBPS score (K), and IL-6 increase rate (L). Box plots illustrate the interquartile range (IQR), with the bottom and top edges representing the first (Q1) and third (Q3) quartiles, respectively. Whiskers extend to the minimum and maximum values, highlighting the data spread. The central line within each box indicates the median value, while the mean is denoted by a '+' symbol within each box. Statistically significant differences were determined by one-way ANOVA followed by *post-hoc* Tukey's multiple comparisons test or unpaired t-test, where *$p \leq .05$; **$p \leq .01$; ***$p \leq .001$; ****$p \leq .0001$.

findings should be interpreted with appropriate caution and regarded as exploratory and hypothesis-generating rather than definitive. Nevertheless, the consistent application of validated predictive tools and the detailed longitudinal assessment of inflammatory markers provide a valuable foundation for further investigation and highlight the importance of continued evaluation in larger patient cohorts. The 50% response rate and 29% remission rate are encouraging and are comparable to findings from other institutions.[17] The occurrence of adverse events emphasizes the need for careful monitoring and treatment personalization.

The intriguing results on IL-6 increase rates offer a new perspective on its role in the context of CAR T cell therapy in adult DLBCL patients. Although IL-6 is a central mediator of inflammation, our findings challenge the expected correlation with toxicity, revealing no association with adverse events or treatment outcomes. Contrary to initial hypotheses, an inverse correlation was observed between the increase rate of IL-6 and the occurrence of severe cytopenias after treatment, indicating higher IL-6 increase rate might lead to fewer cytopenias. Although this finding was unexpected, several potential mechanisms may be considered. Hematologic toxicity after CAR T cell therapy is increasingly recognized as a complex process influenced not only by lymphodepleting chemotherapy but also by systemic inflammation and alterations of the bone marrow and tumor microenvironment.[18] In this context, a slower IL-6 increase may reflect an underlying inflammatory state or impaired hematopoietic reserve that predisposes patients to prolonged or late cytopenias, as previously suggested by studies linking baseline inflammation with CAR T – related hematotoxicity.[10] Conversely, IL-6 has also been shown to exert hematopoietic effects, including stimulation of thrombopoiesis and support of hematologic recovery, raising the possibility that a more pronounced early IL-6 kinetic response could, in some patients, be associated with less severe cytopenias.[19] Given the small cohort size and retrospective design, these interpretations remain speculative and warrant validation in larger, prospective studies with broader immune profiling.

In common practice, baseline assessments of predictive metrics on Day 0 are prioritized due to their proximity to the actual administration of CAR T cell therapy.[10,20] These assessments are thought to provide a current representation of the patient's status after the lymphodepleting regimen, which is a critical factor influencing the patient's response to therapy.[21] Our study was designed to evaluate the early predictive value of prognostic models calculated on Day −5, before the lymphodepleting regimen, to see if they could effectively forecast patient outcomes and adverse events in comparison to the more traditional Day 0 assessments. By analyzing the predictive power of these scores at Day −5, we sought to uncover whether earlier assessments might offer a valuable lead-time advantage in predicting the success of CAR T cell therapy and its associated complications.

The significant differences observed for the EASIX-C score in predicting ICANS but not CRS, consistent with findings from similar studies, suggest its potential utility in identifying patients at risk for neurotoxicity.[22] However, the lack of significant results for therapeutic outcomes and severe cytopenias points to the complex nature of endothelial injury and its relationship to the efficacy and side effects of CAR T cell therapy. For the CAR-HEMATOTOX score, our analysis showed limited applicability in this particular cohort of patients due to its variable predictive utility for treatment outcomes and severe cytopenias, however, encouraging results were obtained for predicting adverse events. Similar mixed results were observed for the IBPS score, which showed no significant differences in predicting treatment outcomes, adverse events, or severe cytopenias.

There are further clinical characteristics, biomarkers, prognostic systems, and multiparameter analyses being researched to address the efficacy of CAR T cell therapy. As research advances, the development of novel biomarkers and refined prognostic models will be key to enhancing patient selection, ensuring safer treatment administration, and better predicting long-term responses and relapses.

Acknowledgments

LS, IA, SZ, and MS designed the study, all authors contributed to data collection, analysis and interpretation, LS, IA, SZ, and MS wrote the original draft, all authors contributed to reviewing & editing. All authors have read and approved the final manuscript and consent to its publication.

Author contributions

CRediT: **Lucija Sršen:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing; **Irena Auersperger:** Conceptualization, Data curation, Project administration, Writing – review & editing; **Larisa Janžič:** Conceptualization, Project administration, Visualization, Writing – review & editing; **Andreja N. Kopitar:** Conceptualization, Project administration, Visualization, Writing – review & editing; **Katarina Reberšek:** Conceptualization, Project administration, Visualization, Writing – review & editing; **Barbara Jezeršek Novaković:** Conceptualization, Project administration, Visualization, Writing – review & editing; **Polona Novak:** Conceptualization, Project administration, Visualization, Writing – review & editing; **Karla Rener:** Conceptualization, Project administration, Visualization, Writing – review & editing; **Klara Šlajpah:** Conceptualization, Project administration, Visualization, Writing – review & editing; **Alojz Ihan:** Conceptualization, Project administration, Visualization, Writing – review & editing; **Samo Zver:** Conceptualization, Project administration, Visualization, Writing – review & editing; **Matjaž Sever:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Ethics statement

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board at UMC Ljubljana (approval code: SL K 01), with all patients providing written informed consent for participation and data usage.

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