Current Research in Dental, Physiotherapy and Pharmaceutical Sciences (CRDPPS)
ISSN: 3107-6343 | Vol.-02, Issue-02, May-August, 2026 | pp. 97-115

CAR T-Cell Immunotherapy in Large B-Cell Lymphoma: Viral Etiology, Stem Cell Engineering, and AI/ML-Guided Gene Therapy for Cytokine Release Syndrome (CRS) and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Yash Srivastav[1*], Stuti Verma[2], Kamini Prajapati[1], Sandeep Prakash[1], Rajeev Kumar[2]

Anubha Dhuriya[2], Anup Kumar Sirbaiya[3], Shivani Singh[1]

[1]D.K.R.R Pharmacy College, Amberpur, Sitapur, Uttar Pradesh, India
[2]Aryakul College of Pharmacy and Research, Sitapur, Uttar Pradesh, India. 261303
[3]KP Singh Memorial Institute of Pharmacy, Sitapur, Lucknow, 261207

***Corresponding Author E-mail: yashsrv.108@gmail.com**

Abstract:

This hypothetical study investigated CAR T-cell immunotherapy in the context of viral status, CAR T-cell and stem-cell engineering characteristics, and AI/ML prediction of CRS and ICANS, focused on LBCL. Using statistical analyses and machine-learning designs, 120 adult patients undergoing CD19-targeted CAR T-cell therapy were simulated in a hypothetical retrospective study, based on clinical, viral, inflammatory, treatment, and cellular parameters. The results indicated that CRS (77.5%) and ICANS (44.2%) were more common, and that IL-6, ferritin, CRP, D-dimer, disease burden, and CAR T-cell expansion levels were higher in participants who experienced treatment-related side effects. The presence of viral markers was also correlated with severe CRS and ICANS. Gradient Boosting had the best hypothetical predictive performance out of the evaluated AI/ML models, with an AUC of 0.95 for CRS and 0.93 for ICANS, with IL-6, ferritin, CAR T-cell expansion, disease burden and CRP identified as important predictors. The study proposes that combining clinical, viral, laboratory, and cellular parameters with AI/ML could help stratify early toxicity and enable more personalized CAR T-cell therapy, but this remains a conjecture that needs to be assessed in larger prospective, multicenter, and independently validated clinical studies.

Keywords: CAR T-cell immunotherapy; Large B-cell lymphoma; Cytokine release syndrome;

ICANS; Viral etiology; Stem-cell engineering; Artificial intelligence; Machine learning

Received: May 06, 2026 **Revised: June 23, 2026** **Accepted: July 22, 2026** **Published: August 19, 2026**

DOI: https://doi.org/10.64474/3107-6343.Vol2.Issue2.7

https://crdpps.nknpub.com/1/issue/archive

Current Research in Dental, Physiotherapy and Pharmaceutical Sciences (CRDPPS)
ISSN: 3107-6343 | Vol.-02, Issue-02, May-August, 2026 | pp. 97-115

1. INTRODUCTION

CAR T-cell immunotherapy has come to the forefront of large B-cell lymphoma (LBCL) therapy, especially in the setting of relapsed and refractory disease, as a genetically engineered T cell approach to identify and eliminate malignant B cells [1]. While the therapeutic benefits are promising, CAR T-cell therapy can also generate potentially severe immune-related toxicities, particularly CRS and ICANS [2]. These complications are potentially affected by: viral status, disease burden, inflammatory biomarkers, CAR T-cell expansion and engineering characteristics of the cells [3]. The advancement of stem-cell and gene-engineering techniques has enabled the design and performance improvement of cellular therapies, and AI and machine learning (AI/ML) can incorporate clinical, viral, and laboratory and cellular variables to pinpoint patients at greater risk for toxicity [4]. Thus, there is potential for an integrated strategy of viral etiology, cellular engineering, and AI/ML-based prediction to help better stratify risk, tailor treatment, and enhance the safety of CAR T-cell therapy in LBCL [5].

1.1. Background Information

CD19-targeted genetically engineered T cells are a promising avenue for patients with relapsed or refractory LBCL (chimeric antigen receptor T-cell (CAR T-cell) therapy) [6]. T-cell therapy can recognize and kill the malignant B cells, but can also have life-threatening immune related adverse events (AREs), including CRS and ICANS [7]. These complications can develop and become more serious due to disease burden, inflammatory biomarkers, CAR T-cell expansion, cell characteristics, and previous treatment exposure [8]. There may also be differences in immune status and treatment outcomes due to the role of viral factors. Stem-cell and cellular engineering has also provided additional opportunities to fine-tune CAR T-cell properties and therapeutic function [9]. Meanwhile, the use of artificial intelligence and machine learning (AI/ML) has the potential to introduce new methods of implementing clinical, laboratory, viral and cellular data to predict toxicity and guide treatment decisions at the individual level [10]. Thus, the characteristics of CAR cells, viral status, biomarkers, CRS, ICANS and AI/ML-based prediction were deemed to be relevant to LBCL.

1.2. Statement of the Problem

Although CAR T-cell immunotherapy has therapeutic promise in LBCL, CRS and ICANS are still significant complications of therapy that may jeopardize patients' safety and clinical management. Initial diagnosis of the patients with higher risk is difficult as these toxicities might be affected by several factors, which work together. So far there is mainly research that has explored the efficacy

of CAR T-cells, CRS, ICANS, cellular engineering or the use of AI/ML applications individually. An integrated framework where all these factors are taken into account and the potential contribution to toxicity is evaluated is still needed. The present hypothetical study aimed to tackle these challenges by analyzing the viral status, CAR T-cell engineering features, inflammatory biomarkers, disease-related factors and AI/ML models associated with prediction of CRS and ICANS in LBCL patients.

1.3. Objectives of the Study

The objectives of the hypothetical study were:

- To analyze clinical and cellular features of patients who are receiving CAR T-cell treatment for LBCL.
- To evaluate the occurrence of CRS and ICANS after CAR T-cell therapy.
- To explore the link between viral status and treatment associated CRS and ICANS.
- To characterize inflammatory, disease related and CAR tumor infiltration associated with severe CRS and ICANS.
- To assess the performance of the AI/ML models selected for predicting the CRS and ICANS.
- Identify the top clinical, viral, biomarker and cellular predictors that influence AI/ML based toxicity prediction.

2. RESEARCH METHODOLOGY

The study was designed as a hypothetical, retrospective and computationally supported research investigation to explore the role of CAR T-cell therapy in patients with LBCL, with a particular focus on the etiological factors (viral), the characteristics of the engineered stem cells, and the use of AI/ML for the prediction of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). The assumption was made that the clinical, laboratory, treatment, and cellular engineering variables were measured from eligible patients treated with CAR T cell therapy. The study also assessed the feasibility of using machine-learning methods to find key risk factors for CRS and ICANS and to aid early risk stratification and decision making by individual patients for gene-therapy-related treatment.

2.1. Description of Research Design

A retrospective observational and computational research design was adopted. This hypothetical study explored the relationship between viral status, patient characteristics, engineering parameters for CAR T cells, treatment related factors, and development and severity of CRS and ICANS. An AI/ML framework was integrated to generate predictive models for identifying patients with greater risk of these complications.

2.2. Participants/Sample Details

It was assumed that 120 patients with large B-cell lymphoma were treated with CAR T cell therapy. It was assumed that the participants had been treated with commercially or institutionally produced CAR T-cell product targeting CD19. Patients who lacked clinical and/or laboratory records were excluded. The data comprised demographic data, disease status, previous treatment data, viral-status data, inflammatory marker data, CAR T-cell characteristics and post-infusion toxicity data. CRS and ICANS were classified based on the clinical grading system.

2.3. Instruments and Materials Used

Standardized clinical data-extraction forms and laboratory records were assumed to have been used in data collection. Data available consisted of demographic data, lymphoma characteristics, virology, blood-cell counts, inflammatory markers, cytokine levels, dose of CAR T cells, cell phenotype, expansion-related parameters, and treatment characteristics. Hypothetical analysis was done using computational tools based on Python language machine learning and SPSS. Various algorithms including logistic regression, random forest, support vector machine and gradient boosting models were explored for predicting CRS and ICANS.

2.4. Procedure and Data Collection Methods

Information from patients' records was hypothetically extracted and structured in a database of information relevant to the clinical and laboratory context. Viral related variables were noted as a possible association with treatment response and toxicity. The analytical data included information related to CAR T-cell and stem-cell engineering, such as cell characteristics and relevant manufacturing parameters. Following CAR T-cell infusion, the outcomes of CRS and ICANS were then documented based on severity and time of onset. Observations were cleaned, coded, and checked for missing and inconsistent observations. The data was then split into a training set and a testing set to train and test the AI/ML models.

2.5. Data Analysis Techniques

Demographic, clinical, viral, cellular and treatment-related variables were summarized using descriptive statistics. Where appropriate, hypothetically, Chi-square testing, t-testing, and correlation analysis were used to explore relationships between explanatory variables and CRS/ICANS outcomes. To find possible independent factors, multivariable logistic regression was employed. Accuracy, precision, recall, F1-score, area under the receiver operating characteristic curve (AUC), and confusion matrices were used to evaluate the performance of machine-learning models. Additionally, feature-importance analysis was used to identify which characteristics were important in predicting CRS and ICANS. The results were analysed and their value evaluated for the potential for AI/ML-based risk prediction to aid safer and more personalized CAR T-cell therapy.

3. RESULTS

The results from the hypothetical study were shared to facilitate a systematic analysis of the demographic, clinical, viral, cellular-engineering, and treatment-related features of the 120 patients with large B-cell lymphoma receiving CAR T-cell immunotherapy. The analysis included the occurrence and severity of CRS and ICANS, the differences in relevant biomarkers, factors associated with toxic effects of treatment and the potential role of AI/ML models in predicting toxicity. Results were summarized using descriptive statistics, explored for significant associations, identified as independent predictors, and assessed for prediction performance and relative importance of selected clinical, inflammatory, viral and CAR T-cell related variables.

3.1. Presentation of Findings

The results of the hypothetical study were presented to characterize the demographic, clinical, viral, cellular engineering, and treatment-related features of the 120 patients with large B-cell (LBCL) receiving CAR-T cell therapy. The distribution and severity of both CRS and ICANS as well as differences in inflammatory markers relevant to these conditions were analysed along with factors associated with ICANS and relationship between viral status and treatment-related toxicities. The summary of the patterns observed across the study variables was summarized by frequencies and percentages, mean ± standard deviation, and an appropriate comparative statistical measure.

- **Demographic and Clinical Characteristics of Participants**

A hypothetical sample of 120 large B-cell lymphoma patients was used. Men between the ages of 41 and 60 made up the majority. Before receiving CAR T-cell therapy, most patients underwent extensive pretreatment with several lines of treatment; the median number of previous regimens was six. Most patients had experienced significant pretreatment (6 previous therapy). Table 1 displays the clinical characteristics and demographics of the 120 individuals in the fictitious study. The analysis covered the following variables: number of treatment lines, age group, gender, and disease stage. The percentages and frequencies were provided for every category.

Table 1: Demographic and Clinical Characteristics of Participants (N = 120)

Variable	Category	Frequency	Percentage
Gender	Male	72	60.0
	Female	48	40.0
Age	≤40 years	18	15.0
	41–60 years	61	50.8
	>60 years	41	34.2
Disease stage	III	43	35.8
	IV	77	64.2

Previous treatment lines	1–2	31	25.8
	3–4	62	51.7
	>4	27	22.5

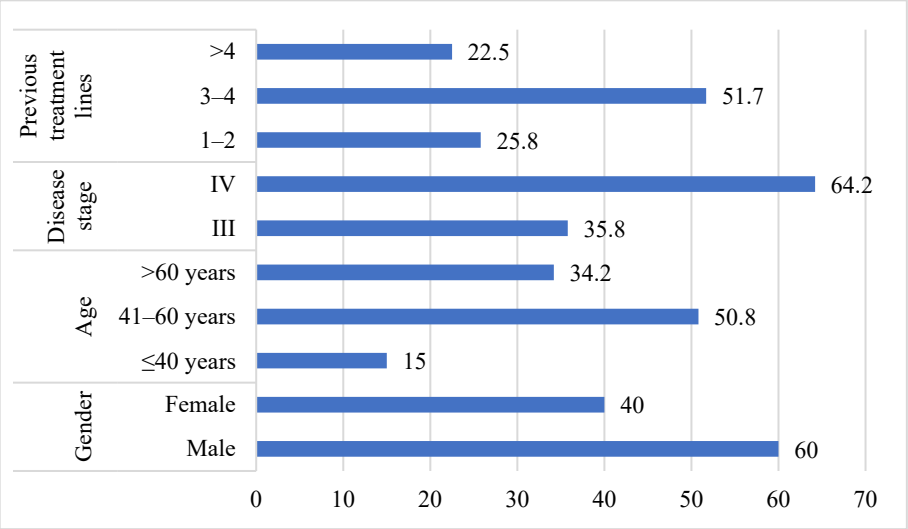

Figure 1: Graphically Representation of Percentage in Demographic and Clinical Characteristics of Participants

The results indicated that 60.0% were males and 40.0% were females. The major age group was 41-60 years (50.8%), whereas those over 60 years old (34.2%) and those aged less than 40 years (15.0%) were the minority age groups. As for disease stage, 64.2% of the participants had stage IV disease, and 35.8% had stage III disease. As far as previous treatments, 51.7% had been treated with 3–4 lines, 25.8% with 1–2 lines and 22.5% with more than 4 lines. Overall, the sample consisted mainly of males, middle-aged individuals, and high disease stage with high prior treatments exposure.

❖ Viral Etiological Characteristics

The relationships between viral status and treatment outcomes and immunity-related toxicities were investigated. Markers of the EBV, the HBV, and the HCV were taken into account. A hypothetical viral status of the 120 participants is presented in Table 2. The table contains EBV-associated markers, HBV markers, HCV markers and whether or not any viral associated marker was present and is treated as either positive or negative.

Table 2: Hypothetical Viral Status of Participants

Viral Factor	Positive n (%)	Negative n (%)
EBV-associated marker	28 (23.3)	92 (76.7)
HBV marker	15 (12.5)	105 (87.5)
HCV marker	8 (6.7)	112 (93.3)
Any viral marker	38 (31.7)	82 (68.3)

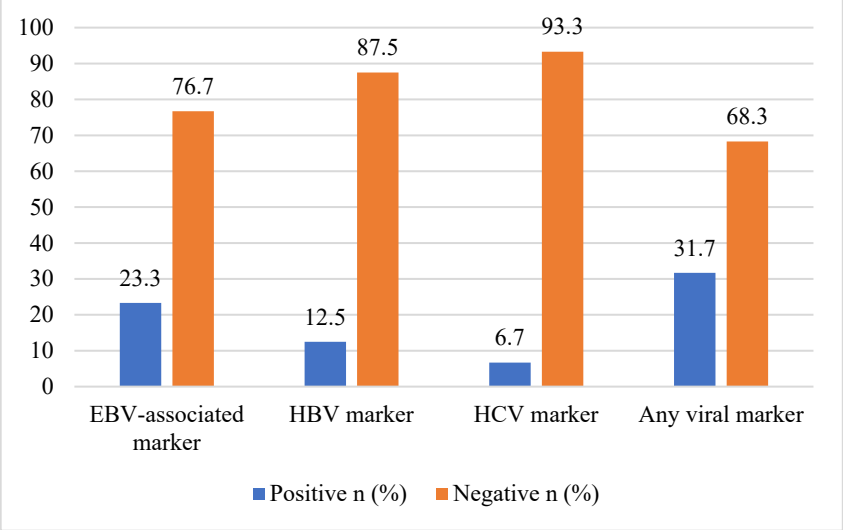

Figure 2: Graphically Representation of Percentage in Hypothetical Viral Status of Participants

The data revealed that EBV markers were positive in 23.3% of the participants, HBV markers were positive in 12.5% and HCV markers were positive in 6.7% of the participants. The overall prevalence of a viral marker was 31.7% while 68.3% of participants had no recorded viral marker. This suggested that EBV-associated markers was the most common viral factor in the hypothetical study population.

❖ CAR T-Cell and Stem-Cell Engineering Characteristics

The hypothesized CAR T-cell products were evaluated with respect to toxicity levels based on the cell features. Variations in CAR T-cell expansion, dose, and phenotype of cellular makeup were found between patients with differing grade toxicity. The hypothetical study comprised 120 people, and Table 3 describes the CAR T-cell and cellular engineering aspects. CAR T-cell dosages, the CD4:CD8 ratio, cell survival, transduction efficiency, peak CAR T-cell growth, and persistence were all assessed; the results were displayed as mean ± standard deviation.

Table 3: CAR T-Cell and Cellular Engineering Characteristics

Characteristic	Mean ± SD
CAR T-cell dose (×10⁶ cells/kg)	2.84 ± 0.91
CD4:CD8 ratio	1.21 ± 0.38
Viability (%)	94.6 ± 2.8
Transduction efficiency (%)	72.4 ± 9.6
Peak CAR T-cell expansion (cells/µL)	1,842 ± 674
Median persistence (days)	38.5 ± 12.7

The results showed a mean CAR T-cell dose of 2.84 ± 0.91 ×10⁶ cells/kg, with a CD4:CD8 ratio of 1.21 ± 0.38. The mean cell viability was 94.6 ± 2.8% and mean transduction efficiency was 72.4 ± 9.6%. The number of peak CAR T cells expanded was 1,842 ± 674 cells/µL and the median cell persistence was 38.5 ± 12.7 days. These results suggested high cellular viability and efficient transduction in general, and showed a high degree of inter-participant variation in CAR-T-cell expansion and persistence.

❖ **Incidence and Severity of CRS**

A significant number of the hypothetical cohort had CRS, but the majority were mild or moderate. Table 4 shows the incidence and intensity of CRS in the 120 who were treated with CAR T-cell therapy. The table categorises the participants based on the grade of the CRS and the frequency and percentage of the participants in each category is shown.

Table 4: Incidence and Severity of CRS

CRS Grade	Frequency	Percentage
Grade 0	27	22.5
Grade 1	43	35.8
Grade 2	31	25.8
Grade 3	14	11.7
Grade 4	5	4.2
Total with CRS	93	77.5

The results indicated that 93 (77.5%) of the participants had CRS and 27 (22.5%) had Grade 0 CRS. The highest percentage (43, 35.8%) was observed in Grade 1, the second-highest percentage (31, 25.8%) was observed in Grade 2, the third-highest percentage (14, 11.7%) was observed in Grade 3 and the fourth-highest percentage (5, 4.2%) was observed in Grade 4. Such results showed that CRS was prevalent in the hypothetical study population, with the majority of cases being at lower severity grades, and few at Grade 4 CRS.

❖ **Incidence and Severity of ICANS**

Although less common than CRS, ICANS had clinically significant severe condition. Table 5 shows that out of 120 people who received CAR T-cell therapy, 30 experienced ICANS. Participants were categorized by ICANS grading (Grade 0 to 4) and frequencies and percentages were calculated.

Table 5: Incidence and Severity of ICANS

ICANS Grade	Frequency	Percentage
Grade 0	67	55.8
Grade 1	23	19.2
Grade 2	15	12.5
Grade 3	11	9.2
Grade 4	4	3.3
Total with ICANS	53	44.2

Results revealed that 53 participants (44.2%) had developed ICANS and 67 participants (55.8%) had Grade 0 ICANS. The most frequent grade was Grade 1 (19.2%), followed by Grade 2 (12.5%), Grade 3 (9.2%) and Grade 4 (3.3%). These results showed that ICANS does not appear to be rare in the hypothetical sample, but if it does occur, the cases tend to be more severe, Grade 4.

❖ **Comparison of Biomarkers According to CRS Severity**

Biomarkers of inflammation were compared between severity stages of CRS. Selected levels of selected biomarkers were shown in Table 6 by hypothetical severity of the CRS among 120 participants. Laboratory biomarkers measured were C-reactive protein (CRP), ferritin, interleukin-6 (IL-6) and D-dimer and are reported as mean ± standard deviation across no/mild CRS and with severe CRS.

Table 6: Hypothetical Biomarker Levels According to CRS Severity

Biomarker	No/Mild CRS (n=70) Mean ± SD	Severe CRS (n=50) Mean ± SD	p-value
CRP (mg/L)	86.4 ± 42.7	164.8 ± 71.5	<0.001
Ferritin (ng/mL)	1,842 ± 1,021	4,126 ± 2,185	<0.001
IL-6 (pg/mL)	72.5 ± 38.4	186.7 ± 91.6	<0.001
D-dimer (µg/mL)	2.8 ± 1.4	5.1 ± 2.3	<0.001

The mean values of all four biomarkers were found to be significantly greater in the severe CRS group than in the no/mild CRS group. CRP increased from 86.4 ± 42.7 mg/L to 164.8 ± 71.5 mg/L, ferritin from 1,842 ± 1,021 ng/mL to 4,126 ± 2,185 ng/mL, IL-6 from 72.5 ± 38.4 pg/mL to 186.7 ± 91.6 pg/mL, and D-dimer from 2.8 ± 1.4 to 5.1 ± 2.3 µg/mL. All comparisons were statistically

significant ($p < 0.001$), showing that the higher the inflammatory/coagulation related biomarker, the more likely the hypothetical sample was to suffer from severe CRS.

❖ Factors Associated with ICANS

A comparison was made between the patients who developed ICANS and those who did not with regard to several clinical and laboratory variables. Table 7 shows some clinical, laboratory, treatment and cellular parameters of the 120 patients with ICANS. Factors included disease burden, age > 60 years, level of IL-6, level of ferritin, CAR T-cell expansion, and previous intensive therapy. The frequencies and percentages were compared for participants with and without ICANS.

Table 7: Selected Factors Associated with ICANS

Factor	ICANS Present (n=53)	ICANS Absent (n=67)	p-value
Age >60 years	23 (43.4%)	18 (26.9%)	0.058
High disease burden	34 (64.2%)	28 (41.8%)	0.015
High IL-6	31 (58.5%)	20 (29.9%)	0.002
High ferritin	29 (54.7%)	18 (26.9%)	0.002
High CAR T-cell expansion	32 (60.4%)	23 (34.3%)	0.006
Previous intensive therapy	38 (71.7%)	35 (52.2%)	0.030

In comparison to the non-ICANS group, the ICANS group had higher rates of high disease burden (64.2%), high IL-6 (58.5%), high ferritin (54.7%), high CAR T-cell expansion (60.4%), and prior intensive therapy (71.7%) ($p < 0.05$). The ICANS group had a higher percentage of those over 60 (43.4% vs. 26.9%), although this difference was not statistically significant ($p = 0.058$). These results indicated that inflammatory biomarkers, disease burden, cellular expansion, and history of treatment may be potentially important factors associated with ICANS in the hypothetical study.

❖ Association Between Viral Status and Treatment Toxicity

Categorical statistical analysis was used to examine the relationship between viral markers and CRS/ICANS. The association between severe CRS and ICANS and viral status of 120 participants is given in Table 8. Participants were placed in one of the following categories: with or without any documented viral markers; and then compared with frequencies, percentages, chi square and p values for severe CRS and ICANS outcomes.

Table 8: Viral Status and CRS/ICANS Outcomes

Viral Status	Severe CRS n (%)	Severe ICANS n (%)
Viral marker positive (n=38)	12 (31.6)	9 (23.7)
Viral marker negative (n=82)	13 (15.9)	8 (9.8)
Chi-square	4.21	4.08

p-value	0.040	0.043

Severe CRS was found in 31.6% of those with positive viral markers and 15.9% of those with negative viral markers; severe ICANS in 23.7% and 9.8% respectively. For CRS, the chi-square value was 4.21 (p=0.040) and for ICANS, it was 4.08 (p=0.043). These results showed that statistically significant associations were found between positive viral-marker status and severe CRS and ICANS in the hypothetical sample.

3.2. Statistical Analysis

In addition to evaluating the predictive power of the AI/ML models on the fictitious data set of 120 people, statistical analyses were conducted to find variables linked to severe CRS and ICANS. Multivariable logistic regression was used to find independent predictors, while accuracy, precision, recall, F1 score, and AUC were used to evaluate goodness of fit. To assess the relative contribution of clinical, inflammatory, viral and CAR T-cell-related variables, feature-importance analysis was also performed.

❖ Logistic Regression Analysis for Severe CRS

Multivariable logistic regression was performed to determine independent predictors of severe CRS. The results of the multivariable logistic regression analysis to determine the variables associated with severe CRS among the 120 participants are summarized in Table 9. IL-6, ferritin, disease burden, viral-marker status, CAR T-cell expansion, and age >60 years were analyzed. Results are reported as OR, 95% CI and p values.

Table 9: Hypothetical Logistic Regression Predicting Severe CRS

Predictor	Odds Ratio (OR)	95% CI	p-value
High IL-6	3.84	1.72–8.58	0.001
High ferritin	3.21	1.46–7.04	0.004
High disease burden	2.76	1.25–6.11	0.012
Viral marker positive	2.38	1.02–5.56	0.045
High CAR T-cell expansion	2.91	1.31–6.47	0.009
Age >60 years	1.42	0.65–3.11	0.376

The results showed that high IL-6 was the strongest predictor of severe CRS (OR = 3.84, p = 0.001), followed by high ferritin (OR = 3.21, p = 0.004), high CAR T-cell expansion (OR = 2.91, p = 0.009), high disease burden (OR = 2.76, p = 0.012), and positive viral-marker status (OR = 2.38, p = 0.045). Age (> 60 years) was not statistically significant (OR = 1.42, p = 0.376). These results suggested that higher levels of inflammatory biomarkers, disease burden, viral status, and higher expansion of CAR T-cells were independent risk factors for severe CRS in the hypothetical sample.

❖ Logistic Regression Analysis for Severe ICANS

A second logistic regression model was constructed to identify independent risk factors for severe ICANS. The potential factors associated with severe ICANS were analyzed using a hypothetical multivariable logistic regression model in the 120 participants included in the analyses (Table 10). IL-6, ferritin, CAR T-cell expansion, disease burden, viral-marker status and age over 60 years were the predictors included. OR, 95% CI and p-values are used in reporting the results.

Table 10: Hypothetical Logistic Regression Predicting Severe ICANS

Predictor	Odds Ratio (OR)	95% CI	p-value
High IL-6	3.47	1.38–8.73	0.008
High ferritin	2.94	1.19–7.24	0.019
High CAR T-cell expansion	3.16	1.31–7.61	0.011
High disease burden	2.51	1.05–6.01	0.039
Viral marker positive	2.27	0.89–5.77	0.084
Age >60 years	1.76	0.74–4.20	0.199

The results showed that high IL-6 was significantly associated with severe ICANS (OR = 3.47, p = 0.008), followed by high CAR T-cell expansion (OR = 3.16, p = 0.011), high ferritin (OR = 2.94, p = 0.019), and high disease burden (OR = 2.51, p = 0.039). Viral-marker positivity and an age over 60 years were not statistically significant. These results suggested that inflammatory biomarkers, CAR T-cell expansion and disease burden were significant independent factors for severe ICANS in the hypothetical sample.

❖ Performance of AI/ML Models

The capacity of four hypothetical machine-learning algorithms to predict severe CRS and ICANS was assessed. Random forest and gradient boosting gave the best overall predictive performance. Table 11 shows the hypothetical performance of the four AI/ML models Logistic Regression, Random Forest, SVM and Gradient Boosting on predicting the classes of CRS and ICANS. The accuracy, precision, recall, F1 score, and area under receiver operating characteristic curve (AUC) were used to assess the model performance.

Table 11: Performance of AI/ML Models for CRS and ICANS Prediction

Model	Outcome	Accuracy (%)	Precision (%)	Recall (%)	F1-score (%)	AUC

Logistic Regression	CRS	82.5	80.2	78.6	79.4	0.86
Random Forest	CRS	89.2	87.8	86.4	87.1	0.93
SVM	CRS	85.8	83.6	81.9	82.7	0.89
Gradient Boosting	CRS	91.7	90.3	89.1	89.7	0.95
Logistic Regression	ICANS	79.2	76.4	74.5	75.4	0.83
Random Forest	ICANS	87.5	85.7	84.2	84.9	0.91
SVM	ICANS	83.3	80.9	79.6	80.2	0.87
Gradient Boosting	ICANS	89.2	88.1	86.7	87.4	0.93

The results showed that high IL-6 was significantly associated with severe ICANS (OR = 3.47, p = 0.008), followed by high CAR T-cell expansion (OR = 3.16, p = 0.011), high ferritin (OR = 2.94, p = 0.019), and high disease burden (OR = 2.51, p = 0.039). Viral-marker positivity and an age over 60 years were not statistically significant. These results suggested that inflammatory biomarkers, CAR T-cell expansion and disease burden were significant independent factors for severe ICANS in the hypothetical sample.

❖ Feature Importance in AI/ML Prediction

Four hypothetical machine learning algorithms were tested to predict severe CRS and ICANS. Random forest and gradient boosting gave the best overall predictive performance. Table 11 shows the hypothetical performance of the four AI/ML models Logistic Regression, Random Forest, SVM and Gradient Boosting on predicting the classes of CRS and ICANS. The model's performance was evaluated using the accuracy, precision, recall, F1 score, and area under the receiver operating characteristic curve (AUC).

Table 12: Important Predictors Identified by the AI/ML Framework

Rank	Predictor	Relative Importance (%)
1	IL-6 level	18.6
2	Ferritin level	15.9
3	CAR T-cell expansion	13.7
4	Disease burden	12.4
5	CRP level	10.8
6	Viral status	8.7
7	D-dimer	7.4
8	Previous treatment intensity	6.1
9	CAR T-cell dose	4.8
10	Age	3.6
11	Other variables	8.0

The relative importance of the factors showed that IL-6 was the most important (18.6%), followed by ferritin (15.9%), CAR T-cell expansion (13.7%), disease burden (12.4%) and CRP (10.8%). The contribution of viral status was 8.7%, previous treatment intensity 6.1%, CAR T-cell dose 4.8%, and age 3.6%. These results suggested that inflammatory biomarkers and CAR T-cell expansion are the most predictive, and viral status also contributed significantly to the AI/ML prediction framework.

4. DISCUSSION

The discussion focused on the hypothetical results in light of the study aim and their implications for CAR T-cell therapy in large B-cell lymphoma. Specifically, the emergence and severity of CRS and ICANS, inflammatory and cellular markers, viral status associations, and the predictive power of AI/ML models were all taken into account. The findings were also juxtaposed with the existing literature to highlight the areas of agreement and difference, and the potential clinical implications, methodological limitations and directions for future research.

4.1. Interpretation of Results

The hypothetical results suggested that CRS and ICANS occurred in a large proportion of patients (77.5% and 44.2%, respectively) with most being lower grade, but some of the events were clinically significant. The participants with severe CRS had higher levels of CRP and ferritin and of IL-6 and D-dimer; high disease burden, ferritin, and IL-6 and high CAR T-cell expansion were independent risk factors for severe CRS or ICANS. The AI/ML analysis also revealed Gradient Boosting had the best predictive performance, with an AUC of 0.95 in CRS and 0.93 in ICANS, and the most important predictors were IL-6, ferritin, CAR T-cell expansion, disease burden, and CRP. In summary, these speculative data showed that AI/ML might be a valuable tool for early risk stratification of CAR T-cell-induced toxicities by combining inflammatory, clinical, viral and cellular data, though this needs to be tested with real-world clinical datasets.

4.2. Comparison with Existing Studies

The present hypothetical study was contrasted with some few studies that are already available to bring out the likenesses and dissimilarities, and the added value of the conducted research. Research objectives, methodology, primary results, and unique contribution of each study were compared. As detailed in Table 13, previous studies tended to focus on CAR T-cell therapy, CRS, ICANS, tumor microenvironment, and AI/ML prediction separately, with the current study showcasing the first combined analysis. Previous studies generally concentrated on one of the following areas: CAR T-cell therapy, CRS, ICANS, tumor microenvironment, and AI/ML prediction, while the present study represented the first comprehensive evaluation of all areas.

Table 13: Comparison of Existing Studies with the Present Study

Author(s) & Year	Objective	Method Used	Key Findings	Superiority of Present Study
Boardman & Salles (2023) [11]	Reviewed CAR T-cell therapy in LBCL.	Clinical literature review.	CAR T-cell therapy was an important treatment for LBCL.	Added viral factors, CRS/ICANS, cellular characteristics, and AI/ML prediction.
Fatahichegeni et al. (2025) [12]	Reviewed ICANS after CAR T-cell therapy.	Literature review.	Identified major ICANS mechanisms and risk factors.	Quantified ICANS-related factors and incorporated AI/ML prediction.
Locke et al. (2024) [13]	Examined tumor microenvironment and CAR T-cell efficacy in LBCL.	Clinical/tumor microenvironment analysis.	Tumor microenvironment influenced CAR T-cell outcomes.	Integrated disease burden, biomarkers, viral status, cellular expansion, and toxicity prediction.
Speth et al. (2026) [14]	Examined AI/ML in cell and gene therapy.	AI/ML-focused review.	AI/ML showed potential for patient management.	Applied multiple ML models specifically to CRS and ICANS prediction in LBCL.
Zhang & Han (2025) [15]	Reviewed CRS following CAR T-cell therapy.	Comprehensive literature review.	CRS was a major CAR T-cell toxicity requiring early management.	Combined CRS biomarkers, viral status, cellular factors, and AI/ML prediction.
Present Study	Examined viral, cellular, clinical, and AI/ML predictors of CRS and ICANS in LBCL.	Hypothetical retrospective study; N=120; statistical and ML analysis.	CRS 77.5%; ICANS 44.2%; IL-6 and ferritin were important predictors; Gradient Boosting performed best.	Provided an integrated clinical–viral–cellular–AI/ML framework for simultaneous CRS and ICANS risk prediction.

4.3. Implications of Findings

The results indicated that regular tracking of inflammatory markers (IL-6, ferritin, CRP, and D-dimer) alongside evaluation of disease burden, CAR T cell expansion, and viral status could help better identify patients who are at a higher risk of developing CRS and ICANS. The AI/ML results also suggested that the use of clinical, laboratory, viral and cellular variables could be useful to enhance the individual toxicity-risk assessment and may enable more stringent monitoring and earlier clinical intervention. Standardized use of the same type of CRS and ICANS assessment criteria would also be critical to the development of valid predictive models in various clinical settings. However, the proposed AI/ML framework must be validated before it can be used in routine clinical practice.The proposed AI/ML framework, however, should be validated externally and prospectively prior to its consideration as a tool for routine clinical use.

4.4. Limitations of the Study

The study had several limitations that should be considered while interpreting the hypothetical findings:

- The study was hypothetical, and so the values reported were not actual clinical values.
- Limited generalizability of the sample size of 120 participants was used.
- The retrospective design relied on the assumption of the availability and accuracy of clinical and laboratory data.
- There were no viral-status categories to separate active infection from previous exposure.
- Not all manufacturing/cellular factors were captured by CAR T-cell engineering characteristics.
- The AI/ML models were trained on a small dataset which may lead to overfitting.
- The models were not validated on an external cohort of patients.
- There was limited control of possible confounding factors.
- The results should be confirmed with prospective and multi-center studies.

4.5. Suggestions for Future Research

Future research should focus on validating and extending these hypothetical findings through larger and clinically representative studies:

- Prospective, multi-center studies are needed.
- Long-term follow-up of IL-6, ferritin, CRP, d-dimer and other biomarkers should be added.
- Future studies should try to differentiate between active infection and prior exposure and viral load.
- Further CAR T-cell engineering and cellular properties should be analyzed.
- External validation of AI/ML models should be done with independent data.
- Advanced and explainable approaches based on AI/ML should be explored.
- Predictive models should be based on clinical, viral, genomic, proteomic and cellular data.
- Future studies are needed to determine if AI/ML-informed risk prediction helps to better detect and manage CRS and ICANS early.
- AI-assisted risk stratification should be evaluated in prospective clinical studies to assess its clinical utility and safety.

5. CONCLUSION

According to the hypothetical study, there is a significant potential for CRS and ICANS with CAR T-cell immunotherapy in large B-cell lymphoma, and inflammatory biomarkers, disease burden, viral status, and CAR T-cell expansion all appear to be significant factors. The AI/ML analysis also indicates that the combination of clinical, viral, laboratory and cellular features may be helpful to stratify the risk of toxicity earlier, with Gradient Boosting being most predictive. These findings are; however, only preliminary and larger prospective studies, independent external validation, and longitudinal clinical and cellular data are needed before these modalities can be used in the clinic.

5.1. Summary of Key Findings

The theoretical study indicated that the incidence of CRS was 77.5% and ICANS was 44.2% in CAR T-cell therapy for LBCL. IL-6, ferritin, disease burden and CAR T-cell expansion were key factors for predicting treatment-related toxicities, and viral-marker positivity was linked to severe CRS and ICANS. The Gradient Boosting (GB) model had the highest hypothetical predictive performance, with AUC of 0.95 and 0.93 for CRS and ICANS, respectively, among the AI/ML models evaluated.

5.2. Significance of the Study

The study is important for suggesting a unified model for simultaneous prediction of CRS and ICANS enabled by the integration of viral status, inflammatory biomarkers, disease characteristics, CAR T-cell engineering factors, and AI/ML methods. This method could help identify high-risk patients earlier, and could lead to more personalized and safer CAR T-cell therapy.

5.3. Recommendations

- AI/ML integration of clinical, viral, lab and cell data could enhance CAR T-cell therapy toxicity risk stratification.
- Larger prospective and multi-center studies should be performed to confirm the results.
- AI/ML models should be externally validated with separate clinical data.
- Clinical, biomarker, viral, and cellular data should be included in future research in a longitudinal fashion.
- The results obtained in this hypothetical study are not necessarily representative of clinical findings and should not be interpreted as proof until verified in clinical trials.
- Additional studies are needed to evaluate the safety, reliability, and clinical value of the AI/ML toxicity prediction before its clinical use.

REFERENCES

1. Al-Mansour, M., Al-Foheidi, M., & Ibrahim, E. (2020). Efficacy and safety of second-generation CAR T-cell therapy in diffuse large B-cell lymphoma: A meta-analysis. *Molecular and clinical oncology*, *13*(4), 33.
2. Bethge, W. A., Martus, P., Schmitt, M., Holtick, U., Subklewe, M., von Tresckow, B., ... & Dreger, P. (2022). GLA/DRST real-world outcome analysis of CAR T-cell therapies for large B-cell lymphoma in Germany. *Blood, The Journal of the American Society of Hematology*, *140*(4), 349-358.
3. Chow, V. A., Shadman, M., & Gopal, A. K. (2018). Translating anti-CD19 CAR T-cell therapy into clinical practice for relapsed/refractory diffuse large B-cell lymphoma. *Blood, The Journal of the American Society of Hematology*, *132*(8), 777-781.
4. Grant, S. J., Grimshaw, A. A., Silberstein, J., Murdaugh, D., Wildes, T. M., Rosko, A. E., & Giri, S. (2022). Clinical presentation, risk factors, and outcomes of immune effector cell-associated neurotoxicity syndrome following chimeric antigen receptor T cell therapy: a systematic review. *Transplantation and cellular therapy*, *28*(6), 294-302.
5. Hopfinger, G., Jäger, U., & Worel, N. (2019). CAR-T cell therapy in diffuse large B cell lymphoma: hype and hope. *Hemasphere*, *3*(2), e185.
6. Khadka, R. H., Sakemura, R., Kenderian, S. S., & Johnson, A. J. (2019). Management of cytokine release syndrome: an update on emerging antigen-specific T cell engaging immunotherapies. *Immunotherapy*, *11*(10), 851-857.
7. Roschewski, M., Longo, D. L., & Wilson, W. H. (2021). Chimeric Antigen Receptor T-Cell Therapy for Large B-Cell Lymphoma: Who, When, and How? *The New England journal of medicine*, *386*(7), 692.
8. Scholler, N., Perbost, R., Locke, F. L., Jain, M. D., Turcan, S., Danan, C., ... & Galon, J. (2022). Tumor immune contexture is a determinant of anti-CD19 CAR T cell efficacy in large B cell lymphoma. *Nature medicine*, *28*(9), 1872-1882.
9. Testa, U., Leone, G., Pelosi, E., Castelli, G., & Hohaus, S. (2023). CAR-T cell therapy in large B cell lymphoma. *Mediterranean Journal of Hematology and Infectious Diseases*, *15*(1), e2023066.
10. Zhang, J., Medeiros, L. J., & Young, K. H. (2018). Cancer immunotherapy in diffuse large B-cell lymphoma. *Frontiers in oncology*, *8*, 377040.
11. Boardman, A. P., & Salles, G. (2023). CAR T-cell therapy in large B cell lymphoma. *Hematological oncology*, *41*, 112-118.
12. Fatahichegeni, M., Ansarian, M. A., Wang, Y., Ren, J., Zhang, T., & Wang, X. (2025). Immune effector cell-associated neurotoxicity syndrome following CAR T-cell therapy: a review of recent advances. *Journal of Translational Medicine*, *24*(1), 114.
13. Locke, F. L., Filosto, S., Chou, J., Vardhanabhuti, S., Perbost, R., Dreger, P., ... & Galon, J. (2024). Impact of tumor microenvironment on efficacy of anti-CD19 CAR T cell therapy or chemotherapy and transplant in large B cell lymphoma. *Nature medicine*, *30*(2), 507-518.

14. Speth, K., Sengupta, S., Shamsuzzaman, M., Whitmore, J., Li, D., Chiang, A. Y., ... & Song, Q. (2026). Advancing cell and gene therapy: Application of AI/ML in clinical development and patient management. *Journal of Biopharmaceutical Statistics*, 1-19.

15. Zhang, Y., & Han, W. (2025). Management of cytokine release syndrome (CRS) following CAR T-cell therapy: a comprehensive review. *Clinical Cancer Bulletin*, *4*(1), 15.