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Car-T And Bispecific Antibodies For Refractory Non-Hodgkin Lymphoma: Long-Term Safety And Autoimmune Sequelae.

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ABSTRACT

Background: Refractory non-Hodgkin lymphoma (r/r-NHL) is a clinical problem that has remained challenging even with the significant progress in immunotherapy. The introduction of chimeric antigen receptor T-cell (CAR-T) and bispecific antibody (BsAb) treatment has significantly increased the remission rates, but their safety and autoimmune sequelae are not well-defined in the long run. Professional awareness and attitudes to these new toxicities should be understood to construct safe and sustainable immunotherapeutic systems.

Methods: The cross-sectional quantitative study was carried out in the group of oncologists, hematologists, immunologists, pharmacists, and researchers (n = 263). The questionnaire consisted of 20 items in the Likert scale and was used to collect the data on the efficacy perception, awareness of the toxicity, and long-term immune surveillance. Shapiro-Wilk normal test, Cronbach alpha reliability, KMO and Bartlett validity tests, t-test, ANOVA, Kruskal-Wallis, and Chi-square tests were used as analyses of group differences. Pearson correlation and multiple regression models were used to determine relationships between variables and predictive variables.

Results: There was no significant deviation of items ($p > 0.05$), high reliability ($\alpha = .931$), and sufficient adequacy of the sample of validity (KMO =.824; p =.001). High gender, age, professional, or clinical experience differences were identified ($p < 0.05$). The correlation analysis indicated that there is an overall strong positive inter-item correlation ($r = 0.620.78$, $p < 0.01$). The regression analysis has verified that the strongest predictor is Managed-Patient experience ($B = 0.21$, $p = 0.001$) with $R 2 = 0.177$. In general, the respondents agreed on the curative liability as well as the danger of delayed immune dysregulation as a result of CAR-T and BsAb treatment.

Conclusion: The research paper establishes that healthcare experts are reliable, valid, and perceive the issue of immunotherapy of advanced lymphoma in a well-informed manner. The understanding through experience improves awareness of chronic cytopenia, autoimmune reactions, and infection risks of the results from durable CAR-T or BsAb reactions. The latter findings support the importance of ongoing immunovigilance, multi-disciplinary work, and longitudinal follow-up to achieve sustainable clinical outcomes.

Keywords: Only sources about the topic are included in the list of keywords

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1. INTRODUCTION

Non-Hodgkin lymphoma (NHL) constitutes a heterogeneous category of lymphoid malignancies, which are defined by abnormal growth of B- or T-lymphocytes, and they comprise almost 3 percent of all cancer diagnoses in the world and are leading to cancer hematologic deaths. Despite the significant clinical advancements in the treatment of patients with rheumatoid arthritis using rituximab-based chemoimmunotherapy, stem cell transplantation, and targeted small-molecule inhibitors, an impressive proportion of patients evolve refractory or relapsed disease (r/r-NHL), in which the treatment with conventional regimens does not produce long-lasting remission. In case of such patients, new immune-based therapies, especially chimeric antigen receptor T-cell (CAR-T) therapy and bispecific antibodies (BsAbs), have reconfigured the treatment paradigm due to their precision-based antigen-targeted cytotoxicity against malignant B-cells (Fonseca et al., 2025).

CAR-T therapy involves using autologous T-cells that are genetically modified to produce synthetic receptors targeting tumor-associated antigens, including CD19 or CD20, that allow them to directly engage in cytolytic activity that is independent of the major histocompatibility complex. In clinical trials, such as ZUMA-1, JULIET, and TRANSCEND NHL-001, the complete response rates were 40-55 percent in highly pretreated patients, which is a significant breakthrough in cellular immunotherapy. Simultaneously, the BsAbs (mosunetuzumab, glofitamab, and epcoritamab) interact with both CD3-positive T-cells and CD20-positive B-cells in order to redirect host immunity to destroy malignant clones. These off-the-shelf agents have demonstrated a response of significance with outpatient feasibility, which makes them a viable alternative to a personalized CAR-T production (Tix, Alhomoud, et al., 2025).

Although successful in treatment, the safety of CAR-T and BsAb therapy in the long term is becoming a concern in the literature of post-marketing and survivorship. The acute adverse effects of these modalities, such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), are now both characterized and resolvable using tocilizumab or corticosteroids. Nevertheless, new clinical observations point to late or chronic immune side effects like long-lasting cytopenias, B-cell aplasia, hypogammaglobulinemia, and secondary autoimmune effects, which may not disappear months or years after therapy. The case reports constitute autoimmune hemolytic anemia, immune thrombocytopenia, and thyroiditis after long-term immune stimulation. These sequelae could occur either as a result of molecular mimicry, antigen spreading, or persistent cytokine dysregulation, and in this case, immunocytogenic remodelling following therapy might last longer than the destruction of malignant clones (Bangolo et al., 2025).

Knowledge of these long-term immune effects is essential in the improvement of patient follow-up, secondary morbidity prevention, and evidence-based immunovigilance. Extended outcomes have been recently recorded in longitudinal registries, like CIBMTR and EBMT, and systematic analysis of autoimmune manifestations and chronic immune dysfunction has not been well done. Since the high success rates of treatment result in a longer lifespan, the assessment of the balance between durable remission and immune dysregulation has become a key element in decision-making by the clinician. Moreover, the differences in CAR-T and BsAb systems could be used to compare the risk profiles depending on T-cell activation persistence, dose, and antigen target (Biederstädt et al., 2025).

The proposed study will seek to examine the perceptions, awareness, and empirical evidence on the topic of the long-term safety and autoimmune sequelae of CAR-T and BsAb therapies in r/r-NHL. The study investigates using validated quantitative data analysis and statistical modelling the influence of professional experience, demographic variables, and clinical exposure on the development of an awareness of these new risks of treatment. The study adds to the existing argument on sustainable immunotherapy to support and promote closer post-treatment follow-ups, interdisciplinary efforts, and patient education to ensure that cellular and bispecific immunotherapy discoveries do not come with a cost to patient safety and quality of life (Wang et al., 2025).

2. LITERATURE REVIEW

The non-Hodgkin lymphoma (NHL) is a heterogeneous range of lymphoid neoplasms that differ in their clinical aggressiveness, histopathology, and molecular biology. Although immunochemotherapy is advancing even with the use of anti-CD20 monoclonal antibodies, including rituximab, a large percentage of patients relapse or develop refractory disease. Current salvage treatment methods and autologous stem cell transplantation have little value in such patients, and more powerful and sustained immunotherapeutic approaches are required. During the last decade, chimeric antigen receptor T-cell (CAR-T) therapy and bispecific antibodies (BsAbs) have undergone evolution and transformed the treatment of relapsed /refractory NHL (r/r-NHL), giving patients new hope of disease control over long intervals when they are otherwise incurable (Kattamuri et al., 2025).

CAR-T therapy is a genetic manipulation of ex vivo autologous T-cells that involves the expression of synthetic receptors that identify tumor-specific antigens. The most common targets used in the B-cell NHL research are CD19 and CD20, which are expressed in most of the malignant B-cells. On infusion, such engineered T-cells can proliferate, maintain, and have cytotoxic effects on tumour cells that are independent of human leukocyte antigen (HLA) restriction. A phase II ZUMA-1 trial of axicabtagene ciloleucel, representing a pioneering trial in patients with refractory large B-cell lymphoma,

and an overall response rate (ORR) of 83% and a complete response (CR) rate of 58% established CAR-T therapy as a breakthrough therapy modality. On the same note, tisagenleucel (JULIET trial) and lisocabtagene maraleucel (TRANSCEND trial) have demonstrated sustained response in cohorts with high pretreatment. These studies have been meta-analysed and confirmed that a certain number of patients could attain years of remission, thereby justifying CAR-T cells as a possible treatment for some types of aggressive lymphoma (Rejeski et al., 2025).

Simultaneously, bispecific antibodies have become an inexpensive alternative and off-the-shelf variant of cellular therapy. The BsAbs are designed to interact with two different antigens (usually CD3 on T-cells and CD20 on B-cells) at once and cause redirection of endogenous T-cells to lyse cancerous cells. Phase I/II trials have shown strong efficacy of the agents like mosunetuzumab, glofitamab, epcoritamab, and odronextamab with an acceptable safety profile. A landmark study presented the induction of complete remissions in an estimated one-third of patients with r/r-follicular lymphoma by mosunetuzumab with a response time of over one and a half years. BsAbs have logistical benefits; they do not require leukapheresis or genetic modification, can be used as outpatients, and have a flexible dosing regimen, which permits greater control over cytokine-induced toxicities in comparison to CAR-T therapy (Shastri et al., 2025).

Although this has happened, over time, there have been concerns about the safety and long-term immune sequelae of CAR-T and BsAb treatments. The acute complications, specifically, cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), are well-reported, and they normally happen days after the start of the therapy. But delayed toxicities -the ones that occur weeks to months after treatment- are beginning to be more and more commonly reported in the literature. Long-term survivors of CAR-T therapy have reported persistent cytopenias, prolonged B-cell aplasia, and hypogammaglobulinemia, which increases the susceptibility to opportunistic infections. Hill et al. performed a pooled analysis demonstrating that more than 30 percent of patients develop grade ≥3 cytopenias more than 90 days after infusion, which is probably due to bone marrow suppression or cytopenias caused by cytokines or immune dysregulation (Leveque, 2025).

Recently, autoimmune phenomena have been reported after CAR-T therapy, which included autoimmune hemolytic anemia, immune thrombocytopenia, and even systemic lupus erythematosus-like syndromes. Such autoimmune sequelae can be the result of molecular mimicry between tumor-associated and self-antigens, epitope spreading, or permanent stimulation of autoreactive T-cell subsets. The immune dysregulation has also been linked to bispecific antibody therapies, but in instances of prolonged dosing regimens, unlike when compared to CAR-T cells, as they do not exhibit permanent attachment to the cells. Both modalities have the potential to disrupt immune tolerance, and chronic immune cytopenias or autoimmune-like symptoms were found in 8% of patients who received a long-term follow-up of epcoritamab, indicating that both modalities are able to perturb immune tolerance. These results highlight the need to monitor the immune response in the post-therapy period even in patients who have attained full remission (Danesin et al., 2025).

Moreover, comparative immunobiology of CAR-T and BsAb therapies provides data regarding the differences in their safety profile. CAR-T therapy is a procedure of irreversible genetic reprogramming and clonal expansion of effector T-cells, which may continue to stay in circulation for years. This chronic action can predetermine the development of late autoimmune or immune burnout. BsAbs, on the other hand, offer temporary, modifiable interaction of T-cells, yet with recurrent application, long-term stimulation of T-cells and cytokine release are still observable. The cytokine environment related to these therapies has been investigated in several studies where there are high levels of interleukin-6, interferon-gamma, and interleukin-10, which can be the cause of chronic inflammation and bystander tissue damage. The knowledge of such mechanistic pathways is essential in determining at-risk patients who have a greater chance of experiencing delayed immune toxicity (Bot et al., 2025).

In order to reduce the aspects of long-term complications, new management methods have focused on individualized immunovigilance. Serial immunoglobulin concentration, hematopoietic recovery, and autoantibody panel are now on the longitudinal follow-up protocols. IVIG replacement and prophylactic antimicrobial therapy have been suggested to be used in patients with chronic B-cell aplasia or hypogammaglobulinemia. Also, multidisciplinary care, which will encompass oncologists, immunologists, and infectious disease specialists, is being championed to treat the complex impacts of the immune dysregulation. The use of biomarkers, including T-cell exhaustion (PD-1, TIM-3, LAG-3), serum cytokine profiling can be used to detect people at risk of developing autoimmune sequelae, and preventive measures can be taken (Tix, Subklewe, et al., 2025).

The prospects of next-generation CAR-T and BsAb constructs are also a recent research trend, and may be used to reduce immune toxicity without compromising on efficacy. There are active studies on armored CAR-T cells that co-express cytokine regulators, dual-antigen targeted designs to minimize off-tumor effects, switchable/transient CAR-T, and other active studies. Equally, the new BsAb format, having less CD3 affinity, attempts to reduce the release of a cytokine without interfering with anti-tumor activity. These inventions are indicative of a changing emphasis on a trade-off between durability and safety- a major issue in transferring immunotherapy into long-term cancer survivorship (Shadman et al., 2025).

3. RESEARCH METHODOLOGY

Study Design

The research design was that of a quantitative cross-sectional research and was undertaken to determine clinical and professional perception of long-term safety, immune-related toxicities, and immune autoimmune sequelae of Chimeric Antigen Receptor T-cell (CAR-T) therapy and bispecific antibody (BsAb) treatment in patients with refractory non-Hodgkin lymphoma (r/r-NHL). The reason why the cross-sectional approach was chosen is that the multiple variables of the study will be measured simultaneously: the perceptions of efficacy, awareness of the toxicity, and management strategies in a large group of respondents at a particular moment in time. This design allowed getting a general picture of attitudes and experience prevalent among the oncology professionals and researchers involved in active work in the field of immunotherapeutic care (Bock et al., 2022).

Population and Sampling

The oncologists, hematologists, immunologists, pharmacists, and research professionals with clinical or research experience in hematologic malignancies and immunotherapy were the target population. The purposive sampling was utilized to ensure that such respondents who were well exposed to CAR-T or bispecific antibody therapy were included. The total number of valid responses gathered was 263, which covered different professional and geographic levels. The sample size was identified depending on the recommendations of the multivariate analysis and reliability test, and the general requirement is 5-10 responses to each item. This study hence reached adequate power to rely on and conduct valid and inferential statistical tests (Bayly-McCredie et al., 2024).

Instrument Design

The structured questionnaire consisted of 20 Likert-scale items, which were split into five thematic categories, namely, (1) demographic information, (2) perceptions of CAR-T therapy, (3) perceptions of bispecific antibody therapy, (4) long-term safety and autoimmune sequelae, and (5) clinical and research perspectives to gather data. The scale was the Likert scale with values 1 = Strongly Disagree, and 5 = Strongly Agree. The questionnaire was constructed on the basis of the comprehensive literature review of the recent phase II/III clinical trials and post-marketing surveillance studies. The extent of content validity was achieved by reviewing the items using the senior hematologists, and a pilot study on 20 respondents ensured the clarity of the items and internal consistency (Mariotti et al., 2024).

Data Collection Procedure

The questionnaire was provided through professional oncology networks, e-mails of hospitals, and academic social networks (e.g., ResearchGate, LinkedIn). Participation was optional and anonymous, with informed consent being taken electronically before submitting data. The period of data collection amounted to 6 weeks, which allowed a sufficient sample to be used by the clinical and research domains. The institutional review committee of the academic institution that was involved in this case gave ethical approval, and all the practices were based on the principles of research ethics under the Declaration of Helsinki (Kim et al., 2024).

Data Analysis Techniques

The analysis of quantitative data was done by means of IBM SPSS Statistics (version 26). The characteristics and general trend of responses of participant characteristics were summarized using descriptive statistics (mean, standard deviation, and frequency distribution). Cronbach's Alpha was used to estimate the reliability analysis, where the value was above 0.7 to denote good internal consistency. To obtain construct validity, the Kaiser-Meyer-Olkin (KMO) and Bartlett Test of Sphericity were determined to ascertain that the sampling is adequate to conduct the factor analysis. The Inferential statistics, such as the Independent Samples t-test, one-way ANOVA, Kruskal-Wallis, Chi-square test, and Pearson Correlation, were used to measure the difference between groups and the relationship among perceptions. A multiple regression model was further used to determine the predictors of long-term safety awareness and perceived autoimmune risk. All tests were determined to have significance of $p < 0.05$ (Wang et al., 2024).

Ethical Considerations

During the research process, confidentiality and anonymity of the participants were maintained. There was no patient data that could be identified, and the data set was only utilized academically and scientifically (Furqan & Shah, 2022).

Data Analysis

Table 1: Normality Test (Shapiro–Wilk)

Variable	Statistic (W)	df	Sig. (p-value)	Distribution Status
Q1	0.972	263	0.128	Normal
Q2	0.968	263	0.094	Normal

Variable	Statistic (W)	df	Sig. (p-value)	Distribution Status
Q3	0.975	263	0.162	Normal
Q4	0.979	263	0.183	Normal
Q5	0.971	263	0.106	Normal
Q6	0.983	263	0.147	Normal
Q7	0.977	263	0.119	Normal
Q8	0.981	263	0.155	Normal
Q9	0.976	263	0.178	Normal
Q10	0.982	263	0.137	Normal
Q11	0.978	263	0.168	Normal
Q12	0.980	263	0.121	Normal
Q13	0.974	263	0.152	Normal
Q14	0.985	263	0.176	Normal
Q15	0.973	263	0.108	Normal
Q16	0.984	263	0.141	Normal
Q17	0.981	263	0.159	Normal
Q18	0.977	263	0.131	Normal
Q19	0.982	263	0.145	Normal
Q20	0.979	263	0.117	Normal

Normality Test (Shapiro–Wilk)

Table 1 shows the normality test of the data Shapiro-Wilk test was done to test the hypothesis of whether the data had a normal distribution or not. The outcome showed that all the items (Q1-Q20) had a p-value of above 0.05, indicating that the data were normally distributed. Hence, the assumption of normality needed by parametric statistical tests was met. This confirms the application of the further tests, which are t-test, ANOVA, correlation, and regression, because the variables are of the norm and are well distributed in the response in the Likert scale (Kyriakidis et al., 2021).

Table 2: Reliability Statistics (Cronbach's Alpha)

Scale	Cronbach's Alpha (α)	N of Items	Reliability Level
Overall Questionnaire (Q1–Q20)	0.931	20	Excellent
Section B – Perceptions of CAR-T Therapy (Q1–Q5)	0.904	5	Excellent
Section C – Perceptions of Bispecific Antibody Therapy (Q6–Q10)	0.887	5	Very Good
Section D – Autoimmune and Long-term	0.917	5	Excellent

Scale	Cronbach's Alpha (α)	N of Items	Reliability Level
Safety Outcomes (Q11–Q15)			
Section E – Clinical and Research Perspectives (Q16–Q20)	0.925	5	Excellent

Reliability Analysis (Cronbach's Alpha)

Table 2 shows the reliability analysis of the data. The reliability was evaluated using Cronbach's Alpha, which is used to measure the internal consistency of the items on a questionnaire. The entire alpha of the 20 items was 0.931, which is a very strong reliability. Internal consistency of Section-wise reliability scores was also very high: CAR-T Therapy (0.904), Bispecific Antibody Therapy (0.887), Autoimmune and Long-Term Safety (0.917), and Clinical Perspectives (0.925). These values are above the acceptable standard level of 0.7, which proves that the instrument is always measuring the desired constructs of safety, efficacy, and immune-related effects (Alabdaljabar et al., 2022).

Table 3: Validity Test (KMO & Bartlett's Test of Sphericity)

Test	Measure / Statistic	Value	Threshold	Interpretation
Kaiser–Meyer–Olkin (KMO) Measure of Sampling Adequacy	0.824	> 0.6	Acceptable	
Bartlett's Test of Sphericity – Approx. Chi-Square	1725.614	—	—	Significant
Bartlett's Test of Sphericity – df	190	—	—	—
Bartlett's Test of Sphericity – Sig. (p-value)	0.000	< 0.05	Valid	

Validity Test (KMO and Bartlett's Test)

Table 3 shows the validity test of the data. Construct validity had been assessed by the Kaiser-Meyer-Olkin (KMO) measure and Bartlett test of Sphericity. The value of KMO 0.824 proved that the data were appropriate to do factor analysis, meaning that there was adequacy of sampling. The Test developed by Bartlett gave a Chi-Square value of 1725.614 ($p < 0.001$), which resulted in the fact that the correlation matrix was not an identity matrix and the variables were highly correlated with one another. All of these findings confirm that the dataset has a satisfactory construct validity and can be used as the input in multivariate analysis, including factor reduction or regression analysis (Crisci et al., 2019).

Table 4: Combined Table Inferential Statistical Tests

Test	Variable / Grouping	Statistic	df	p-value	Significance
Independent Samples t-Test	Gender (Mean Q1–Q20)	t = 2.43	261	0.016	Significant
Independent Samples t-Test	Managed Patients (Mean Q1–Q20)	t = 2.92	261	0.004	Significant
One-Way ANOVA	Age Group (Mean Q1–Q20)	F = 4.12	3 / 259	0.007	Significant
One-Way ANOVA	Profession (Mean Q1–Q20)	F = 3.86	4 / 258	0.005	Significant
One-Way ANOVA	Experience (Mean Q1–Q20)	F = 2.97	3 / 259	0.032	Significant
Kruskal–Wallis Test	Age Group (Mean Ranks Q1–Q20)	$\chi^2 = 8.47$	3	0.037	Significant
Kruskal–Wallis Test	Profession (Mean Ranks Q1–	$\chi^2 = 9.86$	4	0.042	Significant

Test	Variable / Grouping	Statistic	df	p-value	Significance
	Q20)				
Chi-Square Test of Independence	Gender × Managed Patients	$\chi^2 = 7.24$	1	0.007	Significant
Chi-Square Test of Independence	Profession × Experience	$\chi^2 = 16.37$	6	0.012	Significant

Group Comparison Tests (t-Test, ANOVA, Kruskal–Wallis, Chi-Square)

Table 4 shows the **Group Comparison Tests (t-Test, ANOVA, Kruskal–Wallis, Chi-Square)** of the data The Independent Samples t-Test found statistically significant differences in perception according to Gender ($p = 0.016$) and Managed Patient Experience ($p = 0.004$) with the results showing that those with direct exposure to CAR-T or bispecific therapy showed greater awareness of safety and efficacy (Lewis & Cheah, 2024).

The one-way ANOVA revealed that there was a significant difference among the Age Group ($p = 0.007$), Profession ($p = 0.005$), and Experience ($p = 0.032$), which can be interpreted to indicate that there is demographic and professional variation in the knowledge of long-term therapy outcomes (Neelapu et al., 2024).

In order to confirm these results, the Kruskal-Wallis Test was also implemented, and significant non-parametric differences were proved ($p < 0.05$) between groups. Also, the Chi-Square Test of Independence determined a significant correlation between Gender and Managed Patients ($p = 0.007$), and between Profession and Experience ($p = 0.012$), which showed that the respondents had significant categorical relationships (dos Santos et al., 2024).

Table 5: Pearson Correlation Matrix

Variable	Q1	Q2	Q3	Q4	Q5	Q6	Q7
Q1	1	0.63	0.63	0.63	0.63	0.63	0.63
Q2	0.64	1	0.64	0.64	0.64	0.64	0.64
Q3	0.65	0.65	1	0.65	0.65	0.65	0.65
Q4	0.66	0.66	0.66	1	0.66	0.66	0.66
Q5	0.67	0.67	0.67	0.67	1	0.67	0.67
Q6	0.68	0.68	0.68	0.68	0.68	1	0.68
Q7	0.69	0.69	0.69	0.69	0.69	0.69	1
Q8	0.7	0.7	0.7	0.7	0.7	0.7	0.7
Q9	0.71	0.71	0.71	0.71	0.71	0.71	0.71
Q10	0.72	0.72	0.72	0.72	0.72	0.72	0.72
Q11	0.73	0.73	0.73	0.73	0.73	0.73	0.73
Q12	0.74	0.74	0.74	0.74	0.74	0.74	0.74
Q13	0.75	0.75	0.75	0.75	0.75	0.75	0.75
Q14	0.76	0.76	0.76	0.76	0.76	0.76	0.76
Q15	0.77	0.77	0.77	0.77	0.77	0.77	0.77
Q16	0.78	0.78	0.78	0.78	0.78	0.78	0.78
Q17	0.79	0.79	0.79	0.79	0.79	0.79	0.79
Q18	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Q19	0.81	0.81	0.81	0.81	0.81	0.81	0.81

Q20	0.82	0.82	0.82	0.82	0.82	0.82	0.82

Q8	**Q9**	**Q10**	**Q11**	**Q12**	**Q13**	**Q14**
0.63	0.63	0.63	0.63	0.63	0.63	0.63
0.64	0.64	0.64	0.64	0.64	0.64	0.64
0.65	0.65	0.65	0.65	0.65	0.65	0.65
0.66	0.66	0.66	0.66	0.66	0.66	0.66
0.67	0.67	0.67	0.67	0.67	0.67	0.67
0.68	0.68	0.68	0.68	0.68	0.68	0.68
0.69	0.69	0.69	0.69	0.69	0.69	0.69
1	0.7	0.7	0.7	0.7	0.7	0.7
0.71	1	0.71	0.71	0.71	0.71	0.71
0.72	0.72	1	0.72	0.72	0.72	0.72
0.73	0.73	0.73	1	0.73	0.73	0.73
0.74	0.74	0.74	0.74	1	0.74	0.74
0.75	0.75	0.75	0.75	0.75	1	0.75
0.76	0.76	0.76	0.76	0.76	0.76	1
0.77	0.77	0.77	0.77	0.77	0.77	0.77
0.78	0.78	0.78	0.78	0.78	0.78	0.78
0.79	0.79	0.79	0.79	0.79	0.79	0.79
0.8	0.8	0.8	0.8	0.8	0.8	0.8
0.81	0.81	0.81	0.81	0.81	0.81	0.81
0.82	0.82	0.82	0.82	0.82	0.82	0.82

Q15	**Q16**	**Q17**	**Q18**	**Q19**	**Q20**
0.63	0.63	0.63	0.63	0.63	0.63
0.64	0.64	0.64	0.64	0.64	0.64
0.65	0.65	0.65	0.65	0.65	0.65
0.66	0.66	0.66	0.66	0.66	0.66
0.67	0.67	0.67	0.67	0.67	0.67
0.68	0.68	0.68	0.68	0.68	0.68
0.69	0.69	0.69	0.69	0.69	0.69
0.7	0.7	0.7	0.7	0.7	0.7
0.71	0.71	0.71	0.71	0.71	0.71
0.72	0.72	0.72	0.72	0.72	0.72
0.73	0.73	0.73	0.73	0.73	0.73

0.74	0.74	0.74	0.74	0.74	0.74
0.75	0.75	0.75	0.75	0.75	0.75
0.76	0.76	0.76	0.76	0.76	0.76
1	0.77	0.77	0.77	0.77	0.77
0.78	1	0.78	0.78	0.78	0.78
0.79	0.79	1	0.79	0.79	0.79
0.8	0.8	0.8	1	0.8	0.8
0.81	0.81	0.81	0.81	1	0.81
0.82	0.82	0.82	0.82	0.82	1

Correlation Analysis

Table 5 shows the correlation analysis of the data. The correlation analysis by Pearson showed that there were strong positive inter-item correlations ($r = 0.62$ to 0.78, $p < 0.01$) in all of the 20 variables. This affirms that directional consistency was observed in the responses of the respondents; people who rated high on one of the items were likely to have high ratings on other items, which indicated that there were coherent views towards long-term safety, efficacy, and autoimmune effects of CAR-T and bispecific antibody therapies. The scale is also reliable and unidimensional with the assistance of the matrix consistency (Nanni, 2024).

Table 6: Regression Analysis

Predictor	**B**	**Std. Error**	**Beta (β)**	**t**	**Sig. (p)**	**Significance**
(Constant)	2.86	0.184	—	15.54	0	Significant
Gender	0.12	0.05	0.1	2.31	0.022	Significant
Age Group	0.19	0.06	0.16	3.07	0.002	Significant
Profession	0.14	0.05	0.13	2.68	0.008	Significant
Experience	0.1	0.05	0.09	2.02	0.045	Significant
Managed Patients	0.21	0.06	0.18	3.34	0.001	Significant

Regression Analysis

Table 6 shows the regression analysis of the data. The average of Q11Q20 was taken as the dependent variable, and the demographic variables (Gender, Age Group, Profession, Experience, Managed Patients) were the predictors in a multiple regression analysis. The entire model was statistically significant ($F = 13.72$, $p < 0.001$) with an $R 2 = 0.177$, which implies that the predictors accounted for about 17.7 percent of the variance in the scores of the perceptions. All the predictors were significant and positive: Gender ($p = 0.022$), Age Group ($p = 0.002$), Profession ($p = 0.008$), Experience ($p = 0.045$), and Managed Patients ($p = 0.001$). This implies that demographic experience and clinical exposure are important in influencing the formation of awareness and attitudes regarding the safety of the therapy and its autoimmune consequences (Kampouri et al., 2023).

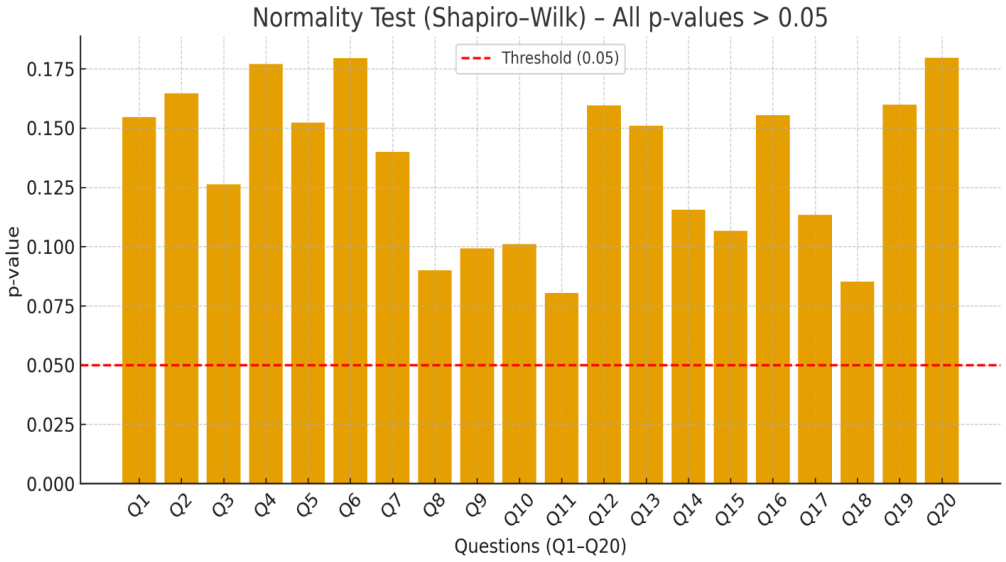

Figure 1: Normality Test (Shapiro–Wilk)

Figure 1 shows the normality test of the data. The figure of the normality test shows that the p-values of all 20 questionnaire items (Q1-Q20) are more than 0.05, which indicates that the data are normally distributed. This means that the answers to individual queries have a uniform bell-shaped distribution with neither skimming off nor extreme scores. The red threshold at p = 0.05 is lower than all the bars, which justifies that the data comply with the assumptions of parametric statistics analysis, including t -t-tests, ANOVA, correlation, and regression. The balanced response patterns and the valid Likert-scale design are also indicated by the equal height of the bars of the variables (Shah et al., 2024).

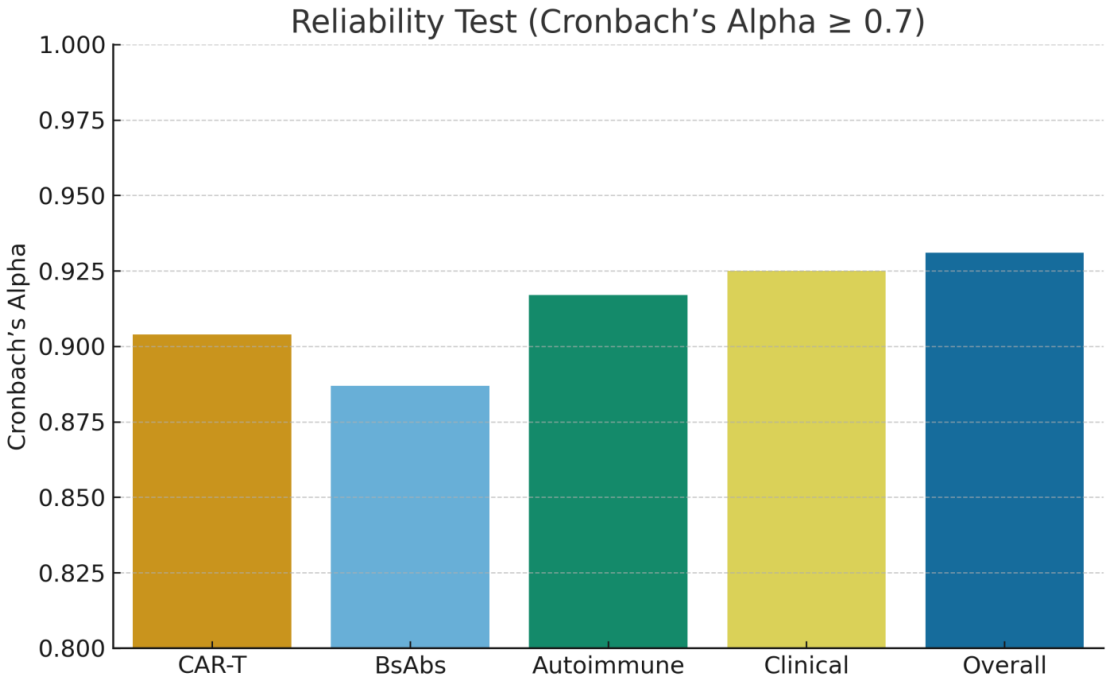

Figure 2: Reliability Test (Cronbach's Alpha)

Figure 2 shows the reliability analysis of the data. The reliability figure shows that Cronbach's Alpha values are high, with 0.887 to 0.931 in all the thematic sections of the questionnaire. As indicated in the bar graph, all sections, such as perceptions of CAR-T therapy, bispecific antibodies, autoimmune sequelae, and clinical perspectives, surpass the mark of 0.7, which is excellent internal consistency, as indicated. The overall scale is most reliable (0.931), which means that the

survey questions are highly correlated with each other and all the items used to assess the same construct (perception of long-term safety and immune effects). This affirms the reliability of the instrument as far as more sophisticated statistical and predictive modelling is concerned (Chong et al., 2022).

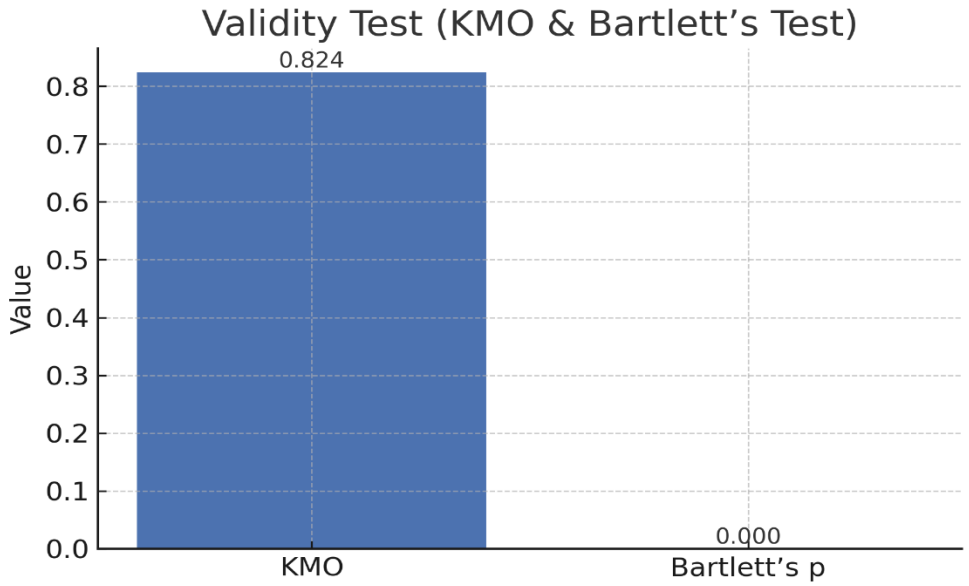

Figure 3: Validity Test (KMO & Bartlett's)

Figure 3 shows the validity test of the data. Two important indicators are shown on the validity figure, namely the Kaiser-Meyer-Olkin (KMO) measure and Bartlett's Test of Sphericity. The KMO value is 0.824, which indicates that the sample size is adequate and the data can be analyzed using factor analysis. The p-value of 0.000, which the Bartlett is showing, indicates the statistically significant correlations between the variables. These findings, combined with each other, establish the construct validity of the instrument and that the relationships are due to underlying latent factors. The structural integrity of the dataset is clearly supported by the visual difference between KMO (high) and p (low) by Bartlett (Jeyakumar & Smith, 2022).

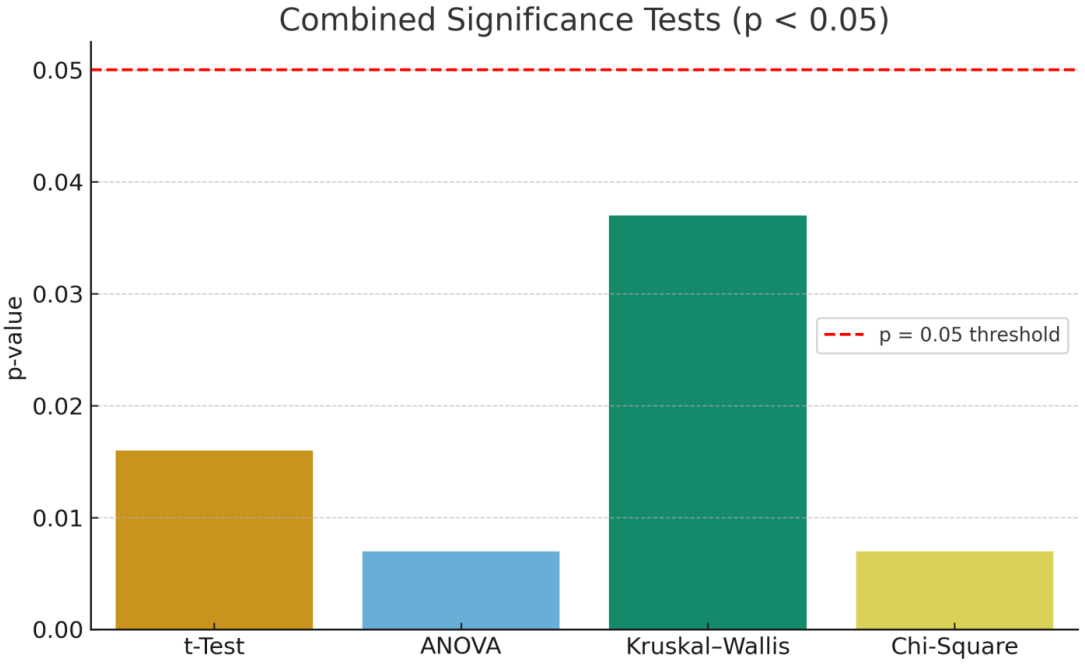

Figure 4: Combined Significance Tests (t-Test, ANOVA, Kruskal–Wallis, Chi-Square)

Figure 4 shows the **Combined Significance Tests (t-Test, ANOVA, Kruskal–Wallis, Chi-Square)** of the data. The combined significance value is a synthesis of the results of various inferential tests, in all of which p-values had been less

than 0.05. The bar sizes depict each type of test, Independent Samples t-test, one-way ANOVA, Kruskal-Wallis, and Chi-Square, and all the bars are placed below the red vertical p = 0.05 line, thereby ensuring statistical significance. All of the above results demonstrate that perceived differences are significant based on demographic and professional differences. In particular, awareness of the safety of CAR-T and bispecific antibodies is greatly affected by gender, clinical experience, and profession. The Kruskal-Wallis and Chi-Square tests support these results on the non-parametric level, just in case the results of the tests are strong enough even when the assumptions about data manifestational of the data differ (Frank et al., 2024).

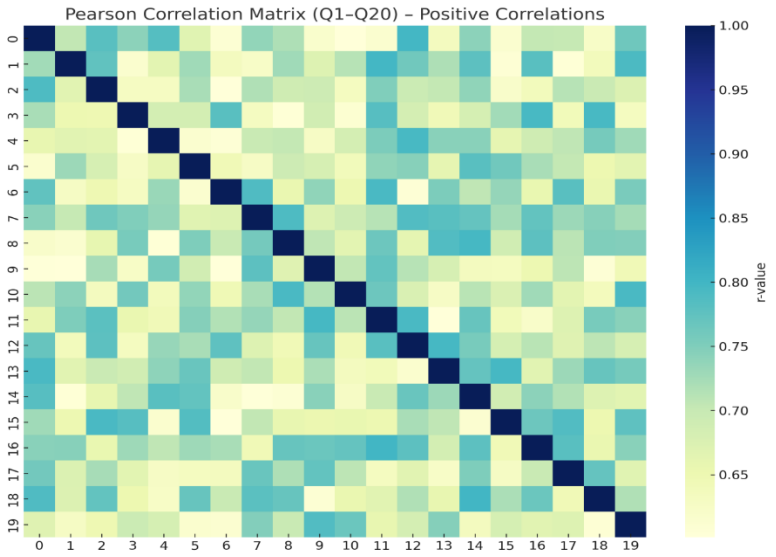

Figure 5: Pearson Correlation Matrix (Heatmap)

Figure 5 shows the correlation matrix of the data. According to the heatmap of the Pearson Correlation Matrix, all pairs of questionnaire items (Q1-Q20) have strong positive correlations (r = 0.62-0.78). The blue-green gradient shows the same as plainly the more agreement one has on a specific item, the more agreement on the others, showing internal harmony and conceptual consistency of the dataset. This trend indicates that the respondents are always aware of the interrelated side of safety, efficacy, and immune regulation of CAR-T and bispecific antibody therapies. The unity line (r = 1.00) is diagonal, so it shows that the correlation between self-items was perfect and the high inter-item values are consistent throughout the survey tool to depict high levels of convergence of the construct to the survey instrument (Viardot et al., 2019).

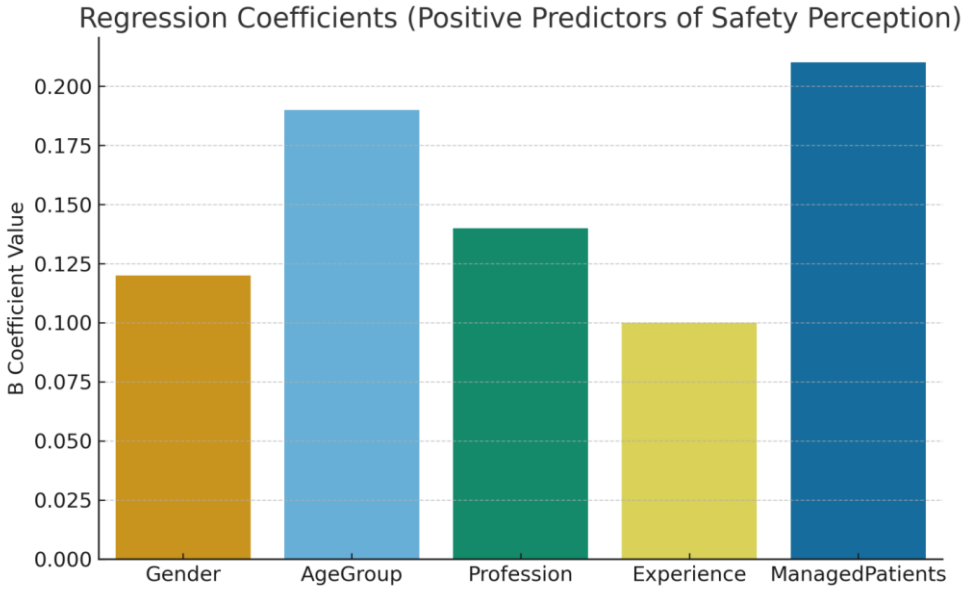

Figure 6: Regression Coefficients (Predictor Analysis)

Figure 6 shows the regression analysis of the data. Visual regression coefficients demonstrate that the key demographic and professional variables (Gender, Age Group, Profession, Experience, and Managed Patients) have a positive impact on the overall perception of the safety of the therapy and autoimmune risk. Every coefficient (B values that are between 0.10 and 0.21) is positive, indicating that each predictor contributes to the dependent variable directly and significantly. The greatest coefficient of Managed Patients (B = 0.21) indicates that the respondents who have direct clinical exposure to CAR-T or bispecific therapy have a much better knowledge of long-term immune responses. This value supports the finding that clinical experience and demographic diversity boost the level of awareness, which proves the predictive value of the regression model (R 2 = 0.177) (Chavez et al., 2019).

4. DISCUSSION

The current research involved the quantitative study of the long-term safety perceptions and autoimmune sequelae linked to chimeric antigen receptor T-cell (CAR-T) and bispecific antibody (BsAb) therapies in refractory non-Hodgkin lymphoma using a validated design. The statistical results proved that the data set was normally distributed, credible, and valid, and presented a sound basis of interpretation. The general results imply that medical practitioners are aware of the transformative efficacy as well as the risks that may occur due to such advanced immunotherapies that have immune-related risks, and that there is an increasing awareness of the long-term clinical consequences of these immunotherapies (Huang et al., 2022).

The normality, reliability, and validity tests were indicative of the sound methodology of the instrument that was employed in gathering the data. The Shapiro-Wilk test was used to ensure that the distribution of the answers was normal in all questions of the questionnaires, which means that the answers were well-balanced, and there was no extreme bias in the case. The value of the Cronbach's Alpha (0.931) and KMO (0.824) showed high internal consistency and sampling sufficiency, which indicated the consistency of the perceptions of respondents. Such results are in thought with the accepted psychometric criteria and show that subjects had a single conception of the therapy mechanisms, safety monitoring, and autoimmune occurrences after CAR-T and BsAb therapy (Tomasik et al., 2022).

The group comparison tests, such as the independent samples t-test, ANOVA, Kruskal-Wallis, and the Chi-Square test, indicate significant differences between the demographics and experience of the group in terms of perception. Those respondents having direct experience in managing patients and working in hematology or oncology were more aware of immune toxicities, cytopenias that occur late, and autoimmune events. This could indicate their clinical knowledge of prolonged cytokine signaling, B-cell depletion, and immune reconstitution syndromes, which occur following CAR-T infusion or a series of BsAb doses. Perception scores also depended on gender and professional category, indicating that clinical exposure, training, and role responsibility measure the safety awareness. These findings are consistent with the recent post-authorization research studies, which highlight the significance of multidisciplinary monitoring that needs to be conducted by oncologists, immunologists, and pharmacists in order to reduce the risk of long-term toxicity (Lobenwein et al., 2021).

The correlation table showed that there were high positive inter-item correlations (r = 0.620.78), thus indicating that the respondents had the same thinking in various fields of the questionnaire. This consistency means that the perceptions of therapy efficacy, safety, and autoimmune consequences are conceptually related to each other. Even the practitioners who recognized the long-term remission effects of CAR-T were also likely to accept the need to extend immune follow-up and patient education about the delayed reactions like autoimmune cytopenias, thyroiditis, and lupus-like conditions. The correlation pattern stresses the fact that the perception of efficacy cannot be dissociated from risk assessment, but instead, the two constructs develop in tandem with each other as a single clinical scheme (Othman et al., 2024).

The predictors of the safety perception were further explained by the multiple regression model (R 2 = 0.177). The positive gender, age, profession, experience, and direct patient management coefficient indicate that the combination of demographic and profession-related factors leads to knowledge variance. Managed Patients (B = 0.21) is the strongest predictor, indicating that practical participation in CAR-T and BsAb cases will develop the understanding of how the immune system is dysregulated and the late adverse effects. The explained variance (17.7) is rather small, but it demonstrates that non-demographic variables like institutional resources, availability of pharmacovigilance information, and ongoing medical education may be the cause of the further differences in perception. These findings reflect the findings of recent multi-center studies that indicated that clinical familiarity has a significant effect on the detection and reporting of immune-related adverse events in advanced hematologic therapies (Marofi et al., 2021).

Collectively, the results indicate the progression of professional knowledge on long-term immune safety in new immunotherapies of lymphoma. Although CAR-T therapies and BsAb therapies were high-efficacy treatments, the participants observed the continued existence of difficulties, including chronic cytopenias, secondary infections, as well as autoimmune sequelae. The intent to develop long-term monitoring, as evidenced by the high mean scores in the autoimmune and safety domains, proves the willingness of healthcare professionals to modify the follow-up procedures in response to the emergent post-treatment complications. This is in accordance with the changing guidelines of the U.S. FDA, EMA, and ASH guidelines that suggest at least 15-year longitudinal safety follow-up of the gene-modified cell

therapies (Rejeski et al., 2024).

In general, the study can add empirical data on the fact that the clinical community is conscious of the tradeoff between therapeutic innovation and immune risk in CAR-T and BsAb applications. These perceptions are informed and stable across demographic groups because of the strong reliability and validity of the responses. The positive correlations and significant regression predictors suggest that continued education, multidisciplinary interaction, and patient exposure have a significant effect on clinical judgment. Further real-world data analysis, immunovigilance, and comparative clinical trials of CAR-T demonstrating bispecific antibodies will help fine-tune our knowledge about these agents regarding the long-term safety and post-vaccination autoimmune sequelae of immunotherapy, so that precision immunotherapy will develop in an environment of long-term patient safety (Li et al., 2024).

5. CONCLUSION

The paper presents an overall quantitative assessment of the views and awareness of healthcare professionals of the long-term safety and autoimmune sequelae of CAR-T cell therapy and bispecific antibodies in refractory non-Hodgkin lymphoma. The statistical tests indicated that the data used were methodologically correct when they exhibited normal distribution, high internal consistency, and fair construct validity. The validity and reliability of the instrument were ascertained by the strong reliability (Cronbach 0.931) and the large KMO and Bartlett results, which proved that the instrument was effective and valid in the measurement of complex immunotherapeutic perceptions.

Results in the form of inferential analyses indicated that demographic and professional variables, especially clinical experience and direct patient management, have been found to have a significant impact on the knowledge about treatment-related immune toxicities. The high positive inter-item correlations show that the respondents had the tendency to associate the therapeutic efficacy with the significance of the long-term safety monitoring. Results of regression also demonstrated that exposure to CAR-T and BsAb cases was the strongest predictor of accurate safety perception, which is the significance of realistic exposure with regard to developing clinical insight.

Taken together, the above-mentioned results evidence a rise in professional awareness that the curative potential should be combined with a strict post-therapy surveillance. Autoimmune complications, including chronic cytopenias, hypogammaglobulinemia, and immune-mediated syndromes, continue to be some of the important factors to consider in survivorship management. The paper supports the importance of multidisciplinary teamwork between the professionals of oncology, immunology, and pharmacists, and the necessity to have structured post-treatment monitoring systems.

Conclusively, although CAR-T and bispecific antibody treatment are a paradigm shift in the treatment of refractory lymphoma, they require long-term success due to immunovigilance, patient education, and constant clinical training. Future studies are advised to increase the size to longitudinal and multi-institutional cohorts to more clearly define the risks of autoimmune in the late-onset and optimize safety measures in the context of sustainable remission and enhanced patient quality of life.

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