THE EUROPEAN SOCIETY OF MEDICINE
Medical Research Archives, Volume 12 Issue 9

RESEARCH ARTICLE

Accessibility to Rituximab and its impact on treatment outcomes in major Non-Hodgkin Lymphoma subtypes: Insights from a resource-limited setting

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OPEN ACCESS

PUBLISHED
30 September 2024

CITATION
Jacob, L., A., Gupta, A., et al., 2024. Accessibility to Rituximab and its impact on treatment outcomes in major Non-Hodgkin Lymphoma subtypes: Insights from a resource-limited setting. Medical Research Archives, [online] 12(9). https://doi.org/10.18103/mra.v12i9.5791

DOI
https://doi.org/10.18103/mra.v12i9.5791

ISSN
2375-1924

ABSTRACT

Objective: Non- Hodgkin's lymphoma is a relatively uncommon cancer and outcome data in Indian setting is scarce. This study aimed to evaluate the accessibility to rituximab and its impact on treatment outcomes in major non-Hodgkin's lymphoma (NHL) subtypes at a tertiary care cancer hospital in South India.

Methods: This was a single-centre, hospital-based retrospective study of all newly diagnosed NHL patients between April 2015 and March 2020, at Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka. Case files of the patients were retrieved, relevant data was collected and analysed.

Results: In total, 929 patients were diagnosed with NHL [diffuse large B-cell lymphoma =478(51.4%), follicular lymphoma =82(8.8%), mantle cell lymphoma=65(6.9%), peripheral T-cell lymphoma=50(5.4%), and high-grade B-cell lymphoma=49(5.2%) and rest others]. Diffuse large B cell lymphoma patients mostly presented with stage IV disease (n=162(33.5%)). More than one-third (188(39.3%)) of the patients had extra-nodal disease with gastrointestinal tract involvement being the most common. The median progression free survival and overall survival of diffuse large B cell lymphoma patients were 15.2 and 23 months respectively. Only 37% of these patients had access to rituximab, and those who received rituximab-based chemotherapy demonstrated significantly better overall survival (HR=0.64, p=0.001). Follicular lymphoma patients also presented primarily with stage IV (n=40(49%)) disease, with 31(37.8%) and 58(70%) patients showing bone marrow involvement and extra-nodal involvement respectively. The median progression free survival and overall survival for these patients were not reached, however, the 2-year median progression free survival was 75%. Only 58% of the follicular lymphoma patients had access to rituximab. Response rates were higher with rituximab-based therapy, with complete response rates of 62% with rituximab vs 49% without rituximab. The progression free survival of patients who received rituximab was 61 months vs 41 months for those who did not (p=0.012).

Conclusion: There is significant gap in treatment outcomes of NHL patients between richer and poorer countries. There is an urgent need for framing of policies and public health interventions to improve access to newer therapies in resource constrained countries to further enhance cancer treatment outcomes.

Keywords: Chemotherapy, non-Hodgkin's lymphomas, DLBCL, Follicular lymphoma, Rituximab.

Introduction

Cancer remains the second leading cause of death worldwide, affecting individuals across all age groups[1]. Lymphomas are relatively uncommon types of cancers ranking ninth in incidence worldwide and in India according to recent GLOBOCAN 2022 data[2]. Lymphomas are broadly classified into Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL), with each category encompassing various subtypes. The incidence of both HL and NHL has been steadily increasing each year, with males showing a higher susceptibility than females. In 2022, there were 553,389 new cases of NHL globally, accounting for 2.8% of all cancer diagnoses, and resulting in 250,679 deaths. In India alone, 39,736 cases were diagnosed, leading to 22,972 deaths[2]. In India, the growing number of NHL cases presents a significant public health challenge, adding pressure to an already overburdened healthcare system. To effectively address this, it is vital to strengthen healthcare infrastructure and improve access to advanced treatments, ensuring better patient outcomes and longer survival rates.

The etiological factors contributing to NHL remain largely unexplained and vary across geographical regions. Immunodeficiency or factors influencing immunity are major risk factors for lymphomas. Other contributing factors include infections such as Helicobacter pylori, Hepatitis C virus, Epstein-Barr virus, and exposure to occupational hazards or environmental chemicals[3-5].

NHLs are a heterogeneous group of diseases characterized by distinct morphology, clinical features, natural history, prognosis, and response to treatment. The distribution of various subtypes of NHL varies with geography. In the Western world, the most common subtypes of NHL include diffuse large B-cell lymphoma and small lymphocytic lymphoma (SLL)[6,7]. Studies from India also report DLBCL as the most common subtype of NHL, followed by FL and T-cell NHL[8,9].

The treatment of NHL depends significantly on the specific subtype and how the disease presents in each patient. Rituximab, a type of monoclonal antibody that targets CD20 on B-cell lymphomas, was a major breakthrough in treating B-cell cancers like NHL and chronic lymphocytic leukemia[10]. It is generally better tolerated than chemotherapy, with fewer blood-related side effects. In the Western world, rituximab greatly improved the outlook for people with B-cell NHL. Unfortunately, access to advanced therapies including rituximab remain limited in developing countries due to high costs, inadequate healthcare infrastructure, and unequal access to care. The innovator rituximab has been available in India since the early 2000s, but the higher price made it inaccessible to the majority. The Indian biosimilar rituximab became available in 2007 at a much lower price, and subsequently many other biosimilars were launched significantly reducing the cost. But did this ensure easy and universal accessibility to rituximab over a short span of time? Even though there is sufficient amount of data on the clinical spectrum and histopathological distribution of NHL subtypes from the Indian subcontinent, there is a paucity of information on the access to newer forms of treatment and its impact on clinical outcomes. We conducted this analysis to ascertain the accessibility to rituximab therapy at approximately 2 decades after the initial approval of this drug. Such information is pivotal for effective treatment planning and for framing important health policies.

Materials and Methods:

This single-centre, hospital-based retrospective analysis was conducted at Kidwai Memorial Institute of Oncology, Bengaluru, Karnataka, India from April 2015 to March 2020. The study spanned all adult patients (aged ≥18 years) newly diagnosed with NHL at the inpatient and outpatient services of the Department of Medical Oncology. Medical records of the patients were retrieved, reviewed and relevant data was captured in a case record form. The data collected encompassed demographic details like age and gender; associated comorbidities; history and physical examination

findings; performance status and reports of relevant investigations like complete blood counts, peripheral smear, renal and liver function tests, serum lactate dehydrogenase, histopathology, immunohistochemistry, contrast-enhanced computed tomography/ fluorodeoxyglucose-positron emission tomography, bone marrow biopsy, cerebrospinal fluid analysis (when performed), two-dimensional echo and 12 lead electro-cardiogram. NHL were classified into subtypes according to the 4th edition of World Health Organization classification system[11]. Patients were staged according to Cotswold's modification of the Ann Arbor classification system[12]. DLBCL and FL patients were risk stratified according to the International Prognostic Index (IPI) and the Follicular Lymphoma International Prognostic Index (FLIPI) prognostic scores respectively[13,14]. The treatment administered, toxicities experienced, and responses attained were meticulously recorded and analysed. The end of treatment response was categorized as complete response, partial response, stable disease, or progressive disease per the Lugano classification for NHL[15]. Survival data was analysed for the major NHL subgroups. Response rates (RR), progression-free survival (PFS) and overall survival (OS) of the patients who received rituximab were compared with the non-rituximab groups.

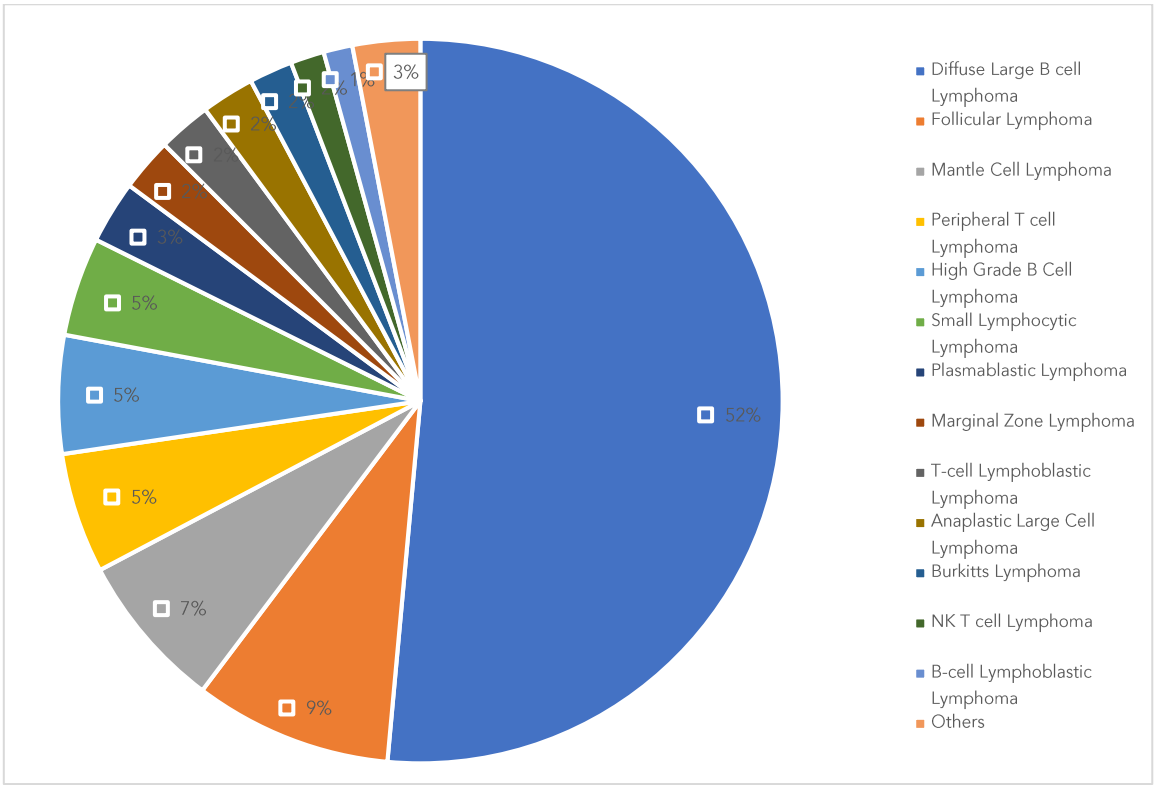
Statistical Analysis:

Data analysis utilized the Statistical Package for Social Sciences (SPSS) software version 23. Qualitative data were reported as numbers (percentages), and quantitative data as mean (standard deviation) and median. The t-test was employed for continuous variables, and the Kaplan–Meier product-limit method was used for estimation of OS and PFS. A P value <0.05 was considered statistically significant.

Results:

A total of 929 patients were diagnosed with NHL during the study period. Major NHL categories observed were diffuse large B cell lymphoma in 478(51.4%) followed by follicular lymphoma in 82(8.8%), mantle cell lymphoma in 65(6.9%), peripheral T cell lymphoma (NOS) in 50 (5.4%), high-grade B-cell lymphoma in 49 (5.2%) of patients and rest others. (Figure 1).

Figure 1: Subtypes of NHL.



For the DLBCL cohort, the median age of presentation was 54 years with a male preponderance (1.7:1). Majority of the patients were stage IV (33.5%) and stage II (31.4%) at diagnosis. While 60.6% had primary nodal disease, 39.3% presented with extra-nodal disease, with the majority showing gastrointestinal and bone involvement, followed by liver and kidney. (Table 1) Among the 478 DLBCL patients, 429 were available for outcome analysis, and only 160 (37.2%) of them received rituximab-based treatment. The median follow-up period was 18 months. The median PFS and OS were 15.2 months and 23 months respectively. (Table 2)

Table 1. Baseline characteristics of patients with DLBCL

Patient characteristics	N=478
Sex (men: women)	1.70:1
Male	301 (63.0)
Female	177 (37.0)
Age (years), mean (range)	54 (13-90)
Stage at presentation	
I	50 (10.4)
II	150 (31.4)
III	116 (24.3)
IV	162 (33.5)
Nodal disease	290 (60.6)
Extra-nodal disease	188 (39.3)
Extra-nodal site	
GI Involvement (stomach, small and large intestine)	54 (11)
Bone involvement	32 (6)
Liver	20 (4)
Kidney and suprarenal	8 (1)
Bone Marrow	7(1)
Others (effusion, CNS, testis, breast, lung)	67 (14)
IPI score	
Risk group	
Low risk (0,1)	172 (36.0)
Intermediate risk (2,3)	234 (49.0)
High risk (4,5)	72 (15.1)

Data shown as n (%), unless otherwise specified.
KCI, Kidwai Cancer Institute; *CNS*, central nervous system; IPI, Integrated prognostic index.

Table 2: Outcome analysis of patients with DLBCL.

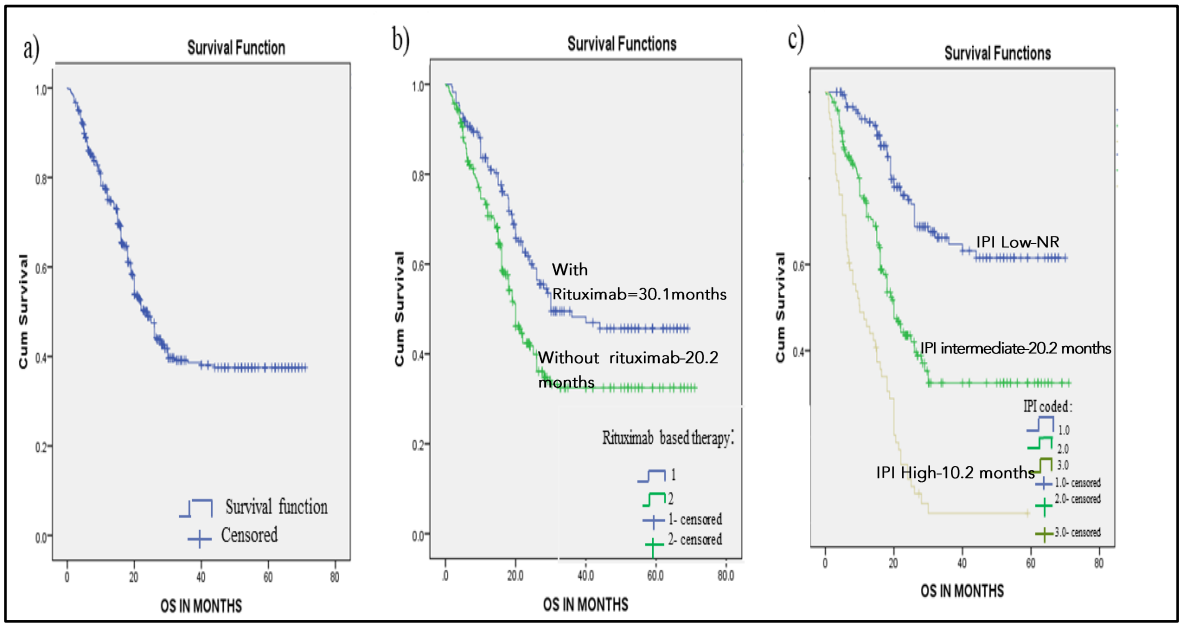
Patient characteristics	N=429
Patients available for analysis	429 (89.7)
Not taken treatment in KCI	21 (4.4)
Defaulted/ mortality prior to starting therapy	28 (5.9)
Median follow up (months)	18
Treatment regimens received	
Rituximab based	160 (37.2)
Non-rituximab based	269 (62.7)

Patient characteristics	N=429	
Not taken treatment	49 (11.4)	
Treatment response	Rituximab	Non-rituximab
Complete response (CR)	102(64.2)	127(48.9)
Partial response/Stable disease (PR/SD)	42(26.3)	91(35.2)
Progressive disease (PD)	16(9.5)	42(15.9)
Deaths	219 (51)	
PFS, median (months)	15.2	
OS, median (months)	23	

Data shown as n (%), unless otherwise specified.
KCI, Kidwai Cancer Institute; PFS, progression-free survival; OS, overall survival.

Multivariate analysis demonstrated improved OS with nodal disease vs extra-nodal disease (HR=0.38 (0.76-0.53), p=0.001), rituximab therapy vs non-rituximab therapy (HR=0.64 (95% CI: 0.47-0.87), p=0.001) and low risk IPI vs high risk IPI (HR=0.32 (95% CI:0.17-0.61), p<0.001) and CR vs non-CR (HR=0.19, p=<0.001). The median survival of DLBCL patients who received rituximab-based therapy was 30.1 months, compared to 20.2 months for those who did not receive rituximab. The median survival based on IPI score was 20.2 months and 10.2 months in intermediate and high-risk categories while in low risk IPI median OS was not reached. (Figure 2).

Figure 2: a) Overall survival in Diffuse large B-cell lymphoma; b) Overall survival based on rituximab treatment; c) Overall survival based on International Prognostic Index score



A total of 82 patients were diagnosed with FL, with a median age of 55 years. Patients primarily presented with stage III (n=37,45%) and IV (n=40,49%) disease, with 31 (37.8%) showing bone marrow involvement and 58 (70%) showing extra-nodal involvement. (Table 3). Among 82 FL patients, 68 were available for outcome analysis and only 40 (58%) of them received rituximab-based treatment. The median follow-up for the entire cohort was 31 months. The median PFS and OS was not reached in both the subgroups. The 2-year PFS for all patients was found to be 75%. Patients who received rituximab had better rates of CR (62% vs 49%), and PR/SD (25% vs 24%). The PFS of patients who received rituximab was 61 months vs 41 months for those who did not (p=0.012). (Table 4, Figure 3)

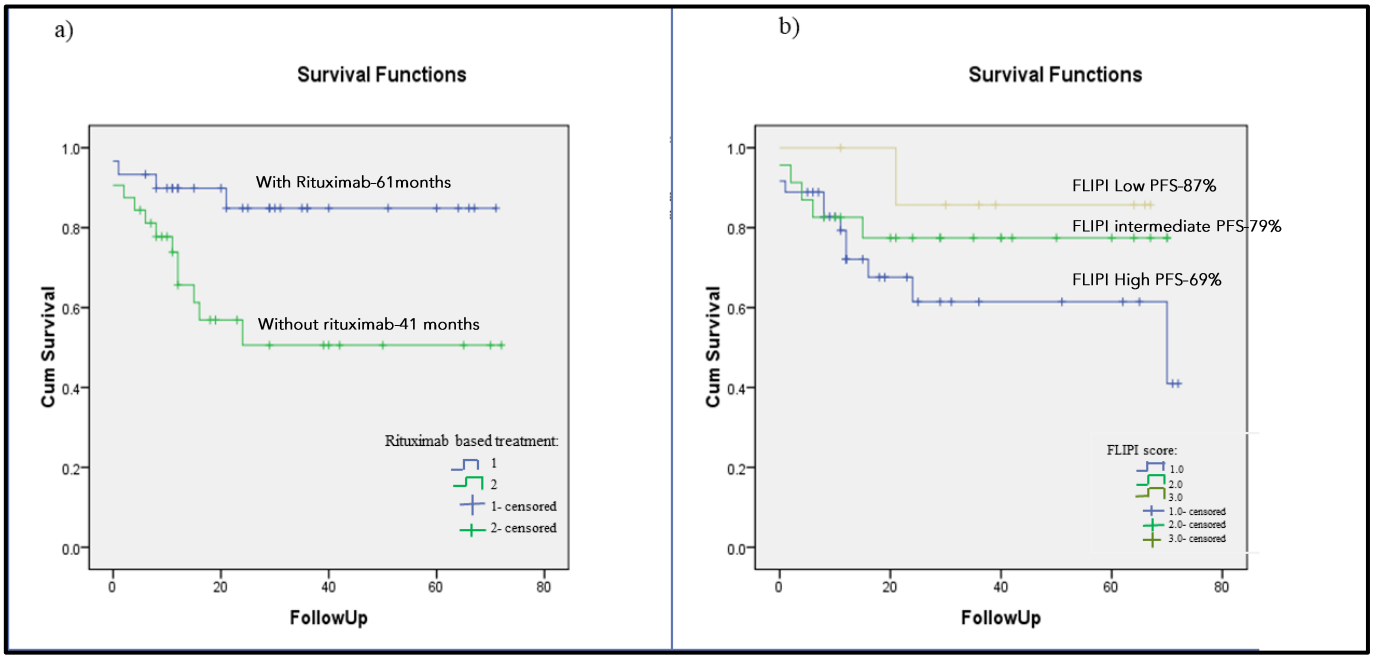
Table 3. Baseline characteristics of patients with follicular lymphoma

Patient characteristics	N=82
Sex (men: women)	1.27:1
Male	46 (56)
Female	36 (43)
Age (years), mean (range)	55 (17-81)
FLIPI scores	
Low (0,1)	12 (14)
Intermediate (2)	29 (35)
High (3 or more)	41 (51)
Extra-nodal involvement	58 (70)
Bone marrow involvement	31 (37)
Stage at presentation	
I	-
II	5 (6)
III	37 (45)
IV	40 (49)
Grade	
I	24 (29)
II	34 (42)
III	24 (29)
Data shown as n (%), unless otherwise specified. FLIPI, Follicular Lymphoma International Prognostic Index;	

Table 4: Outcome analysis of patients with follicular lymphoma.

Patient Outcomes	N=68	
Median follow-up	31 months	
Rituximab based treatment	40 (58)	
Treatment response	Rituximab (40)	Non-rituximab (28)
Complete Response (CR)	25 (62)	14(49)
Partial Response/Stable disease (PR/SD)	10(25)	6(24)
Progressive Disease (PD)	5 (12)	8(27)
Median PFS	NR	
Median OS	NR	
2 years PFS (%), median	75	
2 years PFS as per FLIPI score (%)		
0-1	87	
2	79	
3 or more	69	
Data shown as n (%), unless otherwise specified. FLIPI, Follicular Lymphoma International Prognostic Index; PFS, progression-free survival. OS, overall survival.		

Figure 3: Progression-free survival in follicular lymphoma based on a) Rituximab treatment. b) Follicular lymphoma International Prognostic Index score.



Among the 929 NHL patients, 13% had T-cell NHL, with PTCL being the most common subtype, comprising 5.4% of all lymphoma cases. Among the 50 patients diagnosed with PTCL, the majority were males (78%) with a median age of 54 years. Among these, 44% were diagnosed at stage IV, and 40% at stage III, with bone marrow and extra-nodal involvement at 32% and 14%, respectively.

Discussion

The present study aimed to investigate the accessibility to rituximab and its impact on treatment outcomes of the major subtypes of NHL in a resource constrained setting. A total of 929 NHL patients diagnosed over a period of 6 years were analysed.

The most common NHL type was DLBCL (51.4%), making up more than half of all diagnosed cases, followed by FL (8.8%), MCL (6.9%), PTCL NOS (5.4%), and others. This contrasts with data from a large dataset from the USA (n=104,506), where DLBCL accounted for 23% and CLL/SLL for 16% of NHL cases. The incidence of SLL was higher in the USA compared to India (16% vs. 5%), while T-NHL was less common in the USA than in India (13% vs. 5.9%)[16]. The higher incidence of CLL in the Western world compared to India is attributed to a variety of genetic and environmental factors, but the exact cause remains unknown, warranting further research[17].

Chinese data indicated a higher incidence of extranodal NK/T cell lymphoma (17% vs. 1%), making it the second most common lymphoma in their series[18]. Studies have shown that environmental factors such as excessive exposure to insecticides and pesticides, along with EBV exposure, are strongly associated with this disease, but further research is needed[19].

Our results were comparable to most Indian studies, except for those conducted in Mumbai and Jodhpur, which showed a lower incidence of DLBCL (35.2-36.5%)[20,8]. The variation in frequencies across studies can be attributed to differences in geographic, demographic, genetic, etiologic, ethnic, socioeconomic, and environmental factors. Mondal et al. reported a higher proportion of T-NHL compared to the rest of India, likely due to the small sample size and single-centre data (Table 5)[21].

The high incidence of B-cell lymphomas in India underscores the critical role that therapies like Rituximab can play in patient treatment. Improved availability of this therapy could significantly enhance patient outcomes.

Table 5: Studies comparing distribution of common subtypes of NHL.

	Naresh et al.[20]	Devi et al.[32]	Mondal et al[21]	Sharma et al[33]	Arora et al.[34]	Gogia et al[35]	Patel et al[8]	Yang et al.[18]	Morton et al[16]	Present study
Region	Mumbai, Maharastra	Imphal, Manipur	Kolkata, W. Bengal	Guwahati Assam	Vellore Tamil Nadu	New Delhi	Jodhpur Rajasthan	China	USA	Bangalore Karnataka
Year	2000	2017	2014	2019	2013	2018	2022	2011	2022	2024
Patients	2773	100	347	130	4026	390	178	5549	104506	929
B-NHL(%)	79	66	74	74	78	89	75	62	83	87
Percentage of all NHL cases (%)										
DLBCL	34	45	35.2	60.8	46.9	68.5	36.5	41	23	52
FL	12	5	19.3	4.8	10.5	9	6.7	5	10.2	8.8
BL	1.8	6	5.8	0.8	3.4	1.3	3.9	1.9	1	1.9
MCL	3.4	5	2.6	3.2	1.6	5	8.4	3.1	9	7
SLL	5.7	-	5.5	3.2	4	1.3	2.2	4.6	16	5
MZL	2.1	1	-	0.8	0.3	2.3	1.1	-	3	2
MALT	6.1	1	2	-	2.17	-	2.2	6.3	-	-
T-NHL	16.2	23	25.9	24	20.2	11	24.7	30.2	5.9	13
T-LBL	6	-	8.6	4	0.4	1.8	3.9	-	0.8	2
ALCL	4.3	15	12.1	4	5	2.3	4.5	3.5	0.8	2
PTCL	2.9	-	1.7	15.2	5.9	3.9	10.7	4	0.9	5
NK-T	-	-	-	-	-	-	-	17.1	-	-
AITL	1	5	1.4	-	1.4	0.8	1.1	3.3	0.1	-

Diffuse large B cell lymphoma patients demonstrated PFS and OS of 15 months and 23 months, respectively, which is lower than what is reported in other Indian and Western studies (Table 6). Only 37% of DLBCL patients received rituximab-based chemotherapy, primarily due to the low socioeconomic status of the patients at our centre and lower availability of biosimilars during the study period. This probably explains the poorer responses observed in our cohort. As expected, our analysis showed that survival was better for patients who received rituximab-based treatments which was consistent with multiple Western trials[22,23] Patients with higher IPI scores exhibited worse survival, consistent with multiple trials conducted elsewhere[24].

Table 6: Comparison of treatment outcomes of DLBCL

	Prakash et al.[26]	Gogia et al.[36]	Nair S. et al.[37]	Pavlovsky et al.[38]	Present study
Patient No.	185	775	224	1457	478
Year	2012	2020	2022	2022	2024
Percentage of patients receiving rituximab (%)	18	62.8	73	97.5	37
RR (%)	73	82	76	-	79.7
mPFS	4 year EFS 54%	3 year EFS 78%	3 year PFS 65%	5 year PFS 45-56%	15.2 months
mOS	4 year OS 64%	3 year OS 88%	2 year OS 82%	5 year OS -69%	23 months
RR, Response Rate; PFS, Progression Free survival; OS, Overall Survival					

In Western countries patients have near 100% accessibility to rituximab, which contributes to their better survival data for DLBCL. However, financial constraints in resource-limited countries like India limit access to newer treatments. Rituximab has been available in India since 2000 as an innovator molecule, and was initially very expensive. By 2007, biosimilars entered the Indian market, significantly reducing the cost[25]. The use of rituximab in adult aggressive B-NHL patients as per a study reported by Prakash et al [26] from a centre in Delhi, India was about 18% during the period 2007-2009. The same centre reported (Gogia et al) an increase in rituximab usage in DLBCL patients to approximately 62% during the period 2014-2018[36]. which also led to an improvement in outcomes for these patients. Similarly, Ganeshan et al reported that only 26% of DLBCL patients received rituximab during the period 2000-2013 at a study conducted in South India.[27] A 2022 report on real world outcomes of lymphoma by the Onco-collect Lymphoma registry with data of over 9000 lymphoma patients from India pegged rituximab usage at 83.7% of DLBCL patients[28]. All these reports clearly demonstrate that even though access to rituximab has increased over the years with availability of biosimilars and reducing costs, accessibility rates remain abysmally low even more than two decades after its approval. Although using rituximab initially increases financial strain on patients, it results in cost savings over time. A trial in the Middle East and Africa found that including rituximab in government health programs could save up to $50 million in the long run[29]..

We found that patients with follicular lymphoma had a median age of 55 years, which is younger compared to Western data[30]. Approximately 90% of the patients presented with advanced disease, a significantly higher percentage than reported by the SEER program in the USA[30]. This discrepancy may be attributed to delayed hospital visits by patients and the indolent nature of the disease. The use of rituximab in our study was lower than in Western data (58% vs. 81%). Patients treated with rituximab experienced better progression-free survival (PFS) rates than those who did not receive the treatment. Western studies with higher rituximab usage, such as the one by Pavlovsky et al. in the USA, reported a 5-year PFS rate of 65% and an overall survival rate of 87%. Our analysis observed a PFS rate of 75% after 2 years (Table 7).

Table 7: Comparison of treatment outcomes of follicular lymphoma.

	Gogia et al.[39]	Pavlovsky et al.[38]	Present study
Patients No.	181	578	82
Year	2017	2022	2024
Percentage of patients receiving rituximab (%)	18	81	58
RR (%)	70	-	74
mPFS	2.5 years	5 year PFS-65%	2 year PFS-75%
mOS	5.5 years	5 year OS -87%	NR
RR, Response Rate; PFS, Progression Free survival; OS, Overall Survival			

Our study aimed to provide an epidemiological overview of NHL subtypes at a hospital in South India and the pattern of rituximab usage in B-NHLs. The data indicate that even 2 decades after its approval, rituximab access could not reach 100% of patients thereby compromising outcomes. It also highlights the fact that availability of biosimilars alone does not automatically guarantee 100% access. The same holds good for newer therapies like immunotherapies and CAR-T cell therapies that are approved for patients with difficult-to-treat NHL. They are likely to remain largely out of reach for most patients in India for the next decade or so. Recently, Polatuzumab

vedotin, a novel CD79b-directed antibody-drug conjugate was incorporated into the first-line therapy of DLBCL .[31] Similar to rituximab in its initial stages, this molecule is expensive and will likely remain inaccessible for the majority in India; until generics and biosimilars reach clinical practice a decade or so later. It is therefore imperative for the governments to take up urgent steps to address the disparities in cancer care globally and crank up regulatory and financing mechanisms to support cancer care systems. Additionally, as the majority of patients present at an advanced stage, more efforts should be directed to educate the general public so that patients present to cancer hospitals at an earlier stage, thereby improving prognosis.

Limitations of our study include its single-centre design, which may introduce selection bias, the lack of division into various DLBCL subtypes, and the absence of markers like C-MYC and BCL2/BCL6, which have prognostic implications. Additionally, PET scans were performed in only a minority of patients, despite being the investigation of choice in many high-grade lymphomas. Furthermore, bone marrow transplants, a standard treatment for relapsed lymphomas, were not performed for these patients.

Conclusion

Diffuse large B cell lymphoma and follicular lymphoma patients with access to rituximab had better outcomes than those who did not. Access to rituximab has increased over the years with availability of biosimilars and reducing costs. Public health interventions and framing of policies to improve access to monoclonal antibodies and newer therapies are the need of the hour to further improve cancer treatment outcomes in resource constrained countries like India.

Conflict of Interest:

No conflict of interests.

Funding Statement:

This study did not receive any funding.

Acknowledgements:

None.

Authors Contribution:

Dr. Linu Jacob-Conceptualization and methodology, writing-original draft, writing-review, editing and data curation; Dr. Animesh Gupta- Formal analysis, writing-original draft, writing-review, editing and data curation; Dr. Praveen Khandare- resources, methodology Dr. M C Suresh Babu, Dr. Rudresha, Dr. Lokesh, Dr Rajiv, Dr. Smitha- resources, supervision.

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