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ORIGINAL RESEARCH

Comprehensive Evaluation of Drug-Related Problems and Pharmacotherapy Patterns in Non-Hodgkin's Lymphoma Patients in Yemen

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Background: Drug-related problems (DRPs) are critical challenges in oncology practice, particularly among patients with non-Hodgkin lymphoma (NHL), due to complex regimens and high toxicity potential.

Purpose: This study aimed to identify, classify, and evaluate the prevalence of DRPs and associated factors, and explore the pattern of chemotherapy prescribing for NHL patients.

Methods: A cross-sectional study was conducted from November 2022 to September 2023 at National Oncology Centre (NOC), Al-Jomhouri Teaching Hospital. Adult NHL patients undergoing chemotherapy were enrolled, with a final sample of 279 patients. DRPs were identified and classified using the validated Pharmaceutical Care Network Europe (PCNE) and cross-checked against National Comprehensive Cancer Network (NCCN) guidelines. Potential drug-drug interactions (DDIs) were evaluated using the Lexicomp® drug interactions database. Data was collected from patients' interviews, treatment charts and medical records. Descriptive statistics and linear regression were used for analysis.

Results: Among the 279 NHL patients included in the study, a total of 1870 DRPs were identified (average 6.7 per patient). Advanced-stage disease was observed in 79.6% of patients, and 63.4% received rituximab-containing regimens. The R-CHOP regimen being the most frequently used, which was associated with 52.7% of all DRPs. The most frequent DRPs involved dosing issues, including drug doses too low (26.5%) and incorrect or missing dose calculations (13.1%). DDIs contributed to 13% of the total identified DRPs, with the majority classified as mild interaction. Multivariate regression analysis identified comorbidities, lymphoma subtype, and number of chemotherapy cycles as significant predictors of DRP occurrence.

Conclusion: A high number of DRPs were identified among NHL patients in Yemen, with an average of 6.7 DRPs per patient, predominantly due to dosing issues. Integration of clinical pharmacy services, guideline-based prescribing, and systematic medication reviews are essential to minimize DRPs and improve treatment outcomes.

Keywords: non-Hodgkin lymphoma, drug-related problems, drug-drug interactions, PCNE, Yemen

Introduction

Non-Hodgkin's lymphoma (NHL) is the most common type of lymphoma, accounting for approximately 85% of all lymphoma cases globally.[1] It encompasses a diverse group of lymphoid malignancies that vary in morphology, clinical behavior, and treatment response, and affects individuals across all age groups.[2] Pharmacologic management of NHL depends on the specific subtype, disease stage, and individual patient factors. Chemotherapy remains the primary treatment approach, particularly in aggressive forms of NHL. The CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone), often combined with rituximab (R-CHOP) for CD20-positive B-cell lymphomas, is the most widely adopted first-line regimen, administered in three-week cycles to maximize treatment outcomes.[3,4] However, such

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regimens are often associated with significant toxicities, including chemotherapy-induced nausea and vomiting (CINV), myelosuppression, infections, and mucositis, necessitating comprehensive supportive care to mitigate adverse effects.[4,5]

Drug-related problems (DRPs) pose a substantial challenge in clinical practice, particularly in complex conditions such as NHL. DRPs are defined by the Pharmaceutical Care Network Europe (PCNE) as "events or circumstances involving drug therapy that actually or potentially interfere with desired health outcomes".[6] The complexity of chemotherapy regimens for NHL, often involving multiple agents, increases the risk of polypharmacy and associated challenges. This can lead to a higher incidence of DRPs, including adverse drug reactions (ADRs), drug-drug interactions (DDIs), unnecessary drug therapy, inappropriate drug choices, untreated conditions, and the need for additional medications to manage side effects, which can significantly impact patient outcomes.[7,8]

While DRPs are well documented in various cancers, data on NHL remain limited, especially in low-resource settings. Studies from Ethiopia and India report frequent DRPs, mainly ADRs, DDIs, and therapy-related issues, particularly among elderly patients and those with comorbidities.[9,10] Similar findings from Singapore and the Netherlands showed DRP rates exceeding 60% in oncology patients receiving chemotherapy.[11,12] However, NHL-specific evidence is scarce. This study addressed that gap in a resource-constrained Yemeni setting.

In Yemen, NHL ranks as the sixth most common cancer across both sexes and the third most prevalent among males, with the ninth highest mortality rate.[13] Despite this significant disease burden, there is a scarcity of data on DRPs among NHL patients in Yemen, limiting the understanding of their prevalence and clinical impact on these populations. Although DRPs have been investigated in various cancer populations, no studies have specifically examined their occurrence in NHL patients, leaving a critical gap in the literature.

This study aimed to identify, classify, and assess the prevalence of DRPs among NHL patients, evaluate associated risk factors, and explore chemotherapy prescribing patterns at the NOC, Yemen's largest cancer treatment facility. By addressing this knowledge gap, the findings may inform strategies to optimize pharmacotherapy and improve clinical outcomes for NHL patients.

Materials and Methods

Study Design and Setting

A cross-sectional study was conducted from November 2022 to September 2023 at the National Oncology Centre (NOC), located in Al-Jomhouri Teaching Hospital in Sana'a, Yemen. The NOC was selected as the study site for its prominent role in cancer care, being the oldest and largest cancer treatment facility in the country. As the only specialized cancer treatment center in Sana'a, the NOC serves as a referral center for patients from several governorates. Furthermore, the majority of treatment costs at this center are subsidized by the government, enhancing its accessibility for patients.

Study Population

The study included adult patients (≥18 years) with NHL who received chemotherapy and/or immunotherapy at the NOC during the study period. Eligible participants were received a comprehensive explanation of the study's objectives and procedures, and written informed consent was obtained from each participant prior to enrollment. Exclusion criteria comprised patients admitted only for observation, those not undergoing chemotherapy at the center, and individuals unable to provide informed consent due to cognitive impairment. According to WHO reports, Yemen records approximately 862 new NHL cases annually.[14] Based on NOC records, 30% of these cases were excluded as they involved patients less than 18 years of age, resulting in a total study population of 604 eligible NHL patients.

Sample Size Calculation

The sample size was calculated using Yamane's formula[15]

$$n = \frac{N}{1 + N(\alpha 2)} = \left[604/1 + 604 * (0.05)^2\right]$$

Where n is the required sample size, N is the total population (604), and α is the margin of error (0.05) at a 95% confidence level. Substituting the values yields a minimum sample size of 241 patients. To account for non-response and enhance the study's statistical power, a 14% was added, resulting in a final sample of 279 participants.

Procedure of Data Collection

Data were collected prospectively during patients' visits to the NOC using a structured data collection form. Information was obtained on the first day of the treatment cycle while patients were receiving care at the center and included demographic details, clinical characteristics, treatment regimens, and potential risk factors. Data on prescribed medications, such as drug category, dosage, route of administration, treatment cycles, frequency, and duration, were obtained from patient directly, medical records, and treatment charts.

Identification of DRPs

DRPs were identified and counted for each patient following an evidence-based approach. DRPs were classified according to the PCNE classification system (Version 9.1).[16–18] The PCNE system is a validated, comprehensive tool widely used for DRP identification and management, particularly in oncology settings. Its standardized framework ensures systematic categorization, facilitating communication among healthcare providers and improving patient care.[17,18] Moreover, many previous studies have utilized the PCNE classification system for DRPs identification in cancer patients, further supporting its applicability in this context.[7,9,19] The PCNE classification structure includes three main domains for problems, nine for causes, five for planned interventions, three for intervention acceptance, and four for outcome status, with additional subdomains to further specify each category.[20–22] In this study, all identified DRPs were further evaluated in alignment with the National Comprehensive Cancer Network (NCCN) guidelines[3,23] to detect any deviations or issues in medication prescribing practices. For CINV prophylaxis, although the NCCN guidelines serve as the primary reference at the NOC, the standard practice involves administering ondansetron 8 mg IV and dexamethasone 8 mg IV 30 minutes prior to all chemotherapy regimens, irrespective of their emetogenic risk classification. Additionally, body surface area (BSA) was calculated using the Mosteller formula, a standard method employed by oncologists at the NOC,[7] and the resulting BSA values were used to assess dosage appropriateness based on NCCN recommendations.

Polypharmacy as a part of DRPs was calculated as the average number of medications per encounter. It was defined as the most common definition, which is the concurrent use of five or more medications, including chemo-immunotherapy and supportive care therapy.[24] The combination chemotherapy regimen was counted as one medication.[24]

Identification of Potential DDIs

Potential DDIs related to chemotherapy and supportive care regimens were identified using the Lexicomp® drug interaction database, a validated tool known for its high sensitivity and specificity.[20] Lexicomp classifies interactions into five categories: A (no interaction), B (no action needed), C (mild, requiring monitoring), D (moderate, needing review), and X (combinations to avoid). Only categories C, D, and X were included in the analysis due to their clinical significance.[25] Appropriate monitoring or therapeutic adjustments were applied for C and D interactions, while category X interactions were immediately reported to the healthcare team at the NOC for review and intervention. In clinical practice, C-type interactions triggered additional monitoring or interventions only when standard protocols were insufficient, for example, ordering ECGs for QT-prolonging drugs or delaying chemotherapy in the presence of toxicity risk. In this study, C-type interactions were only classified as DRPs if such monitoring or adjustments were absent. Categories A and B were excluded given their minimal clinical relevance.[25]

Quality Assurance

The DRPs were identified through a detailed review of each patient's medical file, prescription records, and treatment chart, using the BCNE tool. The evaluation assessed the appropriateness of treatment frequency, duration, drug selection, and drug dosing, alongside with the comorbidities, treatment tolerance, clinical judgment, contraindications, and disease progression. This process was guided by the NCCN guidelines to ensure adherence to evidence-based protocols. The

identified DRPs were initially reviewed by a team of expert clinical pharmacists from the Department of Clinical Pharmacy at the Hospital and University of Science and Technology, Sana'a. Any discrepancies in classification were resolved through thorough discussion until consensus was achieved. To ensure further accuracy and clinical validity, DRPs underwent an independent secondary review by an external panel of clinical pharmacy specialists from Universiti Sains Malaysia, with expertise in pharmacotherapy and oncology practice.

Ethical Approval

This study was approved by the Ethical Committee of Medical Research at the University of Science and Technology, Sana'a, Yemen, as part of a broader project on (Medication Use Evaluation for Non-Hodgkin Lymphoma in Yemen; EAC/UST201). It adheres to the principles of the Declaration of Helsinki for ethical research involving human subjects. Informed consent was obtained from all participants, ensuring anonymity and minimizing risk. Patients were provided with a clear explanation of the study's aims and given the opportunity to ask research-related questions before participation.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics software, version 27.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were employed to summarize demographic and clinical characteristics of the study population, including variables such as age, sex, cancer stage, and associated risk factors. NHL subtypes were classified based on histopathological reports from medical records. Given the heterogeneity of NHL, we categorized cases as DLBCL or non-DLBCL for analysis. For the statistical analyses, only categories C (mild), D (moderate), and X (major) drug interactions were analyzed due to their clinical relevance, while categories A and B were excluded. To identify independent predictors variables of DRPs in patients with NHL, linear regression model analysis was used. Initially, simple linear regression was performed, and variables with a P-value < 0.25 were selected for inclusion in the multiple linear regression analysis. Statistical significance was set at $p < 0.05$.

Results

Participants Sociodemographic Data

A total of 279 patients were included in this study. Table 1 presents a summary of their sociodemographic characteristics. The majority were male (55.6%), married (85.6%), and unemployed (90.0%). Regarding social habits, 64.5% reported chewing khat, and 29.0% reported smoking. The median age was 45 years, with 42.6% aged between 18 and 40 years. In terms of family size, 43.7% had more than four children. Educational levels were low, with 49.8% reporting no formal education. Geographically, 22.9% resided in Sana'a governorate, while 77.1% were from other governorates.

Table 1 Participants' Sociodemographic Data (N= 279)

Variable		**N**	**%**
Sex	Male	155	55.6
	Female	124	44.4
Age, Median (IQR): 45 (24)			
Age	18 to 40	119	42.6
	41 to 64	111	39.8
	≥ 65	49	17.6

(*Continued*)

Table 1 (Continued).

Variable		N	%
Marital status	Married	239	85.6
	Single	37	13.3
	Divorced	3	1.1
No. of children	No children	54	19.4
	One child	14	5.0
	Two to four children	89	31.9
	More than four children	122	43.7
Occupation	Employed	28	10.0
	Unemployed	251	90.0
Education level	No formal education	139	49.8
	Primary education	93	33.4
	Secondary education or above	47	16.8
Smoking	Yes	81	29.0
	No	198	71.0
Khat chewing	Yes	180	64.5
	No	99	35.5
Shamma use	Yes	40	14.3
	No	239	85.7
Residency	Sana'a governorate	64	22.9
	Other governorates	215	77.1

Abbreviations: IQR, interquartile range; Shamma, a traditional smokeless tobacco product; N, frequency.

Clinical Characteristics and Treatment Protocol of NHL Patients

Table 2 summarizes the clinical characteristics and treatment protocols of the study population. A past medical history was present in 17.6% of patients, and a family history of disease was reported by 18.6%. Regarding treatment duration, 57.7% had received treatment for one year or less, while 34.1% had been treated for two to five years. Among 279 NHL patients, DLBCL was the most common subtype (44.8%, n=125). Non-DLBCL subtypes (55.2%, n=154) included undifferentiated lymphoma; Not Otherwise Specified (NOS) (36.6%), follicular lymphoma (29.5%), Burkitt lymphoma (15.8%), mantle cell lymphoma (7.5%), marginal zone lymphoma (7.0%), and peripheral T-cell lymphoma (3.6%). Rituximab-containing regimens were used in 63.4% of patients, and 79.6% were presented with advanced-stage disease. Chemotherapy alone was the predominant treatment modality, administered to 77.1% of patients. The median number of chemotherapy cycles was 3, with median totals of 9 medications and 7 DRPs.

Classification for Drug-Related Problems

Table 3 presents the classification of DRPs. A total of 1870 DRPs were documented among 279 among NHL patients, with each patient experiencing between 2 and 12 cumulative DRPs, and a mean of 6.7 DRPs per patient. Issues related to

Table 2 Participants' Clinical Characteristics and Treatment Protocol

Variable		**N**	**(%)**
Diseases history	Yes	49	17.6
	No	230	82.4
Family history	Yes	52	18.6
	No	227	81.4
Treatment duration	≤ 1 year	161	57.7
	2–5 years	95	34.1
	≥ 6 years	23	8.2
Morphology and Subtype	DLBCL	125	44.8
	Non-DLBCL	154	55.2
Stage	Early stage	57	20.4
	Advanced stage	222	79.6
Treatment protocol	Rituximab-containing therapy	177	63.4
	Non-Rituximab-containing therapy	102	36.6
Treatment modalities	Chemotherapy alone	215	77.1
	Chemotherapy with surgery	39	14.0
	Concurrent chemoradiotherapy (with/without surgery)	25	9.0
Cycle No, Median (IQR): 3 (3)			
Total number of medications, Median (IQR): 9 (3)			
Total number of DRPs, Median (IQR): 7 (3)			

Notes: The treatment duration of ≥ 6 years includes repeated or intermittent chemotherapy courses, maintenance therapy, particularly for recurrent cases.
Abbreviations: DLBCL, diffuse large B-cell lymphoma; IQR, interquartile range; N, frequency.

Table 3 Classification for Drug-Related Problems

DRPs Categories	**Subtype**	**No. of Patients**	**No. of DRPs**	**DRPs (%)**
Drug selection	Inappropriate chemotherapy according to guidelines/formulary	78	86	4.6
	Inappropriate antiemetics/supportive care according to guidelines/formulary	190	223	11.9
	No indication for drug	5	5	0.3
	Inappropriate duplication of therapeutic group or active ingredient	1	1	0.1
	No or incomplete drug treatment	91	126	6.7

(*Continued*)

Table 3 (Continued).

DRPs Categories	Subtype	No. of Patients	No. of DRPs	DRPs (%)
Dose selection	Drug dose too low	221	495	26.5
	Drug dose too high	60	106	5.7
	Dose calculation wrong, unclear or missing	199	245	13.1
Treatment duration	Inappropriate treatment frequency/duration	19	22	1.2
Dispensing	Necessary information not provided or incorrect advice provided	90	101	5.4
	Wrong drug or strength dispensed	21	21	1.1
Others Polypharmacy/DDIs	Polypharmacy	195	195	10.4
	Total number of DDIs	194	244	13.0
	Mild DDI	194	238	97.5[a]
	Moderate DDI	3	6	2.5[a]
	Major DDI	0	0	0.0[a]

Note: [a]proportion per total number of DDIs.
Abbreviations: DDIs, drug-drug interactions; N, frequency.

dose selection were the most common, particularly underdosing. The most frequent DRP was drug doses being too low, affecting 221 patients and accounting for 495 DRPs (26.5%). This was followed by dose calculation errors (wrong, unclear, or missing), resulting in 245 DRPs (13.1%). Regarding drug selection, inappropriate use of antiemetics and supportive care medications according to guidelines or formulary, accounted for 223 DRPs (11.9%). Corticosteroids were administered to 114 patients as part of chemotherapy regimens such as R-CHOP, CHOP, and ESHAP, while 269 patients received corticosteroids for supportive purposes, including antiemetic therapy. Polypharmacy issues represented 195 DRPs (10.4%), while DDIs accounted for 244 DRPs (13.0%) among 194 patients. Most DDIs were classified as mild (238 occurrences, 97.5%), with moderate interactions observed in 3 patients (6 occurrences). No major DDIs were reported.

Classification and Frequency of Potential Drug-Drug Interactions

Potential DDIs were identified in 194 patients (69.5%). Most DDIs (97.5%) were classified as mild (Type C), requiring monitoring, while no major interactions (Type X) were observed. Identified DDIs involved all medications administered, including chemotherapy, supportive care, and treatments for comorbidities such as metformin, phenytoin, and allopurinol. Notably, in patients receiving R-CHOP, the most frequent interaction was cyclophosphamide-doxorubicin (190 occurrences), associated with enhanced cardiotoxicity risk due to anthracycline exposure. Additional interactions relevant to R-CHOP or supportive therapy, moderate interactions were identified between metformin and dexamethasone/prednisolone or ondansetron (21 occurrences each), posing risks of hyperglycemia and elevated metformin levels. Other notable mild interactions included cyclophosphamide-allopurinol, phenytoin-chlorpheniramine, corticosteroids-aspirin, and methotrexate-proton pump inhibitors (PPIs). A focused review of R-CHOP-related DDIs revealed relevant interactions with commonly co-prescribed supportive and chronic medications, particularly those involving corticosteroids, antidiabetics, and antiemetics. Although generally mild, these interactions may lead to adverse effects if not closely monitored. All interactions are detailed in Table 4.

Table 4 Classification and Frequency of Potential Drug-Drug Interactions of All Medications Received by the Patients

Category	Interacting Pair	N	Potential Consequences
Mild interaction, requiring monitoring (n=238, 97.5%)	Cyclophosphamide with Doxorubicin	190	Cyclophosphamide may enhance the cardiotoxic effect of doxorubicin (Anthracycline).
	Metformin with Dexamethasone/ prednisolone	21	Dexamethasone/prednisolone: These agents, associated with hyperglycemia, can diminish the therapeutic effect of Antidiabetic medications.
	Ondansetron with Metformin:	21	Ondansetron may increase the serum concentration of metformin.
	Cyclophosphamide with Allopurinol	1	Allopurinol may enhance the adverse effects of cyclophosphamide if allopurinol is initiated or the dose is increased, especially if a patient is receiving long-term allopurinol therapy.
	Phenytoin with Chlorpheniramine	2	Chlorpheniramine may increase the serum concentration of Fos-phenytoin.
	Dexamethasone with Aspirin	2	Aspirin may enhance the adverse/toxic effect of dexamethasone. These specifically include gastrointestinal ulceration and bleeding. Corticosteroids may decrease the serum concentration of Salicylates. Withdrawal of corticosteroids may result in salicylate toxicity.
	Methotrexate and PPIs (omeprazole)	1	Omeprazole may increase serum concentration of MTX
Moderate interaction, consider therapy modification (n=6, 3.5%)	Phenytoin with Doxorubicin	2	Phenytoin (CYP3A4 inducer) may strong decrease serum concentration of doxorubicin.
	Phenytoin with Dexamethasone	1	Phenytoin (CYP3A4 inducer) may decrease the serum concentration of Dexamethasone. Dexamethasone may decrease the serum concentration of Phenytoin. Dexamethasone may increase the serum concentration of Phenytoin.
	Phenytoin with Ondansetron	2	Phenytoin: CYP3A4 Inducers (Strong) may increase the metabolism of ondansetron: CYP3A4 Substrates (High risk with Inducers).
	Ondansetron / Domperidone	1	Domperidone may enhance the QTc-prolonging effect of Ondansetron.

Notes: Mild interaction = class C, Moderate interaction = class D.
Abbreviations: MTX, methotrexate; CYP3A4, Cytochrome P450 3A4; PPIs, proton-pump inhibitors.

Clinically significant interactions included all moderate (Type D) DDIs, which required intervention or therapy adjustment, this involved phenytoin with dexamethasone, doxorubicin, and ondansetron. Mild (Type C) interactions, though common, required only close monitoring and did not necessitate therapy changes.

Pattern of Chemotherapy Regimens and Their Association with DRPs

Table 5 displays the pattern of chemotherapy regimens administered to NHL patients at the NOC and their association with DRPs. The R-CHOP regimen was the most commonly used, associated with 52.7% of the 1870 total DRPs across 138 patients (49.5%). This was followed by the CHOP regimen, accounting for 15.1% of DRPs in 47 patients (16.8%). Other regimens, including monoclonal antibody (MAB) monotherapy, ABVD, and CVP/R-CVP, were associated with DRP rates of 7.6%, 6.1%, and 7.9%, respectively.

Table 5 Pattern of Chemotherapy Regimens and Their Association with DRPs

Chemotherapy Regimen	No. of Patients	(%)[a]	No. of DRPs	(%)[b]
R-CHOP	138	49.5	986	52.7
CHOP/VACA	47	16.8	283	15.1
R-CVP/COP	7	2.5	48	2.6
CVP/COP	21	7.5	99	5.3
ABVD	15	5.4	115	6.1
MAB monotherapy	24	8.6	143	7.6
R-EPOCH	3	1.1	30	1.6
DHAP	2	0.7	11	0.6
ESHAP	1	0.4	10	0.5
FCR	2	0.7	17	0.9
Cyclophosphamide+ cytarabine/prednisolone	2	0.7	11	0.6
Cisplatin	2	0.7	12	0.6
Irinotecan + temozolomide	2	0.7	14	0.7
ICE	5	1.8	30	1.6
MTX+L-asparagine	1	0.4	9	0.5
R-GDP	4	1.4	33	1.8
Vincristine + dexamethasone	1	0.4	7	0.4
Hyper CVAD/R-CVAD	2	0.7	12	0.6

Notes: [a]proportion per number of patients; [b]proportion per total number of DRPs.

Abbreviations: DRPs, Drug-related problems; CHOP/R-CHOP, cyclophosphamide, doxorubicin, vincristine and prednisone ± Rituximab; ABVD, Adriamycin, Bleomycin, Vinblastine, and Dacarbazine; MAB, monoclonal antibody; hyper-CVAD, hyper-fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; EPOCH, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin; ESHAP, etoposide, methylprednisolone, high-dose cytarabine, and cisplatin; DHAP, dexamethasone, cisplatin, and cytarabine; R-GDP, rituximab, gemcitabine, dexamethasone, and cisplatin; ICE, ifosfamide, carboplatin, and etoposide; FCR, fludarabine, cyclophosphamide, and rituximab; VACA, vincristine, doxorubicin, cyclophosphamide, and Actinomycin D; MTX, methotrexate.

Pattern of Chemotherapy Medications and Supportive-Care and Their Association with DRPs

Table 6 summarizes the patterns of chemotherapy agents, supportive-care medications (administered pre- and post-chemotherapy), and concomitant medications associated with DRPs. Cyclophosphamide was the most frequently implicated medication, accounting for 10.5% of the 1870 total DRPs. This was followed by antiemetic agents (9.3%), rituximab (9.1%), and doxorubicin (7.8%). Overall, chemotherapy and supportive-care medications contributed to 932 DRPs, representing 49.8% of all identified DRPs. Additionally, concomitant medications, including antiepileptics and hypoglycemic agents, were associated with 52 DRPs (2.8%).

Association Between DRPs and Predicting Variables in NHL Patients

Table 7 presents the results of linear regression analyses examining the association between DRPs and various predictor variables in NHL patients. Both simple and multiple linear regression analyses were conducted, considering demographic

Table 6 Pattern of Chemotherapy and Supportive-Care Medications and and Their Association with DRPs

Chemotherapy/Supportive-Care Medications	No. of DRPs	%
Chemotherapy medications		
Vincristine	43	2.3
Cyclophosphamide	196	10.5
Prednisolone/Dexamethasone	47	2.5
Rituximab	170	9.1
Other MAB	10	0.5
Doxorubicin (Hydroxydaunorubicin)	146	7.8
Cisplatin/Oxaliplatin	7	0.4
Cytarabine	6	0.3
Ifosfamide	4	0.2
Methotrexate	1	0.1
Etoposide	12	0.6
Gemcitabine	4	0.2
Dactinomycin	2	0.1
Irinotecan/temozolomide	4	0.2
Vinblastine	8	0.4
Dacarbazine/fludarabine	19	1.0
Bleomycin	10	0.5
Supportive-care medications		
Antiemetics	174	9.3
Chlorpheneramine	13	0.7
Paracetamol	46	2.5
Mesna	9	0.5
Leucovorin	1	0.1
Total number of DRPs of Chemotherapy/Supportive-care medications	932	49.8
Other medications		
Antiepileptic agents	7	0.4
Hypoglycemic agents: Metformin.etc	42	2.2
Aspirin	2	0.1
Allopurinol	1	0.1
Total No. of other medications received by patients	52	2.8

Notes: Supportive care therapy is also known as pre- and post-chemotherapy medication.
Abbreviations: MAB, monoclonal antibody; DRPs, Drug-related problems.

Table 7 Linear Regression Analysis for DRPs and Predicting Variables in NHL Patients

Parameter	Simple Linear Regression			Multiple Linear Regression		
	Dependent Variable: DRPs			Dependent Variable: DRPs		
	β -Estimate	SE	p-value	β -Estimate	SE	p-value
Age [1: < 65, 2: ≥ 65]	−0.159	0.299	0.595	-	-	-
Sex [1: male, 2: female]	0.056	0.229	0.805	-	-	-
Marital status [1: Married, 2: Single/divorced]	0.406	0.323	0.211	0.265	0.255	0.154
Have children! [1: Yes, 2: No]	0.208	0.287	0.470	-	-	-
Occupation [1: Employed, 2: Un-employed]	−0.370	0.378	0.328	-	-	-
Education level [1: Low education level, 2: High education level]	0.181	0.227	0.425	-	-	-
Diseases history [1: Yes, 2: No]	−1.302	0.288	<**0.001**	−0.945	0.300	**0.002**
Family history [1: Yes, 2: No]	−0.035	0.292	0.905	-	-	-
Residency of patient [1: Sana'a, 2: Other governorates]	−0.082	0.270	0.762	-	-	-
Smoking [1: Yes, 2: No]	−0.071	0.250	0.776	-	-	-
Khat chewing [1: Yes, 2: No]	0.085	0.237	0.720	-	-	-
Stage [1: Early stage, 2: Advanced stage]	−0.462	0.281	0.101	−0.369	0.266	0.167
Morphology and Subtype [1: DLBCL, 2: Non-DLBCL]	0.389	0.227	0.089	0.436	0.216	**0.045**
Treatment modalities [1: Chemotherapy alone, 2: Chemotherapy with other interventions (surgery/radiation)]	0.001	0.270	0.998	-	-	-
Treatment duration [1: ≤ 1 year, 2: > 1 year]	−0.101	0.230	0.660	-	-	-
Protocol used [1: Rituximab-containing therapy, 2: Non-Rituximab-containing therapy]	−0.814	0.231	<**0.001**	−0.412	0.301	0.172
Cycle number [1: cycle 1–2, 2: Cycle 3 or more]	0.747	0.226	**0.001**	0.689	0.217	**0.002**

(*Continued*)

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Table 7 (Continued).

Parameter	Simple Linear Regression			Multiple Linear Regression		
	Dependent Variable: DRPs			Dependent Variable: DRPs		
	β -Estimate	SE	p-value	β -Estimate	SE	p-value
Polypharmacy [1: No (≤ 5 medications), 2: Yes (> 5 medications)]	1.073	0.239	<**0.001**	0.569	0.347	0.102
DDI [1: Yes, 2: No]	−0.807	0.242	**0.001**	−0.479	0.272	0.080
Number of medications [1: ≤ 9 medications, 2: > 9 medications]*	0.632	0.224	**0.005**	−0.265	0.321	0.410
Model				R=0.416; R2=17.3%, adjusted R2= 14.9%		<**0.001**

Notes: Variables of <0.25 in the simple linear regression analysis were included in the multiple linear regression model; p-value in bold indicate statistical significance at $p < 0.05$; 1: is the reference group. Low education level: No formal education and Primary education; High education level: Secondary education or above. *median = 9 medications.

Abbreviations: DRPs, Drug-related problems; DLBCL Diffuse large B cell lymphoma; DDI, drug-drug interaction; SE, Standard Error.

characteristics, disease history, treatment protocols, and clinical variables. Multicollinearity analysis showed low variance inflation factors (VIFs) for continuous variables.

Patients without prior disease history had significantly fewer DRPs, with both simple ($\beta = -1.302$, $p < 0.001$) and multiple regression ($\beta = -0.945$, $p = 0.002$) confirming this association. Non-DLBCL patients showed a higher incidence of DRPs, with a significant positive association in multiple regression ($\beta = 0.436$, $p = 0.045$).

Non-rituximab therapy was negatively associated with DRPs in simple regression ($\beta = -0.814$, $p < 0.001$), but this lost significance in multiple regression ($\beta = -0.412$, $p = 0.172$). The number of treatment cycles had a significant positive association with DRPs in both regression models ($\beta = 0.747$, $p = 0.001$; $\beta = 0.689$, $p = 0.002$). In the simple linear regression analysis, the presence of polypharmacy and DDIs was significantly associated with an increased number of DRPs ($\beta = 1.073$, $p < 0.001$; $\beta = -0.807$, $p = 0.001$), as patients without DDIs exhibited 0.807 fewer DRPs compared to those with DDIs. The model explained 17.3% of DRP variance ($R^2 = 17.3\%$, adjusted $R^2 = 14.9\%$, $p < 0.001$).

Discussion

The findings of this study outlined the types and frequencies of DRPs, identified predictors and associated factors, and examined chemotherapy medications and regimens patterns for NHL patients at the NOC in Yemen. Sociodemographic profiles, clinical characteristics, and treatment protocols illustrated disease management strategies, offering valuable insights into the study population.

Patients' Sociodemographic and Clinical Characteristics

A significant proportion of NHL patients in this study were diagnosed at advanced stages, with limited formal education contributing to delayed treatment initiation. Low health literacy, associated with illiteracy, impedes early symptom recognition and healthcare access, exacerbating diagnostic delays.[26] These findings align with prior research indicating that 65.4% of illiterate patients presented with advanced-stage malignancies.[27]

In our study of DRPs among NHL patients, the median age was 45 years (IQR: 24), which is notably younger than the typical age at diagnosis reported in international literature, for example, 67 years globally and 70 years in a Swedish cohort.[28,29] This age difference reflects broader population age structures and aligns with the younger demographic

profile of Yemen. Treatment duration varied, with 8.2% of patients undergoing therapy for six years or longer due to NHL recurrence, necessitating intermittent chemotherapy and maintenance regimens. This underscores the challenges of managing refractory disease in resource-limited settings.

Prevalence of Drug-Related Problems

This study identified a higher mean number of DRPs per patient (6.7; 100% prevalence) compared to previous oncology studies, which reported 1.29–2.67 DRPs per patient and a prevalence of 71–75%.[7,12,27] This elevated rate likely reflects both the complexity of the local clinical context in Yemen and the use of the PCNE v9.0 classification system, which offers greater sensitivity than older methods.[17,18] The adoption of guideline-based assessments may have further enhanced DRP detection. Furthermore, the complexity of NHL treatment, often involving aggressive chemotherapy regimens and multiple supportive medications, contributes to increased polypharmacy and a higher risk of adverse events.[30] A recent systematic review (2024) reported a wide range of DRP prevalence in cancer patients (9.6–92.8%), highlighting variability based on patient characteristics, cancer types, and the DRP assessment tools used.[31]

Patient-specific factors such as age, comorbidities, and genetic polymorphisms (eg, CYP450 enzyme variants) may further contribute to DRP risk.[28,32] While some deviations from standard protocols may be clinically justified, appropriate documentation is essential to maintain patient safety and accountability.

Pattern of Chemotherapy Regimens and Medications and Their Association with DRPs

This study identified R-CHOP as the most frequently prescribed chemotherapy regimen among patients with NHL, followed by CHOP, and CVP/R-CVP regimens. However, their multi-drug nature is associated with a higher risk of DRPs, likely due to complex pharmacokinetics, DDIs, ADRs, and additive toxicities. Rituximab-containing regimens, particularly R-CHOP, were the most frequently prescribed for patients with DLBCL, consistent with international guidelines.[3,33] The efficacy of rituximab in CD20-positive B-cell malignancies is well-documented, with previous studies demonstrating improved response rates and survival outcomes.[34,35]

Cyclophosphamide, rituximab, and doxorubicin were the most common agents linked to DRPs, primarily due to dosing inaccuracies (over- or under-dosing) and inappropriate drug selection, as doxorubicin, for example, known for its potent anti-cancer effects but also for its potential to cause serious side effects such as heart damage (cardiotoxicity) and bone marrow suppression.[36]

Similarly, antiemetic agents were the second most common medication contributors to DRPs, frequently due to including overuse in low-risk regimens or underuse in highly emetogenic protocols. While essential for managing chemotherapy side effects, antiemetics were a significant source of DRPs due to factors like adverse reactions, inadequate dosing, and drug interactions. According to NCCN antiemetic guidelines, clinicians should avoid overuse of antiemetics, especially in settings where the anticancer agents are of minimal or low emetic risk, to avoid exposing patients to adverse effects from antiemetics, to decrease possible DDIs.[37] These findings are consistent with those of Sisay et al in cancer patients, who reported that inappropriate and unnecessary antiemetic use were significant contributors to DRPs.[7] Addressing systemic barriers, particularly inconsistent clinical protocols and insufficient integration of pharmacists in oncology care teams, represents a crucial opportunity to enhance medication safety.

Classification and Causes of Drug-Related Problems

The findings of this study showed that dosing problems were the most prevalent type of DRPs (45.3%), particularly underdosing. These issues often stemmed from errors in BSA calculation, documentation gaps, and lack of standardization. Dosing problems during chemotherapy can compromise treatment efficacy and safety, potentially leading to drug-related morbidity and mortality.[31] For example, dexamethasone doses were frequently below recommended levels for moderate-to-highly emetogenic chemotherapy. Similar underdosing of cyclophosphamide and doxorubicin may compromise treatment efficacy, as lower doses can increase the risk of treatment failure and limit the potential for remission, emphasizing the critical importance of adhering to recommended dosing guidelines.[38] Overdosing, particularly with vincristine and cyclophosphamide, was also reported, posing toxicity risks, such as neurotoxicity, manifesting as peripheral neuropathy, myelosuppression, increasing the risk of infections, and gastrointestinal side effects, including

nausea and vomiting.[4] These findings align with the previous study reported that dosing problems, including dosages that are too low or too high, accounted for 39.3% of all DRPs in cancer patients.[31] Moreover, many patients received corticosteroids as part of their chemotherapy regimens, such as R-CHOP and ESHAP. In these cases, the use of corticosteroids in antiemetic protocols may be reduced or omitted, in accordance with NCCN guidelines, when they are already included in the chemotherapy regimen.[37]

In terms of causes of DRPs, inappropriate drug selection, especially within antiemetic and supportive care regimens, also contributed to DRPs. Supportive care regimens, including dexamethasone, metoclopramide, prochlorperazine, and 5-HT3-RA, were overprescribed for patients at low risk of CINV, contrary to guidelines. This overprescription can lead to unnecessary side effects, drug interactions, and increased healthcare costs.[37] Conversely, patients receiving moderately or highly emetogenic chemotherapy (MEC or HEC) were frequently received under-prescribed, with prophylactic antiemetic regimens lacking key components such as an NK1 receptor antagonist (NK1-RA) and/or olanzapine. The recommended triple regimen includes 5-hydroxytryptamine-3 receptor antagonist (5-HT3-RA), dexamethasone, and either an NK1-RA or olanzapine for optimal prevention of CINV.[37] Under-prescription for these high-risk patients can result in poor treatment adherence, dehydration, and worsened outcomes.[7] Both issues arise from inconsistent risk assessment and treatment protocols. A critical analysis should focus on refining individualized treatment strategies, improving adherence to guidelines, and evaluating the pharmacoeconomic impact of overuse versus underuse, aiming to optimize both efficacy and patient quality of life.

Moreover, our findings revealed that potential DDIs accounted for 13% of DRPs, mostly mild using the Lexicomp database. For example, cyclophosphamide may enhance doxorubicin's cardiotoxicity, indicating a major potential consequence with fair reliability. In addition, interactions between metformin and dexamethasone/prednisolone and metformin with ondansetron showed moderate potential consequences with fair to good reliability.[39] However, only 2.5% of the potential DDIs were moderate, including phenytoin with doxorubicin, dexamethasone, and ondansetron, which can alter serum levels and efficacy. Similarly, a previous study found DDIs in 16.8% of patients, with two experiencing serious interactions.[27] While these findings highlight potential risks of DDI, the actual impact depends on patient-specific factors, dosing, and the clinical context. In clinical practice, healthcare providers should carefully assess the risk of DDIs by considering patients' medical histories and current medications, as well as the pharmacokinetic and pharmacodynamic properties of interacting drugs. Routine monitoring, patient education, and close collaboration among oncology teams and pharmacists are essential strategies to mitigate these risks.

Regarding inappropriate drug charts, it was classified in this study under "necessary information not provided or incorrect advice provided", such as weight and height being written for patients, missed personal data (cycle No, age, the procedure used), dose wrong in sheet, and dose very big difference, were reported among 32% of patients. According to Sisay et a, inappropriate drug charts were recorded in 17.7% of the participants.[7] These findings suggest that patient chart registration issues can negatively impact therapeutic outcomes, including treatment delays, suboptimal regimen selection, reduced efficacy, guideline non-adherence, and compromised patient quality of life. However, a direct correlation between these DRPs and patient outcomes was not assessed, improving the accuracy and completeness of documentation through standardized practices and electronic health records is essential to overcome these DRPs. Evidence suggests that enhanced documentation improves medication management, facilitates provider communication, and leads to better patient outcomes.[40,41]

Association Between DRPs and Predicting Variables in NHL Patients

In the current study, the linear regression analysis revealed significant associations between treatment-related variables and the occurrence of DRPs. A significant negative association was found between disease history and DRPs. Specifically, patients without comorbidities such as hypertension, diabetes, or cardiovascular conditions experienced, on average, 1.302 fewer DRPs in the simple linear regression model and 0.945 fewer in the multiple linear regression models than those with such conditions. Chronic comorbidities are known to alter pharmacokinetics and pharmacodynamics, increasing the risk of polypharmacy, DDIs, ADRs, and dosing errors. These findings highlight the importance of integrating a patient's comorbid conditions into therapeutic decision-making to minimize DRPs and optimize clinical

outcomes. These findings are consistent with the study by Degu and Kebed, which revealed a significant negative association between comorbidities and DRPs in cancer patients.[27]

Treatment-related factors emerged as strong predictors, with rituximab-containing regimens significantly associated with a 0.814 increase in DRPs in the simple linear regression analysis. This association may be attributed to the complex administration protocols of rituximab and its higher incidence of infusion-related reactions, such as fever, chills, and nausea as well as serious adverse effects including *Pneumocystis jiroveci* pneumonia and hepatitis B virus reactivation.[42] Similarly, the presence of DDIs was significantly associated with increased DRPs in the single linear regression analysis. DDIs can alter therapeutic drug levels, potentially leading to toxicity, treatment failure, or adverse events such as QT prolongation, arrhythmias, neurotoxicity, gastrointestinal bleeding, and reduced chemotherapy efficacy. These complications can also increase the risk of medication non-adherence and further elevate the likelihood of DRPs.[43] These findings underscore the need for diligent screening and management of DDIs by healthcare providers.

Furthermore, both regression models identified a significant positive association between the number of chemotherapy treatment cycles and DRPs. As each additional treatment cycle significantly elevated DRP risk, emphasizing the cumulative toxicity burden of prolonged therapy. Regular clinical assessments during prolonged treatment are essential to detect and address DRPs early.[44]

Moreover, simple regression analysis indicated that polypharmacy and the median number of medications were significantly associated with increased DRPs, regardless of the chosen treatment regimen. Each added drug increases the potential risk for ADRs, overdoses, and underdoses, while reducing inappropriate polypharmacy through dose reduction or medication discontinuation is critical in minimizing ADRs, DRPs and enhancing treatment safety.[45] While polypharmacy showed significant associations with DRP occurrence, patient age did not independently predict DRPs in this study. This contrasts with findings from Kefale et al and Su et a, who reported older age as a significant predictor of DRPs.[9,21] Discrepancies among studies may be attributed to differences in design, sample size, population characteristics, or statistical methodologies.

These findings underscore the importance of implementing targeted strategies to minimize DRPs in NHL patients. Integrating clinical pharmacists into oncology teams, ensuring guideline adherence through ongoing training for healthcare providers, and utilizing tools such as electronic health records and prescription audits can enhance medication safety. Patient-centered interventions, such as individualized education, medication reconciliation, and regimen simplification, are also vital to improving adherence and reducing preventable DRPs in complex treatment settings.

Study Strengths and Limitations

This study is subject to certain limitations. It was conducted at a single institution using convenience sampling, which may limit the generalizability of findings to the broader NHL population in Yemen. Although treatment duration captured prolonged or recurrent therapy, treatment line (eg, first- vs second-line) was not explicitly documented, introducing potential residual confounding, particularly in analyses involving lymphoma subtypes. Due to small sample sizes in some subgroups, comparisons were limited to DLBCL versus non-DLBCL, potentially overlooking subtype-specific differences. Additionally, the inclusion of guideline-based mild interactions (eg, cyclophosphamide-doxorubicin combinations identified via Lexicomp) may have slightly overestimated DRP prevalence, despite expert validation. Nevertheless, this study offers important insights into pharmacotherapy practices and DRPs in NHL management. It is the first of its kind in Yemen and was conducted at the country's largest oncology center, enhancing the contextual relevance and potential impact of the findings on local clinical practice.

Recommendations

This study underscores the need for a nationwide, structured approach to identify and manage DRPs among NHL patients receiving chemotherapy. Longitudinal and multicenter studies are essential to explore the cumulative effects of DRPs and chemotherapy across multiple treatment cycles. Key recommendations include targeted interventions to optimize NHL pharmacotherapy, such as routine training programs for healthcare professionals on up-to-date clinical guidelines, and the adoption of standardized treatment protocols and electronic decision support systems across healthcare settings in Yemen. NHL Subtypes and treatment intensity-specific analyses remain important for future research.

Conclusion

In conclusion, this study, conducted at the NOC in Yemen, identified a high prevalence of DRPs among patients with NHL, particularly among those receiving CHOP or R-CHOP regimens, with R-CHOP being the predominant protocol. Dosing problems, particularly underdosing, emerged as a major contributor to DRPs, highlighting the need for improved dose optimization practices. Additional factors significantly associated with DRPs included polypharmacy, DDIs, comorbidities, and the number of treatment cycles. These findings emphasize the need for tailored medication management strategies and underscore the importance of adhering to antiemetic and supportive care guidelines. They also reinforce the critical role of clinical pharmacists in reducing DRPs and improving patient outcomes. Interventions such as enhancing patient education and addressing low health literacy are essential to improving treatment adherence and reducing DRPs. Future efforts should prioritize optimizing dosing strategies and integrating multidisciplinary approaches into the management of NHL.

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