RESEARCH ARTICLE

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Metformin in Combination with Standard Therapy in Patients with Diffuse Large B-Cell Lymphoma: A Randomized Phase II Clinical Trial

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Abstract

Background: Metformin has been shown to have antitumor activity in different tumor types. In DLBCL (Diffuse large B cell lymphoma), using metformin with front-line chemotherapy & immunotherapy resulted in improved clinical outcomes. **Objectives:** To assess the effectiveness of incorporating metformin into the standard initial treatment regimen of R-CHOP for patients with DLBCL. The evaluation metrics included response rate, toxicity, progression-free survival (PFS), and overall survival (OS). **Patients and Methods:** This prospective phase 2 trial included 100 adult patients with histopathological evidence of DLBCL, eligible for first-line treatment with R-CHOP, life expectancy of at least 6 months, and performance status (PS) ≤ 2. Patients were randomized to receive either metformin plus R-CHOP or R-CHOP alone. **Results:** Each group included 50 patients. The metformin arm had more females than the standard arm (p=0.016). Nausea was significantly higher in the test arm than the standard arm (p=0.008). Metformin group had higher rates of complete remission (CR) at the end of treatment (92% vs 74%; p=0.017), lower rates of relapse/progression (10% vs 36%; p=0.002), and lower rates of overall mortality (4% vs 20%; p=0.014). The mean disease-free survival (DFS) was 24.5 months in the metformin group versus 20.2 months in the control arm (p=0.023). Likewise, the mean progression-free survival (PFS) was 25.91 versus 19.81 months and the mean overall survival (OS) was 27.39 versus 23.8 months (p-values= 0.002, and 0.013 respectively). By multivariate analysis of response and relapse, the use of metformin was an independent prognostic factor of CR and relapse. **Conclusions:** The addition of metformin to standard R-CHOP could improve clinical outcomes in patients with DLBCL with a tolerable safety profile.

Keywords: DLBCL- Metformin- R-CHOP

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Introduction

Non-Hodgkin lymphoma (NHL) is responsible for a significant percentage of new cancer diagnoses and related fatalities [1]. Non-Hodgkin lymphoma (NHL) ranks as the seventh most common type of cancer. It is responsible for 4-5% of newly diagnosed cancer cases and contributes to 3-4% of cancer-related fatalities [2]. Diffuse large B-cell lymphoma (DLBCL) is the most common adult NHL, accounting for 30–40% of cases. This is a heterogeneous disease that can molecularly be classified into germinal center B-cell–like (GCB) and non-GCB DLBCL [3]. A significant proportion of patients experience disease recurrence or refractory disease, necessitating a more targeted and personalized approach [4].

Treatment of DLBCL has improved markedly in the last decades after the addition of the monoclonal antibody rituximab to chemotherapy. DLBCL has a 5-year disease-free survival of 66% and overall survival of 58% [4]. Numerous research efforts have focused on enhancing the survival rates in difficult cases through the identification and testing of novel therapeutic targets. A phase I trial has evaluated the efficacy of Ibrutinib and Bendamustine in patients with relapsed non-GCB DLBC lymphoma [5]. Additionally, other agents such as Carfilzomib, Bortezomib, and Lenalidomide have been tested and shown promising results [6].

Metformin, a well-established treatment for diabetes mellitus, has shown promise in improving survival outcomes when added to chemotherapy in multiple tumor types. It has been proven to decrease the risk of pancreatic cancer in diabetic patients [7]. The underlying inhibition of mitochondrial complex 1 leads to a series of biochemical reactions that ultimately result in the suppression of cell proliferation [8]. Metformin also reduces circulating insulin concentrations and insulin-like growth factor 1 (IGF-1), preventing the activation of growth-promoting and mutagenic signaling pathways [8]. It is also known to

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inhibit glycolysis, the process by which cancer cells obtain energy. However, a few studies suggest a connection between glycolysis and the anti-apoptotic gene MCL1, whereby glycolysis inhibition blocks its translation [9]. Furthermore, studies have shown that glycolysis inhibition, in combination with other pro-apoptotic compounds, such as ABT-737, can increase the sensitivity of lymphoma cells to chemotherapeutics [10]. Metformin has also been shown to disrupt the communication between oxidative and glycolytic cancer cells, inhibiting tumor growth and promoting cell death in various cancer types [11].

In addition, there has been substantial evidence in favor of using metformin as an adjunct therapy in multiple tumor types including prostate, ovarian, endometrial, pancreas, and colorectal cancers [12]. In DLBCL, the use of metformin with front-line chemo-immunotherapy was shown to result in improved clinical outcomes, where patients on metformin had higher rates of response and longer progression-free survival (PFS) and/or overall survival (OS) [13,14]. The aim of this study was to evaluate the clinical benefit of adding metformin to standard therapy in the first-line treatment of DLBCL.

Materials and Methods

Patients

This Phase 2 clinical trial, which was prospective and randomized, encompassed patients diagnosed with DLBCL. These patients were eligible for initial treatment with R-CHOP. The study was conducted over a two-year period, from January 2021 to January 2023.

Inclusion criteria

Histopathological evidence of DLBCL, age ≥ 18 years, eligible for first-line treatment with R-CHOP, life expectancy of at least 6 months, and ECOG performance status (PS) ≤ 2.

Exclusion criteria

Richter transformation, evidence of active systemic bacterial, fungal, or viral infection upon recruitment, diabetes mellitus, and advanced comorbid conditions such as renal, hepatic, or cardiac impairment.

Patients were randomized into two groups

A metformin group that received metformin 1000 mg twice daily in addition to R-CHOP every 21 days, and a control group that received R-CHOP only. Randomization was performed by assigning random numbers to each patient using computer software. The data of each recruited patient were supplied to a specially designed simple software. The software assigned random numbers to the national ID number of each patient. Odd numbers were selected as the R-CHOP group and even as the metformin plus R-CHOP group.

Methods

All patients underwent thorough history (age, gender, smoking, comorbidities, PS, and B symptoms which include fever >38 ℃, drenching night sweat, unexplained fever, and unintentional weight loss of >10% during the last 6 months), complete physical examination, assessment of body weight, height, body surface area (BSA) and body mass index (BMI)

The patients also underwent laboratory investigations

Complete blood count (CBC), Kidney and liver function tests, Glycosylated hemoglobin (HbA1C), Lactate dehydrogenase (LDH), β2 microglobulin (B2M), Bone marrow aspirates (BMA) or biopsy if indicated, and radiological imaging: CT neck, chest, abdomen, and pelvis with contrast, or PET/CT, and Echocardiography.

In the context of disease characteristics, the following data were meticulously documented: the date of diagnosis, the histopathological diagnosis, the specific type of molecular pathology, and the clinical stage as per the Ann Arbor staging system [15]. Additionally, the presence of extra-nodal involvement and bulky disease (characterized by lymph nodes of diameter greater than or equal to 10 cm or thoracic lymph nodes exceeding one-third of the thoracic diameter) were also recorded. Both the International Prognostic Index (IPI) and the age-adjusted International Prognostic Index (aaIPI) were noted [16].

Group 1 received R-CHOP [rituximab 375 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 750 mg/m2, vincristine 2 mg, and prednisolone 100 mg for 5 days) + metformin at a dose of 1000 mg twice daily in uninterrupted 3-week cycles. Metformin was initiated at a dose of 500 mg twice daily and increased every week by 500 mg till a maximum dose of 1000 mg twice daily is reached. Patients received metformin continuously until disease progression, unacceptable drug toxicity, or patient withdrawal. Metformin was held 48 hours before performing PET-CT scan as it may result in false negative test if not stopped [17,18]. Group II (Control arm) received R-CHOP with the standard doses without using metformin.

In terms of toxicity reporting, the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 was adopted [19]. The study focused on hematological, cardiac, GIT, and neurological toxicities. Additionally, side effects of metformin were recorded if occurred.

The assessment was performed clinically at the start of each treatment cycle. Prior to each cycle, evaluations of hematological parameters, as well as kidney and liver function, were conducted as part of the laboratory assessment. Additionally, consistent monitoring of blood glucose levels was required for the duration of the treatment regimen. Radiological imaging was performed every 3 cycles with whole-body CT scans or PET/CT scans, whichever was feasible. End of treatment PET/CT was mandatory. The response was assessed according to the Deauville 5-point scale, which is based on the visual assessment of fluorodeoxyglucose (FDG) uptake in the involved sites relative to that of the mediastinum and the liver. We used a score of 1 to 3 to designate PET negative results. Scores of 4 to 5 were considered PET-positive. A score of 4 on an interim or end-of-treatment restaging scan was considered a PR, if the FDG avidity had declined from initial staging, while a score of 5 was considered PD [20].

Disease-free survival (DFS) was calculated from the date of complete remission to the date of relapse. PFS was calculated from the date of diagnosis to the date

of progression or the date of last follow-up. OS was calculated from the date of diagnosis to the date of death or the date of last follow-up.

Ethical Approval

All patients signed a written informed consent. Ethical approval from the Ethical Committee of the Faculty of Medicine Menoufia University was obtained prior to starting study procedures (IRB number 5/2021ONCO22). The Helsinki Declaration was followed throughout the study's conduct.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, N.Y., USA). Descriptive data included frequencies and percentages for categorical variables. While mean, standard deviation, median, and range were used to describe continuous variables. Associations between categorical variables were analyzed using the Chi-square test. Fisher exact test or Monte Carlo correlation was used when more than 20% of the cells had an expected count of less than 5. Survival was analyzed using Kaplan-Meier analysis. Univariate and multivariate analyses for PFS and OS were performed using the Cox proportional hazard regression model. Only significant statistical variables in univariate analysis were included in the multivariate Cox regression model.

Results

This study included 100 patients with DLBCL who were eligible for first-line treatment with R-CHOP (Each arm included 50 patients). The median follow-up duration was 15.9 months.

The characteristics of the patients were homogeneous across both groups, except for the Metformin group, which had a higher proportion of female participants (p=0.016). The mean age in the metformin group was 51.18±SD, while in R-CHOP group was 51.59±SD (Figure 1,2,3, Table 1).

No significant differences regarding disease characteristics were observed (Table 2). B symptoms were present in most patients in both groups (72.0% in the Metformin group, 78.0% in R-CHOP group). In both groups, most patients did not present with extra-nodal disease, bulky disease, or bone marrow (BM) infiltration. Specifically, the absence of extranodal disease was observed in 70.0% of the Metformin group and 52.0% of the R-CHOP group. Bulky disease was not present in 78.0% of the Metformin group and 66.0% of the R-CHOP group. Furthermore, 92.0% of the Metformin group and 96.0% of the R-CHOP group did not exhibit BM infiltration. In terms of the International Prognostic Index (IPI), 46.0% of the Metformin group was categorized as low risk, while 40.0% of the R-CHOP group fell into the low intermediate risk category.

Elevated levels of Lactate Dehydrogenase (LDH) were observed in a significant proportion of patients in both groups, specifically 66.0% of the Metformin group

Table 1. Patients Characteristics among the Studied Groups

		Metformin group (N= 50)		Control group (N = 50)		P-value
		N	%	N	%	
Gender	Male	18	36.00	30	60.00	0.016*
	Female	32	64.00	20	40.00	
Age (years)	Mean± SD	51.18± 12.64		51.59± 15.45		0.629
BSA	Mean± SD	1.78± 0.17		1.76± 0.15		0.505
BMI	Normal	13	26.00	19	38.00	0.483
	Obese	15	30.00	10	20.00	
	Over weight	20	40.00	20	40.00	
	Under weight	2	4.00	1	2.00	
Special habits	No	41	82.00	35	70.00	0.16
	Smoking	9	18.00	15	30.00	
Comorbidities	No	35	70.00	37	74.00	0.399
	Hypertension	12	24.00	12	24.00	
	Hypertension+ IHD	2	4.00	0	0.00	
	IHD	0	0.00	1	2.00	
	Rheumatoid arthritis	1	2.00	0	0.00	
HCV Status	Negative	29	58.00	30	60.00	0.839
	Positive	21	42.00	20	40.00	
HBV Status	Negative	50	100.00	50	100.00	
	Positive	0	0.00	0	0.00	
PS	≤1	46	92.00	43	86.00	0.337
	>1	4	8.00	7	14.00	

Table 2. Disease Characteristics among the Studied Groups.

		Metformin group (N = 50)		Control group (N = 50)		
		N	%	N	%	P-value
B Symptoms	No	14	28.00	11	22.00	0.488
	Yes	36	72.00	39	78.00	
Stage	I	4	8.00	4	8.00	0.0504
	II	16	32.00	5	10.00	
	III	16	32.00	19	38.00	
	IV	14	28.00	22	44.00	
Extranodal disease	None	35	70.00	26	52.00	0.15
	One site	12	24.00	17	34.00	
	> one site	3	6.00	7	14.00	
BM infiltration	No	46	92.00	48	96.00	0.691[FET]
	Yes	4	8.00	2	4.00	
Bulky disease	No	39	78.00	33	66.00	0.181
	Yes	11	22.00	17	34.00	
IPI risk group	low risk	23	46.00	15	30.00	0.19
	low intermediate risk	20	40.00	20	40.00	
	high intermediate risk	5	10.00	12	24.00	
	high risk	2	4.00	3	6.00	
LDH	High	33	66.00	41	82.00	0.068
	Normal	17	34.00	9	18.00	
B2 Microglobulin	High	11	22.00	7	14.00	0.298
	Normal	39	78.00	43	86.00	
Type of molecular pathology cells	Activated b cell	8	16.00	13	26.00	0.22
	Germinal center b cell	42	84.00	37	74.00	

and 82.0% of the R-CHOP group. Conversely, Beta-2 Microglobulin (B2M) levels were within the normal range for most patients in both groups, with 78.0% in the Metformin group and 86.0% in the R-CHOP group. All cases in both groups had normal glycosylated hemoglobin (HbA1c). Germinal center B cell was the most frequent molecular pathological subtype in both groups (84.0% of the metformin group, and 74.0% of R-CHOP group). In terms of toxicity, both groups exhibited similar side effect profiles. However, a notable exception was the incidence of nausea, which was significantly higher in the Metformin group (p-value=0.008) (Table 3).

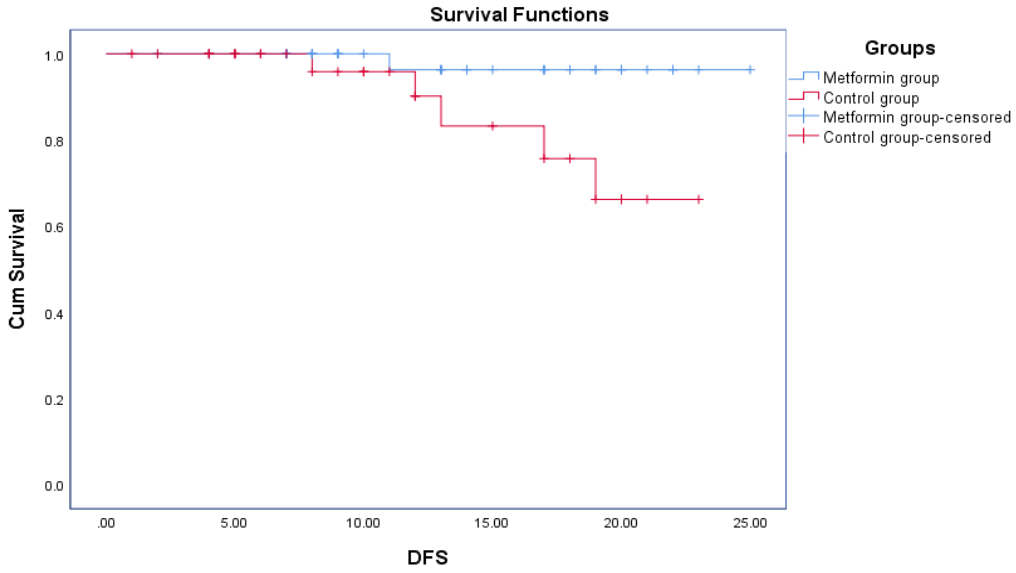

Figure 1. Kaplan-Meier Survival Curves for Disease Free Survival

Table 3. Comparison between the Two Groups Regarding Toxicities

		Metformin group (N = 50)		Control group (N = 50)		Chi- Square test
		N	%	N	%	P-value
Neutropenia	No toxicity	9	18.00	3	6.00	0.064
	Grade 1	12	24.00	7	14.00	
	Grade 2	15	30.00	28	56.00	
	Grade 3	12	24.00	9	18.00	
	Grade 4	2	4.00	3	6.00	
Anemia	No toxicity	23	46.00	18	36.00	0.24
	Grade 1	13	26.00	21	42.00	
	Grade 2	14	28.00	11	22.00	
	Grade 3	0	0.00	0	0.00	
	Grade 4	0	0.00	0	0.00	
Thrombocytopenia	No toxicity	37	74.00	41	82.00	0.201
	Grade 1	12	24.00	6	12.00	
	Grade 2	1	2.00	3	6.00	
	Grade 3	0	0.00	0	0.00	
	Grade 4	0	0.00	0	0.00	
Hypoglycemia	No	46	92.00	50	100	0.339[FET]
	Yes	4	8.00	0	0	
Nausea	No	32	65.30	44	88.00	0.008*
	Yes	17	34.70	6	12.00	
Diarrhea	No toxicity	21	42.00	18	36.00	0.704
	Grade 1	22	44.00	24	48.00	
	Grade 2	6	12.00	5	10.00	
	Grade 3	1	2.00	3	6.00	
	Grade 4	0	0.00	0	0.00	
Mucositis	No toxcisty	23	46.00	27	54.00	0.148
	Grade 1	15	30.00	14	28.00	
	Grade 2	12	24.00	6	12.00	
	Grade 3	0	0.00	3	6.00	
	Grade 4	0	0.00	0	0.00	
Vomiting	No toxicity	25	50.00	25	50.00	0.895
	Grade 1	22	44.00	23	46.00	
	Grade 2	3	6.00	2	4.00	
	Grade 3	0	0.00	0	0.00	
	Grade 4	0	0.00	0	0.00	
Neuropathy	No toxicity	34	68.00	29	58.00	0.353
	Grade 1	12	24.00	18	36.00	
	Grade 2	4	8.00	2	4.00	
	Grade 3	0	0.00	1	2.00	
	Grade 4	0	0.00	0	0.00	
Metallic Taste	No	37	74.00	43	86.00	0.134
	Yes	13	26.00	7	14.00	
Other side effect	liver cell failure	0	0.00	1	2.00	0.500[FET]

The complete response rate (CR) at end of the treatment assessment was higher in the metformin group (92% versus 74%) with a significant difference (p-value=0.017). Through univariate analysis, a significant correlation was observed between the achievement of Complete Remission (CR) and treatment with Metformin. Furthermore, multivariate analysis identified Metformin treatment as an independent prognostic factor for the attainment of CR (Table 4). Highlighting this finding, the rate of disease progression or relapse was notably higher in the R-CHOP group compared to the Metformin group (36% versus 10%, respectively, with a p-value of 0.002),

Table 4. Metformin Effect on Complete Remission, Relapse and Survival by Univariate Analysis

	Control arm	Test arm	Odds ratio (OR) and confidence interval (CI)	P-value
Complete remission	37	46	OR=4.041, 95% CI [1.21, 13.43]	0.023
Relapse	18	5	OR=0.198, 95% CI [0.07, 0.59]	0.004
Survival	40	48	OR=6.0, 95% CI [1.24, 28.99]	0.026

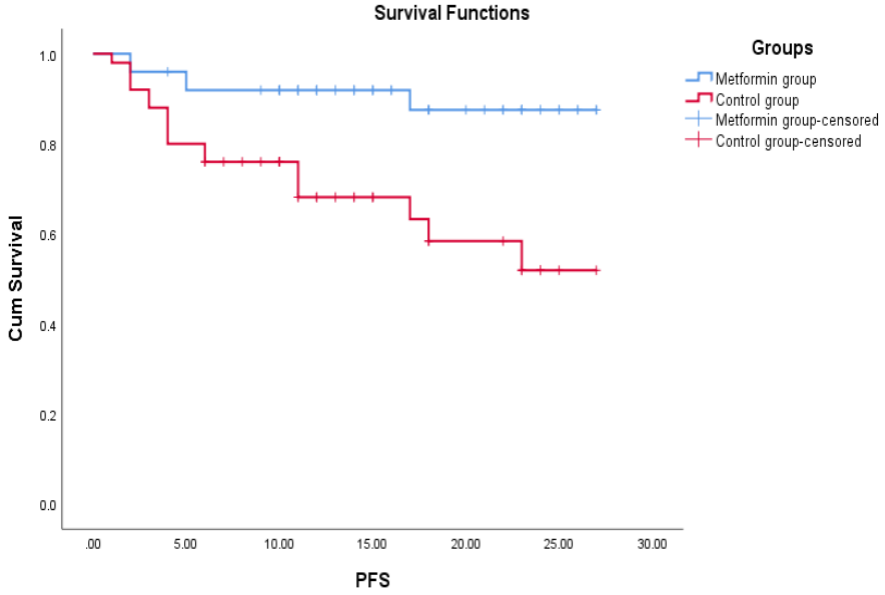

Figure 2. Kaplan-Meier Survival Curves for Progression Free Survival.

indicating a significant difference in treatment outcomes. In addition, the mortality rate was significantly higher in R-CHOP group (20% versus 4%, P=0.014).

The integration of Metformin into the R-CHOP regimen demonstrated a positive impact on survival outcomes (p-value =0.026). Specifically, the Metformin group exhibited a longer mean Disease-Free Survival (DFS) of 24.5 months, compared to 20.2 months in the R-CHOP group, a difference that was statistically significant (p-value=0.023).

Moreover, the mean Progression-Free Survival (PFS) was also significantly extended in the Metformin group, with a mean value of 25.91 months, as compared to 19.81 months in the R-CHOP group (p-value=0.002). In terms of overall survival, the Metformin group outperformed the R-CHOP group, with a mean duration of 25.6 months versus 23.8 months, respectively (p-value=0.013) (Figure 4).

Discussion

Drug repurposing is a way to discover new applications

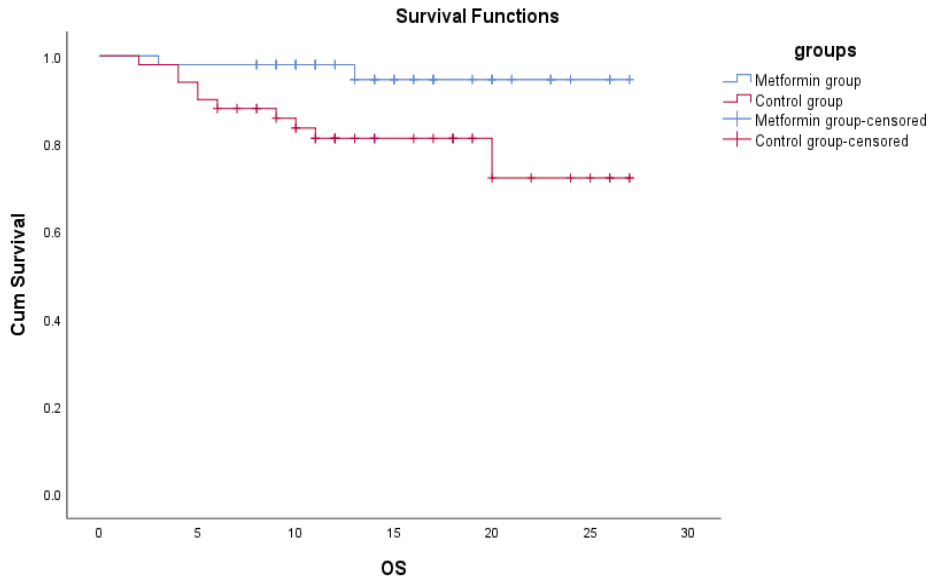

Figure 3. Kaplan-Meier Survival Curves for Overall Survival

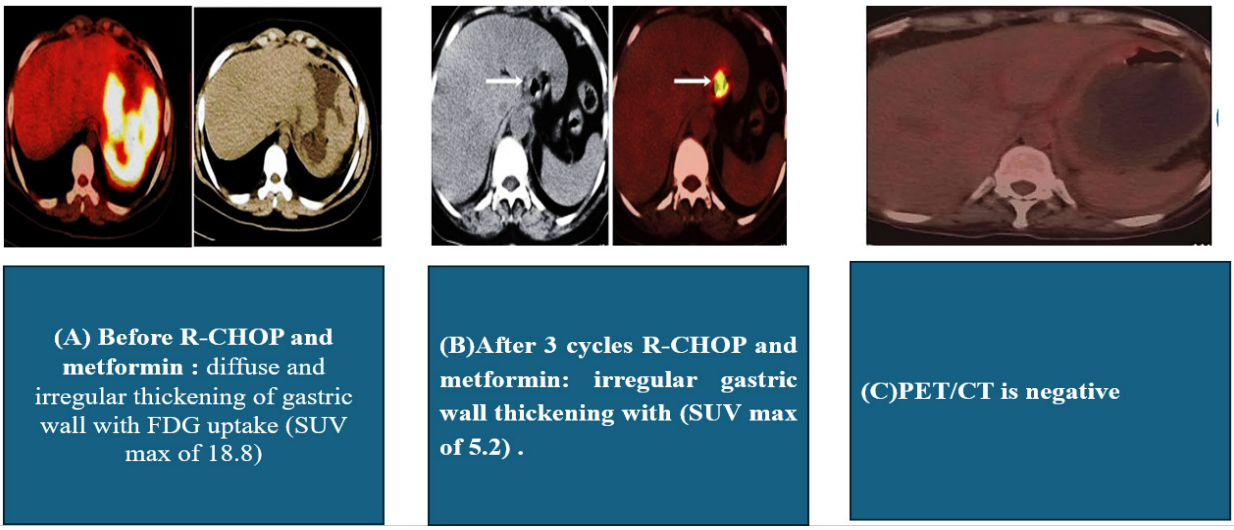

Figure 4. PET/CT Images of Gastric Lymphoma before, after 3 Cycles and 6 Cycles of R-CHOP

for approved drugs beyond their initial uses. This strategy has multiple benefits over developing new drugs, including enhanced efficacy, cost-effectiveness, and reduced risk of toxicity due to established safety profiles [21]. Metformin is a prime example of a drug that has garnered interest in the realm of drug repurposing. It has demonstrated anti-tumor properties [22]. Beyond its molecular mode of action, Metformin can ameliorate secondary hyperglycemia, which may arise due to steroid administration in lymphoma patients. Evidence suggests that the occurrence of such hyperglycemia is linked with a less favorable prognosis in DLBCL [23].

In this study, metformin led to higher rates of complete remission compared to standard therapy alone. Specifically, at the end of treatment, 46 patients in the metformin arm (92%) achieved a complete response compared to 37 patients in the control arm (74%). Our findings are consistent with findings from a previous study which included 48 diabetic patients (24 in the control arm and 24 in the metformin arm). In that study, it was noted that the use of metformin was linked to increased rates of complete remission, with a 92% rate observed in the metformin group as opposed to 54% in the control group [24]. In consistency with our data, Jiang et al., in 2021 conducted a study on patients with DLBCL to investigate the clinicopathological characteristics and treatment outcomes of diabetic patients receiving metformin. Investigators observed significantly higher response rates in the metformin group compared to the control group. Patients on metformin showed an 84% complete response rate compared to 48% of patients in the control group with a median follow-up duration of 35 months. [25]. Of note, both studies included diabetic patients, while our study included non-diabetic patients only.

The administration of Metformin was associated with enhanced Progression-Free Survival (PFS) and Overall Survival (OS), with the median not reached in both groups (p=0.002 for PFS, p=0.013 for OS). This finding aligns with the results from the study conducted by Alkhatib et al., which also reported improved PFS in the Metformin group relative to the control group. In their study, the median PFS was not reached in the Metformin group, while it was 47 months in the control group. However, this did not translate into a statistically significant improvement in OS (median not reached in the Metformin group and 100 months in the control group) [24]. In parallel to that, the research conducted by Jiang et al. demonstrated that, at a median follow-up duration of 33 months, the Metformin group exhibited superior Progression-Free Survival (PFS) relative to the control group ($P = 0.0298$). While the difference was not statistically significant, the investigators noted a tendency towards enhanced Overall Survival (OS) in the Metformin group, a trend that aligns with our observations. This further underscores the potential benefits of Metformin in the treatment of DLBCL [25]. These results were compatible with cumulative data from multiple retrospective studies with longer follow-up durations. For example, a retrospective study examined clinical outcomes among diabetic patients diagnosed with DLBCL. The study specifically investigated the impact of using metformin during front-line chemo-immunotherapy compared to other glucose-lowering agents. Researchers demonstrated that diabetic DLBCL patients who used metformin had significantly improved PFS (94 months vs. 55.4 months) and OS (100 months vs. 70.5 months) when compared to those using alternative glucose-lowering agents [26]. Another retrospective study conducted by Wynn et al., in 2019, found that the use of metformin was associated with significant improvement in long-term survival. In that study, patients who received metformin had a mean overall survival of 5.89 years, whereas those who did not receive metformin had a mean survival of 1.29 years ($P < 0.001$) [27]. In our study, the median duration of follow-up was 15 months. This relatively short timeframe limited our ability to estimate the median survival as a primary endpoint. In either the Metformin or control groups, the majority of patients were censored for survival events. It remains to be seen whether a longer follow-up period would reveal a differential survival similar to that reported by Wynn et al. Longer follow-up of our patients will demonstrate if this effect really exists.

These cumulative results suggest a potential correlation

between metformin use and improved treatment outcomes, particularly in terms of response rate, PFS, and OS, which should be explored in larger phase 3 trials. This benefit is likely due to the molecular mechanism of action of metformin and its effect on the PI3K pathway which is frequently altered in hematological malignancies [22]. Additional research indicates that secondary hyperglycemia, which can occur during cancer treatment due to steroid use, is associated with a less favorable prognosis in DLBCL. This condition can be mitigated by the administration of metformin. Interestingly, this secondary hyperglycemia has been found to exert a more substantial negative impact on prognosis compared to primary hyperglycemia, which is characterized by pre-existing diabetes [23].

On the contrary, a retrospective study conducted by Koo et al. [28] explored the potential clinical activity of metformin concomitant with rituximab in DLBCL. The results did not show any significant differences in treatment outcomes between metformin users and non-metformin users. There was no observed effect of metformin on the overall response rate (p=0.268), event-free survival (p=0.574), or overall survival (p=0.141) in that study [28]. In contrast to the aforementioned studies, research conducted by Wang et al. [29] yielded differing results. Their study, which investigated the use of Metformin in patients newly diagnosed with DLBCL or Follicular Lymphoma (FL), found no correlation between the use of Metformin and improved outcomes in terms of event-free survival, lymphoma-specific survival, or overall survival [29]. This observation could potentially be attributed to the inclusion of patients diagnosed with follicular lymphoma, who may inherently possess a more favorable lymphoma-specific prognosis, irrespective of Metformin administration. Furthermore, the study necessitated a concurrent diagnosis of diabetes mellitus, which could have influenced the outcomes due to the potential presence of additional comorbidities and the therapeutic effects of Metformin in diabetic patients. It's worth noting that the study conducted by Wang et al. [29] was observational in nature, contrasting with our study which employed a prospective experimental design. This difference in methodology is an important factor to consider when comparing the results and conclusions drawn from these studies.

A similar observation was noted in patients with prostate cancer and rectal cancer who received radiotherapy. They showed similar benefits from metformin in a metanalysis by Coyle, [30]. An additional meta-analysis has indicated that Metformin usage significantly enhances Overall Survival (OS), Cancer-Specific Survival, and Recurrence-Free Survival in patients with Prostate Cancer. Specifically, the Hazard Ratios (HR) were 0.72 (95% Confidence Interval (CI): 0.59-0.88, P=0.001) for OS, 0.78 (95% CI: 0.64-0.94, P=0.009) for Cancer-Specific Survival, and 0.60 (95% CI: 0.42-0.87, P=0.006) for Recurrence-Free Survival, respectively, when compared to treatment without Metformin. However, Metformin usage did not significantly decrease the incidence of Prostate Cancer (HR=0.86, 95% CI: 0.55-1.34, P=0.51) [31].

Research conducted by Seliger et al. revealed that metformin intake was associated with improved survival rates in patients with high-grade glioma [32]. Additionally, another study demonstrated metformin's impact on enhancing the response to tyrosine kinase inhibitors in the management of chronic myeloid leukemia [33]. Collectively, these studies prove the benefit of using metformin in improving clinical outcomes in different malignancies not just in lymphoma.

In conclusion, this study suggests that adding metformin to standard treatment for DLBCL patients could improve clinical outcomes in terms of response rate, PFS, and potentially overall survival (OS), with a tolerable safety profile.

Author Contribution Statement

All authors contributed equally in this study.

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