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Correlation of hypovitaminosis D with lymphoma and the value of vitamin D replacement in response to chemotherapy

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Abstract

Background: Vitamin D is a steroid that has long been implicated in calcium homeostasis and bone mineralization.Aside from its classical roles in healthy individuals, Vitamin D has been shown to exhibit numerous anticancer and immunemodulating properties. In multiple cancers and autoimmune diseases, calcitriol inhibits proliferation, induces apoptosis, decreases angiogenesis, and sensitizes cells to chemotherapy. The aim of this study is to evaluate the level of vitamin D in Egyptian lymphoma patients , as well as to evaluate the value of vitamin D replacement in vitamin D-insufficient lymphoma patients regarding response to chemotherapy.. **Patients and methods:**The study was conducted on 100 patients with Diffuse large B cell lymphoma (DLBCL) collected from Internal Medicine Department, Oncology and Hematology Unit at Benha University Hospital during period from February 2020 to May 2022, ptients with established diffuse large B cell lymphoma diagnosed according to WHO guidelines of the 2016 by exicisional or core tissue biopsy. **Results**: There was Significant relation between the studied groups and disease stage (P = 0.018), KI-67 (P = 0.031), and IPI score (P < 0.001). After treatment, vitamin D revealed an overall significant difference between groups. LDH showed an overall significant difference between the studied groups (P = 0.003). A significant association was reported between the studied groups and complete response (P = 0.03. Those with non responsive disease revealed significantly higher age (52 ±6 years vs. 44 ±11 years, P = 0.047) and male predominance (100% vs 60.2%, P = 0.044). Those with non responsive disease demonstrated significantly higher percentage of high Ki-67 (100% vs. 25.8%, P < 0.001). In addition, a significant association was reported between non responsive and IPI score (P = 0.002. Those with non responsive disease revealed significantly higher LDH (916 ±127 mg/dl vs. 714 ±144 mg/dl, P < 0.001) but significantly lower vitamin D (median = 9 vs. 14, P = 0.007). ROC analysis was done for vitamin D to distinguish those with non responsive disease. It revealed a significant AUC of 0.804 with a 95% confidence interval ranging from 0.656-0.953 (P = 0.007). **Conclusion:** vitamin D may have a prognostic index & showed asssosiation between it,s deiciency & lymphoma agressivenes also vitamin D replacement might have a role to iprove outcome of treatment.

Key words: Vitamin D, Non hodgkinlymphoma, cancer.

1. Introduction

Vitamin D is a steroid that has long been implicated in calcium homeostasis and bone mineralization. Vitamin D can be obtained through supplements, dietary intake, and ultraviolet radiation (UVR) exposure [1].

Aside from its classical roles in healthy individuals, Vitamin D has been shown to exhibit numerous anticancer and immunemodulating properties. In multiple cancers and autoimmune diseases, calcitriol inhibits proliferation, induces apoptosis, decreases angiogenesis, and sensitizes cells to chemotherapy. Thus, considerable efforts have been dedicated to understanding the mechanism of vitamin D action and its full range of effects on tumor cells [2].

Vitamin D has been observed to have antineoplastic properties in vitro studies of lymphoma and other cancers, and epidemiologic studies of NHL also indirectly support a protective effect of vitamin D. Low serum 25(OH)D is considered to be the best indicator of vitamin D status; it represents an integrative measure of both dietary and cutaneous sources of vitamin D. It is hypothesized that individuals with low levels of 25(OH) vitamin D are at increased risk of NHL [3].

An association between levels of vitamin D and lymphoma mortality has been reported for patients with DLBCL. Data from the German RICOVER-60 study actually indicated that vitamin D deficiency is a negative prognostic factor for elderly patients with DLBCL, treated with rituximab-containing chemotherapy (R-CHOP) [4].

2. Patients and Methods

A comparative cross sectional study was conducted on 100 patients with Diffuse large B cell lymphoma (DLBCL) collected from Internal Medicine Department, Oncology and Hematology Unit at Benha University Hospital during period from February 2020 to May 2022. The patients were selected from patients who were followed up at Oncology Outpatient Clinic at benha University Hospital.

Diffuse large B cell lymphoma was diagnosed according to WHO guidelines of the 2016 by exicisional or core tissue biopsy with histological and immunophenotyping proved DLBCL that is histologically characterized by diffuse proliferation of large neoplastic B lymphoid cells with a nuclear size equal to or exceeding normal histiocyte nuclei [8]. With Immunophenotypic diagnostic criteria that is CD19, 20, 5, 79, 10 and bcl 6 positive and negative CD23, BCL2 and cyclin D1 [5].

An informed consent was taken from all studied participants after ensuring the data confidentiality. The study was approved by the Institutional Ethics Committee of the Faculty of Medicine, Benha University.

2.1. Inclusion criteria

Age from 20 to 60 years, Both male and female. With biopsy proven diffuse large B cell lymphoma stage

II , III , IV. Patients with nodal & extra nodal involvement and Patients who didn't receive previous lymphoma related treatment

2.2. Exclusion criteria

Patients with other neoplastic disorders, Patients with stage I diffuse large B cell lymphoma as those patients need another treatment regimen and may need radiotherapy, Patients with organ failure (heart, liver, kidney or respiratory).

Patients who already begin treatment regimen.

2.3. Methods

For each patient detailed history was obtained including age , sex , occupation, special habits; also history included an evaluation of nature, duration, and time course of symptoms; assosiated B symptoms, fever, drenching sweats, anorexia, wight loss, swelling at anatomical site of lymph node, pain or swelling at left hypochondrium, pruritis, dyspnea, pallor, past history of neoplastic disorders or family history of similar conditions.

Physical examination stressed on pallor, jaundice, cachexia, lymph node enlargement, hepatomegaly, splenomegaly and performance state.

The Performance Status Scale is one such measurement. It describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability. For each patient imaging was done in the form of CT neck, chest, abdomen and pelvis with contrast at diagnosis for staging and repeated after 6 cycles of chemotherapy for assesment of patient response to treatment.

Assessment of International prognostic index (IPI) was done for each ptient before starting treatment which include :

Age ≥60 years. Advanced stage (III or IV). Extranodal involvement of >1 site. Performance status ≥2. Serum lactate dehydrogenase level raised (above normal).

Patients was categorized according to IPI score into:

- 0–1: Low risk
- 2: Low intermediate risk
- 3: High intermediate risk
- 4 or 5: High risk.

Laboratory invistigations were done including CBC, ESR, LDH, Liver & kidney function tests.

Serum vitamin D level was measured by ELISA technique with expected value :

- Deficient : less than 20 ng/ ml
- Insufficient : 20 – 29 ng/ ml
- Sufficient : 30-100 ng/ ml
- Potential toxicity : above 100 ng/ ml

Vitamin D was measured for all patients before treatment .

According to vitamin D level (cut off 30 ng/ ml), the patients will be devided into three groups:

Group 1 (no =40) with hypovitaminosis D : these patients will be treated by 50 000 IU of vitamin D once weekly for 12 weeks beside chemotherapy regimen (Holick et al., 2011).

Group 2 (no =40) with hypovitaminosis D : these patients will be treated by chemotherapy regimen only.

Group 3 (no =20) with normal vitamin D will be treated by chemotherapy regimen only.

Serum vitamin D level will be reassesed after 12 week of vitamin D replacement in group 1.

After 6 cycles of chemotherapy evaluation by imaging was done for all patients to asses the response of patients to chemotherapy and to vitamin D replacement.

2.4Ethical clearance:

An informed consent was obtained from all subjects after taking approval of Institutional Review Board, Faculty of Medicine, Banha University. The work had been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

2.5Statistical Analysis:

Data management and statistical analysis were done using SPSS version 28 (IBM, Armonk, New York, United States). Quantitative data were assessed for normality using the Shapiro-Wilk test and direct data visualization methods. According to normality, quantitative data were summarized as means and standard deviations or medians and ranges. Categorical data were summarized as numbers and percentages. Quantitative data were compared between the studied groups using one-way ANOVA. Post hoc analysis was done in case of significant overall effect, and all post hoc analyses were adjusted for multiple comparisons. Categorical data were compared between the studied groups using the Chi-square test. Comparisons between those with and without progressive disease were done using independent t-test or Mann-Whitney U test for normally and non-normally distributed quantitative data, respectively, while categorical data were compared using Chi-square or Fisher's exact test. ROC analysis was done for vitamin D to distinguish those with progressive disease. Area Under Curve (AUC) with 95% confidence interval, best cutoff point, and diagnostic indices were calculated. All statistical tests were two-sided. P values less than 0.05 were considered significant.

3.**Results**

Table (1) Demographic characteristics of the studied groups.

		Group I (n = 40)	Group II (n = 40)	Group III (n = 20)	P-value
Age (years)		45 ±10	44 ±11	43 ±11	0.674
	Males	26 (65.0)	25 (62.5)	12 (60)	0.928
Gender	Females	14 (35.0)	15 (37.5)	8 (40)	

Data were presented as mean ±SD or number (percentage)

Comparison between studied groups stage, KI & IPI score

There was Significant relation between the studied groups and disease stage (P = 0.018), KI-67 (P = 0.031), and IPI score (P < 0.001). Stage IV was lower in group III (25%) than in groups I and II (55% and 60, respectively). In addition, High KI-67 was lower in group III (5%) than in groups I (45%) and II (30%). The high-intermediate IPI score was lower in group III (5%) than in groups I and II (40% and 17.5%, respectively) **.**

Table (2) comparison between studied groups stage, KI & IPI score.

	Group I (n = 40)	Group II (n = 40)	Group III (n = 20)	P-value
Stage				
II	6 (15.0)	3 (7.5)	8 (40)	0.018*
III	12 (30.0)	13 (32.5)	7 (35)	
IV	22 (55.0)	24 (60)	5 (25)	
KI-67				
Low	7 (17.5)	7 (17.5)	4 (20)	0.031*
Moderate	15 (37.5)	21 (52.5)	15 (75)	
High	18 (45.0)	12 (30)	1 (5)	
IPI score				
Low	7 (17.5)	2 (5)	9 (45)	<0.001*
Low-intermediate	17 (42.5)	31 (77.5)	10 (50)	
High-intermediate	16 (40.0)	7 (17.5)	1 (5)	

Data were presented as number (percentage); * Significant

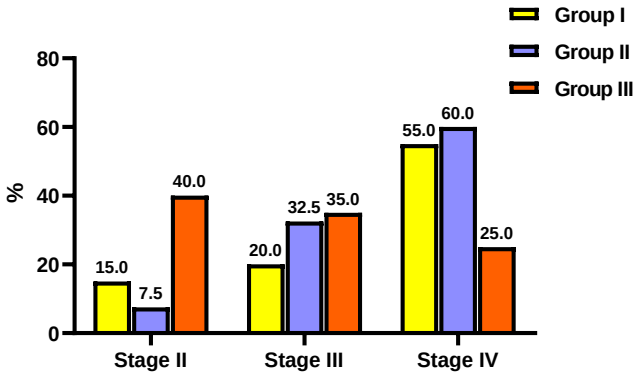

Fig. (1) Disease staging in the studied groups

❖ **Comparison between studied groups vitamin D & LDH level**

Before treatment, vitamin D showed an overall significant difference between the studied groups (P < 0.001). Post-hoc analysis revealed significantly higher vitamin D in group III (46 ±6) than in groups I and II (12 ±3 for each) **.**

After treatment, vitamin D revealed an overall significant difference between groups. Post hoc analysis revealed significantly higher vitamin D in group I (61 ±8) than in groups II (11 ±3) and III (44 ±5). In addition, it was significantly higher in group III than in group II **.**

LDH showed an overall significant difference between the studied groups (P = 0.003). Post-hoc analysis showed significantly lower LDH in group III (636±116 mg/dl) than in groups I (774 ±162 mg/dl) and II (728 ±138 mg/dl), with no significant differences between groups I and II .

Table (3) comparison between studied groups vitmin D & LDH level

	Group I (n = 40)	Group II (n = 40)	Group III (n = 20)	P-value
Vitamin D before treatment	12 ±3 [a]	12 ±3 [a]	46 ±6 [b]	<0.001*
Vitamin D after treatment	61 ±8 [a]	11 ±3 [b]	44 ±5 [c]	<0.001*
LDH (mg/dl)	774 ±162 [a]	728 ±138 [a]	636±116 [b]	0.003*

Data were presented as mean ±SD; * Significant; Different small letters between any two groups indicate significance

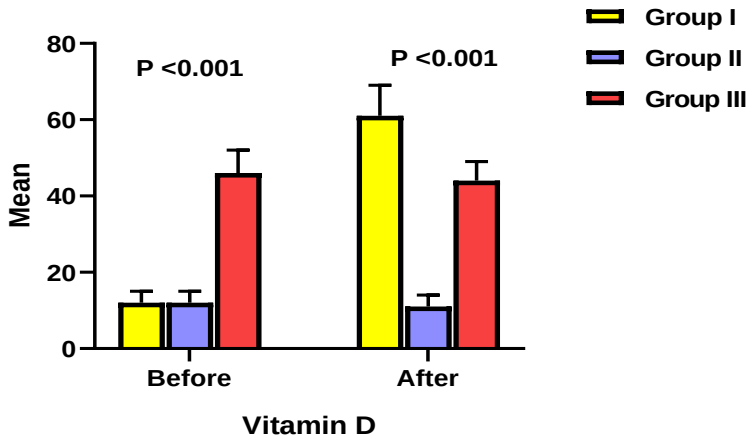

Fig. (2) Vitamin D level in the studied groups before and after treatment.

❖ **Comparison between studied groups response to chemotherapy (table 6)**

A significant association was reported between the studied groups and complete response (P = 0.03), with the complete response being lower in group II (30%) than in groups I (55%) and III (60%) .

Table (4) comparison between studied groups respose to chemotherapy

	Group I (n = 40)	Group II (n = 40)	Group III (n = 20)	P-value
Complete response	22 (55.0)	12 (30)	12 (60.0)	0.03*

Data were presented as number (percentage); * Significant

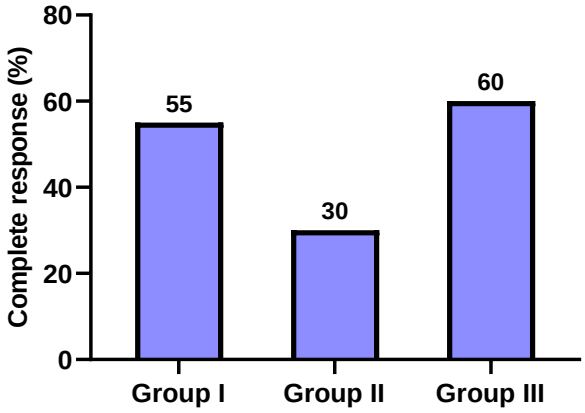

Fig (3) Complete response rate in the studied groups.

❖ **Correlation between non responsive patients and demographics**

The studied patients were classified according to non responsive disease status. Those with non responsive disease revealed significantly higher age (52 ±6 years vs. 44 ±11 years, P = 0.047) and male predominance (100% vs 60.2%, P = 0.044) .

Table (5) correlation between non responsive patients and demographics

		Non reponsive patients		
		Yes (n = 7)	No (n = 93)	P-value
Age (years)	Mean ±SD	52 ±6	44 ±11	0.047*
Gender	Males	7 (100)	56 (60.2)	0.044*
	Females	0 (0)	37 (39.8)	

Data were presented as mean ±SD or number (percentage); * Significant

❖ **correlation between non responsive patients clinical , laboratory & radiological findings**

Those with non responsive disease demonstrated significantly higher percentage of high Ki-67 (100% vs. 25.8%, P < 0.001). In addition, a significant association was reported between non responsive and IPI score (P = 0.002); those with non responsive disease revealed higher percentage of high-intermediate IPI score (85.7% vs. 19.4%), while low IPI score was higher in those with no progressive disease (19.4% vs. 0%). No significant difference was reported regarding stage (P = 0.214)

Table (6) correlation between non responsive patients clinical , laboratory & radiological finding.

		Non responsive patients		
		Yes (n = 7)	**No (n = 93)**	**P-value**
Stage	Stage II	0 (0)	17 (18.3)	0.214
	Stage III-IV	7 (100)	76 (81.7)	
High Ki-67		7 (100)	24 (25.8)	<0.001*
IPI score	Low	0 (0)	18 (19.4)	0.002*
	Low-intermediate	1 (14.3)	57 (61.3)	
	High-intermediate	6 (85.7)	18 (19.4)	

Data were presented as number (percentage); * Significant

❖ **correlation between non responsive patients and vitamin D level**

Those with non responsive disease revealed significantly higher LDH (916 ±127 mg/dl vs. 714 ±144 mg/dl, P < 0.001) but significantly lower vitamin D (median = 9 vs. 14, P = 0.007).

Table (7) correlation between non responsive patients and vitamin D level**.**

	Non responsive patients		
	Yes (n = 7)	**No (n = 93)**	**P-value**
LDH (mg/dl)	916 ±127	714 ±144	< 0.001*
Vitamin D	9 (6 - 15)	14 (8 - 60)	0.007*

Data were presented as mean ±SD or median (min-max); * Significant

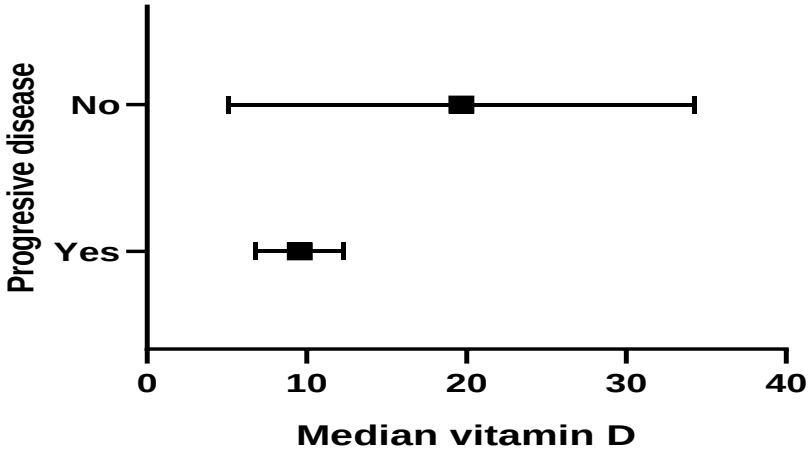

Fig. (4) Vitamin D level according to progressive disease status.

❖ **ROC analysis for vitamin D to distinguish progressive disease patients**

ROC analysis was done for vitamin D to distinguish those with non responsive disease. It revealed a significant AUC of 0.804 with a 95% confidence interval ranging from 0.656-0.953 (P = 0.007). The best cutoff point was ≤ 10, at which sensitivity and specificity were 85.7% and 69.9%, respectively .

Table (8) ROC analysis of vitamin D to distinguish non responsive disease patients

ROC characteristics	
AUC (95% CI)	0.804 (0.656 - 0.953)
Best cutoff	≤ 10
Sensitivity	85.7%
Specificity	69.9%
P-value	0.007*

AUC: Area under curve; 95% CI: 95% confidence interval: * Significant

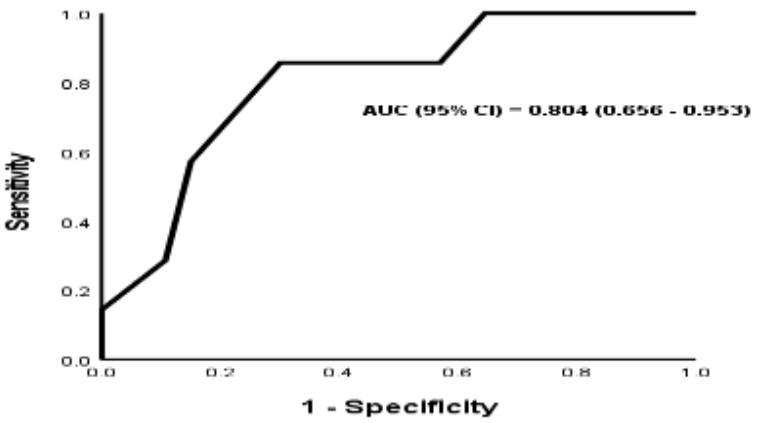

Fig. (5) ROC analysis of vitamin D to distinguish progressive disease patients.

4. Discussion

To Vitamin D is a steroid that has long been implicated in calcium homeostasis and bone mineralization. Vitamin D can be obtained through supplements, dietary intake, and ultraviolet radiation (UVR) exposure [1].

Aside from its classical roles in healthy individuals, Vitamin D has been shown to exhibit numerous anticancer and immunemodulating properties. In multiple cancers and autoimmune diseases, calcitriol inhibits proliferation, induces apoptosis, decreases angiogenesis, and sensitizes cells to chemotherapy. Thus, considerable efforts have been dedicated to understanding the mechanism of vitamin D action and its full range of effects on tumor cells [2].

Vitamin D has been observed to have antineoplastic properties in vitro studies of lymphoma and other cancers, and epidemiologic studies of NHL also indirectly support a protective effect of vitamin D. Low serum 25(OH)D is considered to be the best indicator of vitamin D status; it represents an integrative measure of both dietary and cutaneous sources of vitamin D. It is hypothesized that individuals with low levels of 25(OH) vitamin D are at increased risk of NHL [3].

An association between levels of vitamin D and lymphoma mortality has been reported for patients with DLBCL. Data from the German RICOVER-60 study actually indicated that vitamin D deficiency is a negative prognostic factor for elderly patients with DLBCL, treated with rituximab-containing chemotherapy (R-CHOP) [8].

In this comparitive cross sectional study of 100 patients with diagnosis of diffuse large B cell non hodgkin lymphoma were studied to asses the relation of hypovitaminosis D in those patients as well as studying the impact of Vitamin D replacement.

Relation between vitamin D & lymphoma was studied by comparing the presentation (clinical, stage, IPI score, KI index & treatment) between patients with hyopvitamnosis D & normal vitamin D patients.

There was no significant differences reported between the studied groups regarding age (P = 0.674) and gender (P = 0.928) matched for age & sex.

This result doesn,t agree with the latest GLOBOCAN data, in which an estimated 509,600 new cases of NHL were diagnosed globally in 2018, comprising 2.8% of worldwide cancer diagnoses. The global age standardized risk of NHL was 6.7 among men and 4.7 among women, translating to a 0.72% and 0.35% cumulative lifetime risk for men and women, respectively [9].

Pretreatment significant associations were reported between the studied groups and disease stage (P = 0.018), KI-67 (P = 0.031), and IPI score (P < 0.001). Stage IV was lower in group III (25%) than in groups I and II (55% and 60, respectively). In addition, High KI-67 was lower in group III (5%) than in groups I (45%) and II (30%). The high-intermediate IPI score was lower in group III (5%) than in groups I and II (40% and 17.5%, respectively) (Table 4, Figure 5).

So there may be significant relation between hypovitaninosis D and stage of presentation as high stage more founded in patients with hypovitaminosis D (group 1 & 2) & moderate to low stage were more founded in normal vitamin D patients (group3).

LDH also showed an overall significant difference between the studied groups (P = 0.003). Post-hoc analysis showed significantly lower LDH in group III (636±116 mg/dl) than in groups I (774 ±162 mg/dl) and II (728 ±138 mg/dl), with no significant differences between groups I and II.

The result come in parellel with Vasko Graklanov and Veselin Popov 2020 study about correlation of hypovitaminosis D and lymphoma (Vasko Graklanov and Veselin Popov [11]. In which A total of 103 patients were enrolled in this study. Thirty-seven patients (19 women, 18 men) with a mean age of 68 years had a diagnosis of MM according to the criteria of the International Myeloma Working Group. Thirty-two patients (11 women, 21 men) with a mean age of 68 years had a diagnosis of CLL according to the International Workshop on Chronic Lymphocytic Leukemia criteria. Thirty-four patients (16 women, 18 men) with a mean age of 60 years had a histologically confirmed diagnosis of NHL-DLBCL.

Serum levels of vitamin D below the optimum (<30 ng/mL) were observed in all 103 patients. The lowest measured level of vitamin D was 0.80 ng/mL and the highest measured level was 28.60 ng/mL. In 14.42% of patients, serum vitamin D levels were between 20 and 30 ng/mL, while all other patients had vitamin D deficiency (<20 ng/mL). Severe vitamin D deficiency (<10 ng/mL) was observed in 58.3% of patients and vitamin D levels between 10 and 20 ng/mL were observed in 27.28% of patients (Vasko Graklanov and Veselin Popov [15]

Also the study come in parelle with Bittenbring etal., 2014 which found an association between levels of vitamin D and lymphoma mortality has been reported for patients with DLBCL. Data from the German RICOVER-60 study actually indicated that vitamin D deficiency is a negative prognostic factor for elderly patients with DLBCL, treated with rituximab-containing chemotherapy (R-CHOP) [13].

Before treatment, vitamin D showed an overall significant difference between the studied groups (P < 0.001). Post-hoc analysis revealed significantly higher vitamin D in group III (46 ±6) than in groups I and II (12 ±3 for each). After treatment, vitamin D revealed an overall significant difference between groups. Post hoc analysis revealed significantly higher vitamin D in group I (61 ±8) than in groups II (11 ±3) and III (44 ±5). In addition, it was significantly higher in group III than in group II .

And this finding points to the difference between 3 groups before treatment representing low vitamin D in group 1 & 2 , also this result reflect efficacy of vitamin D replacement by this regemin with differenec betwwen group 1&2 post treatment.

A comparison between vitamin D level pre & post treatment with vitamin D suplementation in different stages in group I was done to asses the efficacy of replacement in each stage, Vitamin D before treatment showed non-significant difference between different stages (P = 0.707), while after treatment, it showed an overall significant difference (P = 0.042). Post hoc analysis revealed significantly higher vitamin D in stage II (68 ±4) than in stage IV (59 ±7). Which point to that patients with stage II respond to vitamin D suplementation better than stage IV.

A significant association was reported between the studied groups and complete response (P = 0.03), with the complete response being lower in group II (30%) than in groups I (55%) and III (60%). And this points to that patients with normal vitamin D followed by patients who received vitamin D suplementation showed higher rate of recovery & treatment response.

The results came in parellel with Stefan Hohaus et al study which was done on 155 pateints with hypovitaminosis D and non hodgkin lymphoma and found that After Correction of 25(OH)D levels with different supplementation regimens.Treatment response was evaluated in 142/155 patients at end of therapy. Response evaluation included PET-CT in 137 patients. Complete remission was documented in 121 patients (78%) and partial remission in 10 patients (7%), while 11 patients (8%) were considered resistant. Response was not evaluable in 13 patients, including 8 (5%) patients who died during therapy, and 5 patients who continued treatment at other centers. 25(OH)D levels were significantly higher in patients with complete remission at end of therapy (median 16 ng/mL), when compared to patients with partial remission (median 11 ng/mL), resistant disease (median 9 ng/mL), or early death (median 8 ng/mL) (P = 0.03) [10].

The studied patients were classified according to non responsive disease status as follow: Those with progressive disease revealed significantly higher age (52 ±6 years vs. 44 ±11 years, P = 0.047) and male predominance (100% vs 60.2%, P = 0.044).

Those with progressive disease demonstrated significantly higher percentage of high Ki-67 (100% vs. 25.8%, P < 0.001). In addition, a significant association was reported between progressive disease and IPI score (P = 0.002); those with progressive disease revealed higher percentage of high-intermediate IPI score (85.7% vs. 19.4%), while low IPI score was higher in those with no progressive disease (19.4% vs. 0%). No significant difference was reported regarding stage.

Those with progressive disease revealed significantly higher LDH (916 ±127 mg/dl vs. 714 ±144 mg/dl, P < 0.001) but significantly lower vitamin D (median = 9 vs. 14, P = 0.007).

All these finding points to that higer age of presentation, male pateints, high IPI score , high KI 67 , high LDH and significant low vitamin D may be negative prognostic factors with decresed response to treatment assaosiated with progressive disease.

The results came in parellel with (Jo¨rg Thomas Bittenbring et al) a study reported in the Journal of Clinical Oncology, Bittenbring et al found that vitamin D deficiency was associated with poorer outcome in older patients receiving R-CHOP (rituximab [Rituxan] plus cyclophosphamide, doxorubicin, vincristine, and prednisone) for diffuse large B-cell lymphoma [18].

ROC analysis was done for vitamin D to distinguish those with progressive disease. It revealed a significant AUC of 0.804 with a 95% confidence interval ranging from 0.656-0.953 (P = 0.007). The best cutoff point was ≤ 10, at which sensitivity and specificity were 85.7% and 69.9%, respectively. This finding may point to that vitamin D level may be added as a prognostic indicator in patients with non hodgkin lymphoma with cutoff vlue was ≤ 10 with acceptable sensetivity & specificity.

The results come in parellel with Jo¨rg et al study Assessment of rituximab-mediated cellular cytotoxicity using a lactate dehydrogenase release assay of CD20-positive Daudi cells showed significantly increased activity at rituximab concentrations > 0.001 µg/mL in seven patients with vitamin D deficiency after an increase in levels to an average of 41 ng/mL with vitamin D substitution.The investigators concluded: "[Vitamin D deficiency] is a risk factor for elderly patients with [diffuse large B-cell lymphoma] treated with R-CHOP. That [vitamin D deficiency] impairs

[rituximab-mediated cellular cytotoxicity] and substitution improves [rituximab-mediated cellular cytotoxicity] strongly suggests that vitamin D substitution enhances rituximab efficacy [14].

The results came to augmnt the role of hpovitaminosis D in disease severity at presentation with the effect of vitamin D replacement which leads to more response rate, less progressive disease & higher cure rate.

5. Conclusion

The study come to investigate the correlation between hypovitaminosis D & non hodgkin lymphoma in point of agressiveness of presentation with the impact of it,s replacemen.

The study results come in parellel to the other studies which found that patient with hypovitaminosis D showed more aggressive disease in comparison to nrmal vitamin D patients, also the results showed that patients with normal vitamin D & patients who receive vitamin D replacement had more favarouble outcome than those with hypovitamiosis D.

Lastly vitamin D may have a prognostic index & showed asssosiation between it,s deiciency & lymphoma agressivenes also vitamin D replacement might have a role to iprove outcome of treatment.

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