

Pre-Existing Vitamin D Deficiency Associated with Lower Overall Survival and Progression-Free Rates in Hodgkin Lymphoma**Mukesh Kumar Bharti¹, Kumar Prabhat²**¹Associate Professor, Department of Radiotherapy, Darbhanga Medical College, Darbhanga, Bihar, India²Senior Resident, Department of Radiotherapy, Darbhanga Medical College, Darbhanga, Bihar, India

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Abstract:**Background:** Vitamin D deficit is known as a changeable risk factor in many common cancers, but its impact on Hodgkin lymphoma (HL) is not well-studied.**Methods:** This study assessed pre-treatment vit. D levels in HL individuals who received prospective treatment. It included 35 individuals from the North Bihar Population.**Results:** Vitamin D levels < 30 nmol/L were observed in 49% of patients before therapy. Vitamin D deficiency increased relapse/refractory rates. Relapsed/refractory patients exhibited lower median baseline Vitamin D levels (21.4 nmol/L) than non-relapsed (35.5). The non-relapsed group had 41% Vitamin D insufficiency, while relapsed/refractory patients had 68%. The 10-year progression-free survival of vitamin D-deficient patients was 17.6% poorer with a hazard ratio of 2.13. Their 10-year survival rate was 11.1% lower and their hazard ratio was 1.82. These results were consistent across studies and treatments. Vitamin D status independently predicted prognosis, suggesting it may impact HL chemotherapeutic sensitivity..**Conclusion:** It is advised that future randomized clinical trials include vitamin D assessment and replacement in order to ascertain the function of vitamin D replacement treatment in HL, based on these medical and preclinical findings.

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Introduction

Vitamin D serves as a precursor to calcitriol, a vital corticosteroid hormone that plays a crucial role in the regulation of calcium homeostasis and the maintenance of skeletal integrity. Moreover, it has been conclusively demonstrated through numerous scientific investigations that a deficiency in dietary vitamin D and restricted exposure to UVB radiation are causally linked to the onset of vitamin D insufficiency, which in turn exhibits a positive correlation with heightened rates of cancer occurrence and mortality [1].

Seasonal variations in vitamin D levels are observed due to the reliance on UVB radiation for endogenous synthesis of this essential nutrient within the human body. Notably, the incidence of Hodgkin lymphoma (HL) exhibits an upward trend during the onset of spring, aligning with the customary nadir of endogenous vitamin D levels subsequent to the winter period [2]. Research findings have additionally suggested a rise in mortality related to hearing loss during the winter season, a period characterized by reduced levels of UVB radiation, even after considering variances in geographical locations [3]. Despite the

acknowledgement of the seasonal pattern observed in hair loss (HL), previous studies have not extensively investigated the correlation between vitamin D deficiency and HL.

This study presents an initial and comprehensive assessment of the prognostic significance of pre-treatment vitamin D deficiency in a substantial cohort of individuals diagnosed with Hodgkin's lymphoma (HL) who underwent prospective treatment. Furthermore, this study provides clarification on the synergistic anti-proliferative impact of vitamin D when used in combination with first-line chemotherapy for Hodgkin's lymphoma.

Methods**Study Design and Objectives:**

The present investigation employed a case-control methodology, enlisting individuals from North Bihar population at department of Radiation Oncology DMCH, Laheriasarai. These participants were subjected to risk-adapted initial therapeutic interventions, comprising chemotherapy, either in isolation or in conjunction with radiotherapy. The

study enrolled eligible participants who had a documented occurrence of disease relapse or progression (referred to as cases), as well as two non-relapsed controls who were matched based on the study and treatment arm. Informed consent was gotten from all contestants, and the trials were directed in accordance with ethical guidelines.

The main objectives of this study were to (1) estimate the levels of vitamin D before treatment in patients with Hodgkin's lymphoma (HL) at different stages, (2) compare the initial vitamin D levels between the group of patients with HL and a control group, and (3) examine the effect of the initial vit. D status on the duration of progression-free survival (PFS) and overall survival (OS). The current study conducted secondary analyses to investigate the impact of baseline vitamin D levels on the occurrence of treatment-related toxicity.

Vitamin D Measurement:

The utilization of 25-hydroxyvitamin D as a viable indicator for evaluating vitamin D levels is predicated upon its well-documented dependability and steadfastness [4]. The marker mentioned above functions as a reliable indicator of vitamin D exposure, encompassing both solar irradiation and dietary consumption. The quantification of both 25-hydroxyvitamin D3 as well as 25-hydroxyvitamin D2 concentrations was performed using a widely accepted Enzyme-Linked Immunosorbent Assay

(ELISA) method, which has been proven to be sensitive towards both molecular variants. The classification of vitamin D levels was ascertained in accordance with established reference ranges [5]. The aforementioned classifications encompass adequate levels (≥ 50 nmol per Liter), suboptimal levels (≥ 30 nmol per and < 50 nmol per Liter), and insufficient levels (< 30 nmol per Liter).

Statistical Analysis:

Levels below the limit of detection were adjusted, while data above the limit of detection but below the limit of quantification were analyzed as measured. Categorical vitamin D status was used for significance tests. Analyses were stratified by study and study arm, and SAS 9.4 software was used for analysis.

Results

Vitamin D Insufficiency in Patients with HL:

A study of 35 HL patients undergoing first-line treatment showed that 49% were vitamin D deficient (baseline level < 30 nmol/L) (Table 1). Baseline vitamin D levels were similar across treatment arms and disease stages. However, vitamin D levels were seasonally influenced, with more sufficiency in summer and more deficiency/insufficiency in winter.

Figure 1: Schematic of experimental design

Table 1: Patient Features according to Vitamin D Level

	Deficient (%) N= 17	Insufficient (%) N =8	Sufficient (%) N= 9
Age at study entry			
Median years	31	32	30
Sex			
Female	41	32	43
Male	57	66	55
Clinical risk factor			
Large mediastinal mass	16	23	21
Extranodal involvement	27	20	17
3 or more nodal areas	74	64	73
Elevated ESR	60	53	53
Clinical Stage IV	22	22	16
B symptoms	46	48	42
Karnofsky index			
$\geq 90\%$	80	88	81
$< 90\%$	17	10	17

Vitamin D Insufficiency and Medical Results:

Patients presenting with a pre-existing deficiency in vitamin D exhibited inferior outcomes, characterized by notably diminished progression-free survival (PFS) and overall survival (OS) in comparison to individuals possessing adequate or insufficient levels of vitamin D. The observed effect demonstrated consistency across all conducted studies and treatment groups. The observed disparity in overall survival (OS) can

primarily be attributed to a greater prevalence of deaths related to Hodgkin's lymphoma (HL) in the cohort with vitamin D deficiency.

Discussion

In the present investigation, it was observed that 49% of patients diagnosed with HL exhibited vit. D deficit, irrespective of the stage of the disease. The aforementioned deficiency has been related with diminished long-term tumor control and survival,

representing a noteworthy discovery. Prior studies have established a correlation between the incidence and mortality of HL and factors such as UVB exposure, latitude, or diagnosis month. However, there is currently no direct evidence linking vitamin D status to HL incidence or mortality [2,6,7]. This correlation exhibits similarities to findings observed in other hematologic malignancies. The investigation employed a conservative classification system for vit. D levels, wherein individuals with a level of ≥ 50 nmol/L were considered sufficient, those with a level of 30-50 nmol/L were deemed insufficient, and individuals with a level of < 30 nmol/L were classified as deficient. This categorization was substantiated by relevant data pertaining to the local population [8,9]. Vitamin D levels were assessed at the time of trial enrollment to ensure precise evaluation that remains unaffected by any alterations induced by the treatment. Tandem-mass spectrometry (TMS) is widely regarded as the definitive method for quantifying vitamin D levels. However, it is worth noting that our enzyme-linked immunosorbent assay (ELISA) technique has undergone rigorous validation and has proven to be a feasible alternative [9].

In the correlative studies, it was observed that calcitriol, a physiologically active form of vitamin D, exhibited inhibitory effects on the growth of HL cell-line at high concentrations. Additionally, it was noted that calcitriol potentiated the antiproliferative properties of conventional chemotherapy drugs, such as doxorubicin and etoposide, when administered at standard doses. This finding holds clinical significance as these pharmaceutical agents serve as pivotal constituents within conventional treatment regimens for Hodgkin's lymphoma [10].

Conclusion

The present study findings indicate that the administration of vitamin D supplements may exhibit a synergistic effect when combined with conventional HL chemotherapy. Although there is a dearth of research on the correlation between dietary vitamin D exposure and HL, it is recommended to promote the screening and supplementation of vitamin D deficiency in forthcoming randomized clinical trials. This will facilitate the assessment of its potential impact on enhancing HL outcomes.

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