# Effect of serum vitamin D deficiency in the prevalence of haematological malignancies

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## Abstract

**Introduction:** The awareness on vitamin D related metabolic activities have drawn attention in the recent times. The studies reported vitamin D deficiency may result in the progression of malignancies.[1,2] Being a tropical country, 80% of the Indians are found to be vitamin D deficient and thus the evaluation of serum vitamin D deficiency helps in understanding its risk association in haematological malignancies.[3,4]

**Materials and Methods:** The study comprised of 250 haematological malignancy cases and 250 age and sex matched healthy controls. The diagnosis was confirmed by blood, bone marrow or lymph node biopsies. Serum vitamin D levels were analysed by Electrochemiluminescence Immunoassay (ECLIA) method and statistical analysis was done by using Medcalc 11.6. The data were expressed as mean ± SD and the risk association of vitamin D deficiency and comparison in the experimental groups was done by using the odds ratio (OR) and odds relative risk ratio (RR).

**Results:** Among the 250 haematological cases, 185(74.0%) showed low serum vitamin D levels, whereas controls had comparatively lesser deficiency rate (60%). Despite significant vitamin D deficiency of control group, haematological malignancies showed highly significant risk association towards the disease occurrence (OR=1.90; t-test =0.0026).

**Conclusion**: Low serum vitamin D levels were significantly associated with haematological malignancies. Additional population based studies are required to evolve therapeutic strategies and treatment protocols for the risk reduction and management of malignancies.

**Keywords:** Vitamin D, Deficiency, Tropical countries, Haematological, Malignancy.

## Introduction

Vitamin D is centrally involved in the bone metabolism and calcium regulation along with other functions. However, extensive studies revealed its multitude activities in numerous biological activities like mediator of calcium and phosphate balance to cellular differentiation and immune modulation etc.[5] In recent days, the deficiency of vitamin D is considered a global problem and of national health concern and the rate is rampantly increasing.[1,6-8] In Indian population more than 80% has serum vitamin D levels below the optimal range.[3] International Agency for Research on Cancer (IARC) Global Cancer (GLOBOCAN) study on incidence rates of leukaemia in 172 countries found that reduced UV-B radiation (UVR) exposure and lower vitamin D levels were associated with higher risks of cancer. Leukaemia rates were highest in countries relatively closer to the poles and lowest in countries closer to the equator.[3]

Multi-country studies, mostly using latitude as a proxy for UVR, showed lower rates of mortality or incidence of breast, lung, ovarian, kidney, brain, and uterine cancer and leukaemia in adults residing in countries closer to the equator where UVR levels are higher.[9] Several epidemiological studies have also suggested that inadequate levels of vitamin D may be a risk factor for the development of leukaemia. Many studies revealed that vitamin D influences the expression of more than 200 genes and almost every tissue (brain, heart, skin, kidney, pancreas etc.) has vitamin D receptors (VDR).[10] VDRs have been identified on haematopoietic and lymphoid cells, leading to efforts to understand the role of vitamin D in blood cell development and immune system function.[5] These effects may impact normal and dysfunctional haematopoietic and immune function, which may allow better understanding of haematologic disorders including malignancies.[8,5,11]

Vitamin D and extracellular calcium is involved in the regulation of cell proliferation, differentiation and function. Vitamin D influences the expression of CYP27B1, which encodes 1α-hydroxylase and extracellular calcium-sensing receptor (CaR), controls the normal and cancer cell growth. Hence, the insufficiency of vitamin D may lead to progression of the cancer. Vitamin D indirectly may suppress the tumour growth and progression by facilitating the immunocytotoxic killing of tumour cells by reducing the levels of immunosuppressive CD34 lymphocytes, which generally confine the cytotoxic activity of infiltrating tumour-specific CD8+T lymphocytes.[2, 9,12,13]

Haematological malignancies are a group of neoplasms that arise through malignant transformation of bone marrow derived cells. Leukaemia, lymphoma and myeloma are the different haematological malignancies that originate in the bone marrow or lymphatic tissues as a result of genetic injury.[14] Several population-based cohort studies have shown a linear association between lower serum vitamin D concentrations and an increased risk of overall mortality in leukaemia and the lymphoma subsets.[2,9,15,16]

However, additional prospective studies are required to investigate the association between serum vitamin D concentrations and overall incidence and prognosis in all malignancies. Though India is a tropical country with plenty of sunshine, Indians are found to be vitamin D deficient and there is lack of awareness regarding the deficiency and related health effects. The studies on haematological malignancies are mostly limited to reviews and research studies on one particular cancer type.[4] The current study evaluated the vitamin D status in all the subsets of haematological malignancies to assess for any risk association.

## Materials and Methods

### Study group and demographics

In this case-control study, 250 subjects of Indian origin with various haematological malignancies and 250 age and gender matched healthy control samples were obtained from volunteers at Basavatarakam Indo-American Cancer Institute & Research Center (BIACI&RC), Hyderabad. The study duration was 6 years and 8 months (Jan 2010 to Aug 2016) and approved by the Institutional Ethics Committee as per the local ethical standards and written informed consent was obtained from all the participants. Baseline clinical and laboratory data related to diagnosis and treatment were collected from the hospital medical records as per the standard protocol.

### Inclusion and exclusion criteria

All freshly registered cases of leukaemia, lymphoma, myeloma and other categories of haematological malignancies with no prior treatment were included in this study. All low volume cases like chronic lymphocytic leukaemia (CLL) and myelodysplastic syndrome (MDS) were included in the category of other haematological malignancies for statistical purpose. The cases with a history of metabolic bone disease, history of drug related to bone mass before diagnosis, cases corrected for vitamin D deficiency and its supplementation and previous history of chronic infections including HIV were excluded from this study.

### Methodology

The diagnosis of haematological malignancies was confirmed by blood, bone marrow or lymph node biopsies. Serum vitamin D levels were analysed for all the cases and control samples by using Electrochemiluminescence (ECLIA) method on cobas e411 analyser (Roche Company) at the time of diagnosis and prior to treatment. ECLIA is a kind of luminescence produced during electrochemical reactions in solutions. It is a one-step sandwich assay patented by Roche Company (USA). The principle of Vitamin D total assay employs Vitamin D binding protein (VDBP) to capture both 25-hydroxyvitamin D3 and D2. First, the sample is incubated with a pretreatment reagent for 9 minutes. Thereby, the natural VDBP in the sample is denatured to release the bound vitamin D (25-OH). Second, the sample is further incubated with a recombinant ruthenium-labeled VDBP to form a complex of vitamin D (25-OH) and the ruthenylated-VDBP. Third, with the addition of a biotinylated vitamin D (25-OH) a complex consisting of the ruthenium-labeled VDBP and the biotinylated vitamin D (25-OH) is formed. The entire complex becomes bound to the solid phase (by the interaction of biotin and streptavidin-coated microparticles which are captured on the surface of the elecrode). Unbound substances are removed. Applying voltage to the electrode induces chemiluminescent emission which is measured by a photomultiplier.

Results are determined via an instrument-specific calibration curve which is generated by 2-point calibration and a calibration master curve provided via the reagent barcode.[17,18] According to the manufacturer's recommendation the vitamin D as a serum 25-OH-D level lower than 20ng/mL is treated as vitamin D deficient. This is due to unavailability of consensus guidelines for the population based hypovitaminosis, especially in Indian population.

### Statistical Analysis

The demographic variables and the descriptive measures in the cases and controls were presented in frequency and percentages. Normally distributed variable data were expressed as mean ± SD. The differences between cases and controls for continuous variables were analysed by using unpaired t-test according to the characteristics of the data distribution. Risk association of vitamin D deficiency and case-control comparison was done by using the odds ratio (OR) and odds relative risk ratio (RR). The study group was categorised into four different groups according to their serum vitamin D levels to find out its deficiency in association with the disease at various levels, i.e. <=10 ng/mL, >10.0-20.0 ng/mL, >20.0-30.0 ng/mL and >30.0-100.0 ng/mL. The OR and RR of above 1.0 is considered as statistically significant. A p-value <0.05 was considered as statistically significant. Vitamin D sufficiency levels were considered as 20-100ng/mL and

above 100ng/mL was considered as toxic range. Data analysis was done by using Medcalc 11.6 software.

## Results

Among 250 haematological malignancy cases, 114 cases were diagnosed as acute lymphocytic leukaemia (ALL), 35 acute myeloid leukaemia (AML), 37 multiple myeloma (MM), 53 lymphoma, and 11 "others". Out of all haematological malignancy cases, ALL was found to be the most prevalent subtype followed by lymphoma, multiple myeloma (MM), AML and others as per the below distribution. In case of ALL, the most affected age group for the disease were children of <14 years, which accounts for 72% of total ALL cases. The prevalence of haematological malignancies were ALL (45.6%) > lymphoma (21.2%) > MM (14.8%) > AML (14.0%) > others (4.4%). Out of the 250 cases 150 (60.0%) were males and remaining 100 (40.0%) were females. Of these, 91 (36.4%) were children and rest of 159 (63.6%) were adults [Table-I]. The mean value of serum vitamin D in the study group was 14.8 ng/mL and of control group was 18.5ng/mL. In the subgroup analysis, the lowest mean value was observed in AML (9.79 ng/mL), followed by "others" (12.84 ng/mL), ALL (14.79 ng/mL), lymphoma (15.86 ng/mL) and MM (18.58 ng/mL).

**Table I: Demographics & characteristics of the study group and control group**

| S. No | HMs | Males (No.) | Females (No.) | Children <14yrs (No.) | Adults >14yrs (No.) |
|---|---|---|---|---|---|
| 1 | Controls (n=250) | 150 (60%) | 100 (40%) | 80 (32.00%) | 170 (68.00) |
| 2 | Total cases (n=250) | 150 (60%) | 100 (40%) | 91 (36.40) | 159 (63.60%) |
| 3 | ALL (n=114) | 60 (52.63%) | 54 (47.37%) | 82 (71.93) | 32 (20.07%) |
| 4 | AML (n=35) | 20 (57.14%) | 15 (42.86%) | 6 (17.14) | 29 (82.86%) |
| 5 | Lymphoma (n=53) | 33 (62.26%) | 20 (37.74%) | 3 (5.66) | 50 (94.34%) |
| 6 | MM (n=37) | 20 (54.05%) | 17 (45.95%) | 0 (0.00%) | 37 (100.00%) |
| 7 | Others (n=11) | 8 (72.73%) | 3 (27.27%) | 2 (18.18%) | 9 (81.82%) |

HMs - Haematological malignancies; N- No. of cases, ALL – Acute Lymphoblastic Leukaemia, AML – Acute Myeloblastic Leukaemia, MM – Multiple myeloma

The distribution of vitamin D levels in various haematological malignancies and controls are presented in Table-II. Comparison between the control group and total haematological malignancy cases had shown statistically significant risk association of vitamin D deficiency towards the disease occurrence with the unpaired t-test, p value of 0.002. In this study, among the 250 participants of experimental group, 185 (74.0%) had shown low vitamin D levels and only 65 (26.0%) of cases had shown sufficient vitamin D levels at the time of disease diagnosis. Comparatively 100 (40%) out of 250 control samples had shown sufficient vitamin D levels and rest of the 150 (60.0%) subjects were found deficient for vitamin D. The percentage of deficiency was found more in leukaemia's (AML > ALL) than in lymphomas and myelomas. Despite, finding significant deficiency levels even in controls, haematological malignancy (HM) cases had shown statistically significant risk association towards the disease with Odds ratio of 1.90 and 95% CI 1.2984 to 2.7727. And the calculated p-value of 0.0009 for this case-control study was found to be highly significant towards the disease association.

**Table II: Distribution of Vitamin D levels in Haematological malignancies**

| | Control | Cases | ALL | AML | MM | Lymphoma | Others |
|---|---|---|---|---|---|---|---|
| Size | 250 | 250 | 113 | 35 | 37 | 53 | 11 |
| Mean (ng/mL) | 18.5 | 14.8 | 14.7934 | 9.79 | 18.5 | 15.86 | 12.84 |
| Std Dev | 14.16 | 13.19 | 11.8956 | 10.2 | 13.61 | 16.66 | 10.74 |
| Std. Error | 0.897 | 0.836 | 1.119 | 1.72 | 2.23 | 2.28 | 3.23 |
| 95% C.I. of Mean (ng/mL) | 16.73 to 20.27 | 13.14 to 6.44 | 12.5761 to 17.0106 | 6.2880 to 13.2994 | 14.0307 to 23.1120 | 11.2714 to 20.4585 | 5.6263 to 20.0573 |
| Max (ng/mL) | 80 | 70 | 69.08 | 56.09 | 50.75 | 70 | 39.55 |
| Min (ng/mL) | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Median (ng/mL) | 14.09 | 10.71 | 12.22 | 6.57 | 13.46 | 11.05 | 8.2 |

HMs - Haematological malignancies; N- No. of cases, ALL – Acute Lymphoblastic Leukaemia, AML – Acute Myeloblastic Leukaemia, MM – Multiple myeloma

**Table III: Risk association of Vitamin D deficiency in total Haematological malignancies**

| Contents | Controls (n=250) | Haematological Malignancy cases (n=250) |
|---|---|---|
| Mean (ng/mL) | 18.5 | 14.79 |
| Standard Deviation (SD) | ±14.1 | ±13.1 |
| Standard Error (ERM) | ±0.89 | ±0.83 |

N= number of cases
Student t-test or unpaired *t* test, p value = 0.0026

Sub-group analysis also showed a statistical significant risk association between low vitamin D levels and the disease causation in almost all subsets of haematological malignancies, especially in leukaemia (ALL, AML, chronic myeloid leukaemia (CML) and chronic lymphocytic leukaemia (CLL) and lymphoma (non-Hodgkin's lymphoma and Hodgkin's disease). In AML the percentage deficiency (85.8%) is very high and was found to be highly significant risk association towards the disease when compared with control group samples (OR=4.0; 95% CI 1.501-10.657; RR=1.43; p-value=0.0001). Similarly in ALL, the percentage deficiency was 72.8% and was found to have significant risk association (OR=1.78; 95% CI 1.10-2.89) and relative risk ratio of 1.21 followed by lymphoma (OR=2.28; 95% CI 1.1410 to 4.5470, RR=1.29), other HMs (OR=1.78; 95% CI 0.4605 to 6.8634, RR=1.21) and MM (OR=1.10; 95% CI 0.5380 to 2.2298; RR=1.04). In MM the risk association is less when compared to other subsets of haematological malignancies. Overall, our study shows that there is a significant risk association between vitamin D deficiency and HMs with the Odds ratio of 1.90 and Odds p-value of 0.0009 [Table-IV]

**Table IV: Risk association of Vitamin D deficiency in Haematological Malignancies**

| S. No. | HMs | OR | 95% CI | Odds P- value | RR | RR p-value |
|---|---|---|---|---|---|---|
| 1 | Total | 1.90 | 1.2984 to 2.7727 | 0.0009 | 1.23 | 0.001 |
| 2 | ALL | 1.78 | 1.1001 to 2.8961 | 0.019 | 1.21 | 0.0121 |
| 3 | AML | 4.00 | 1.5012 to 10.6578 | 0.0056 | 1.43 | < 0.0001 |
| 4 | MM | 1.10 | 0.5380 to 2.2298 | 0.802 | 1.04 | 0.7979 |
| 5 | Lymphoma | 2.28 | 1.1410 to 4.5470 | 0.0196 | 1.29 | 0.005 |
| 6 | Other HMs | 1.78 | 0.4605 to 6.8634 | 0.4038 | 1.21 | 0.3157 |

HMs- Haematological malignancies; N- No. of cases, ALL– Acute Lymphoblastic Leukaemia, AML– Acute Myeloblastic Leukaemia, MM– Multiple myeloma, OR– ODDs ratio, RR- ODDs Relative Risk Ratio

Study group of cases and controls were categorised into four different groups according to their vitamin D levels to find out its deficiency association with disease at various levels, viz, <=10 ng/mL, >10.0 -20.0 ng/mL, >20.0-30.0 ng/mL and >30.0-100.0 ng/mL. It was observed that the percentage of HMs are more in the group having <10 ng/mL of serum vitamin D in comparison to control group.

Furthermore an inverse risk association was observed between vitamin D levels and incidence of HMs. Disease occurrence is more in cases of vitamin D levels <10ng/mL followed by vitamin D levels between >10.0-20.0ng/mL, >20.0-30.0ng/mL and >30.0-100ng/mL. Very high risk association was observed in the category of vitamin D levels <10ng/mL when compared with controls (OR=1.76) followed by the category of vitamin D levels 11-20ng/mL (OR=1.22). There is no risk association in the categories of vitamin D levels, 21-30 ng/mL (OR=0.656) and >30-100ng/mL (OR=0.48) [Table V]

**Table V: Risk association of Vitamin D deficiency in Haematological Malignancies at various deficiency ranges**

| Haematological Malignancies | OR | 95 % CI | P- value |
|---|---|---|---|
| <=10.0 ng/mL | 1.76 | 1.2294 to 2.5292 | 0.0021 |
| >10.0-20.0 ng/mL | 1.22 | 0.8249 to 1.8237 | 0.313 |
| >20.0-30.0 ng/mL | 0.656 | 0.4206 to 1.0351 | 0.07 |
| >30.0-100 ng/mL | 0.48 | 0.285-.808 | 0.005 |

OR– ODDs ratio, CI- Confidence Interval

## Discussion

Studies on vitamin D deficiency and geographic location have shown significant risk association in cancer prevalence and mortality.[1,2] Several reports suggested that vitamin D deficiency leads to an increased incidence and poor outcome in colorectal, breast, lung, melanoma and prostate cancers.[7] Despite the growing evidence of the relationship between vitamin D levels and solid tumour, far less is known about the risk and clinical outcomes in haematologic malignancies. Till date, very limited data is available on vitamin D and incidence of cancer in tropical countries like India and there is no comprehensive data on vitamin D deficiency and its risk association in HMs. Our present study divulges the importance of optimised vitamin D levels for healthy human physiology and its deficiency is directly associated with a relative risk of developing haematological malignancies when compared with healthy control samples (t test = 0.0026).

Vitamin D deficiency is strongly observed in almost all the subsets of haematological malignancies. In our study more than 80% of lymphoma and leukaemia cases were found to be deficient vitamin D which is very high when compared to healthy control population with high risk of developing the disease (OR=1.90 and RR=1.23). Especially in ALL, 82% of children had vitamin D deficiency and having high risk for the disease occurrence. In this study, amongst all the haematological malignancies, AML cases showed very high risk of developing the disease with highest odds ratio of 4.0 and relative risk ratio of 1.43, followed by lymphoma, ALL and others.

Lymphoma patients too showed high deficiency rate of 88% and high risk association towards the disease (OR=2.28; RR=1.29 and p value=0.005). ALL and other HM patients had 72.8% deficiency with statistically significant risk association of the disease (OR=1.78; RR=1.21 and p value=0.0121). Of all subtypes of haematological malignancies, MM cases showed 62.2% of deficiency rate with less risk association (OR=1.10) and no relative risk of the disease unlike the other subtypes of haematological malignancies (RR=1.0 and p value=0.797). However, a few studies contradict our results in MM,[19-22] although Ashraf et al, found similar observations.[23,24] In spite of high prevalence of vitamin D deficiency even in control samples, statistically higher risk association was observed in leukaemia and lymphoma cases when compared with healthy controls, but in myeloma the risk association was comparatively less. Our data supports the individual studies done on AML,[25,26] ALL,[2,12,27] CLL,[7,28-30] lymphoma,[7,16] and MM.[22,24] Ashraf et al, observed high vitamin D deficiency in MM with no significant correlations between vitamin D levels and disease status (remission, relapsed or newly diagnosed). A follow-up study by the Harvard Health professionals discovered that a 25 nmol/L increase in modeled 25-hydroxy vitamin D, was associated with a 66% decrease in risk of leukaemia.[2] The high deficiency rates of vitamin D observed in the Indian subcontinent despite being a tropical country could be due to the changing lifestyles restricting to indoors, dress style and lack of awareness of the deficiency and the associated risk due to deficiency.

Limitations of this study are low numbers of cases in subtypes like CLL, CML, MD etc, due to low incidence of the disease. The vitamin D levels were measured only at the time of diagnosis and their levels post treatment and after correction have not been monitored. Dietary habits, climatic influence, socio-economic status of the participants were not considered. Vitamin D deficiency seems to be a global phenomenon and there is evidence from the literature that confirm its causal relationship with diabetes, bone diseases, autoimmune diseases and cancers.

## Conclusions

Low serum vitamin D levels were significantly associated with haematological malignancies in comparison to control subjects at the time of diagnosis. The present study indicates that vitamin D deficiency is associated with an increased risk of haematological malignancies by providing the immediate attention of vitamin D and correction strategies. Additional population based studies are required for determining serum vitamin D concentrations and it's overall incidence risk association and prognosis in various malignancies which may help to evolve strategies on therapy, treatment protocol and dosages for risk reduction and improved survival.

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