# "SERUM VITAMIN D STATUS AND OUTCOME AMONG CRITICALLY ILL CHILDREN WITH RESPIRATORY INFECTIOUS DISEASE ADMITTED TO THE PEDIATRIC INTENSIVE CARE UNIT"

**By**

**Dr. SANJEEVANI. MAHESHKUMAR. UMARANI.** MBBS

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In

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UNDER THE GUIDANCE OF

**DR. S S KALYANSHETTAR ,** MD
PROFESSOR,
DEPARTMENT OF PEDIATRICS

**BLDE (DEEMED TO BEUNIVERSITY'S) SHRI B.M. PATIL MEDICAL COLLEGE,**

**HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR**

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**SHRI.B.M.PATIL MEDICAL COLLEGE, HOSPITAL &**

**RESEARCH CENTRE, VIJAYAPUR.**

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Date:

Place: Vijayapur **Dr.SANJEEVANI.M.UMARANI**

**B.L.D.E (DEEMED TO BE UNIVERSITY'S)**
**SHRI.B.M.PATIL MEDICAL COLLEGE, HOSPITAL &**
**RESEARCH CENTRE, VIJAYAPUR.**

## CERTIFICATE BY THE GUIDE

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Date:

Place:

**DR.S S KALYANSHETTAR M.D.**
Professor
Department of Paediatrics
Shri B. M. Patil Medical College, Vijayapur.

**B.L.D.E (DEEMED TO BE UNIVERSITY'S)**

**SHRI.B.M.PATIL MEDICAL COLLEGE, HOSPITAL &**

**RESEARCH CENTRE, VIJAYAPUR.**

## ENDORSEMENT BY THE HOD AND PRINCIPAL

This is to certify that the dissertation entitled "**SERUM VITAMIN D STATUS AND OUTCOME AMONG CRITICALLY ILL CHILDREN WIH RESPIRATORY INFECTIOUS DISEASE ADMITTED TO THE PEDITRIC INTENSIVE CARE UNIT"** a bonafide research work done by **DR SANJEEVANI MAHESHKUMAR UMARANI** under the guidance of **DR. S S KALYANSHETTAR , M.D.,** Professor, Department of Paediatrics, Shri B. M. Patil Medical College Hospital and Research centre, Vijayapur

**DR. S.V. PATIL MD**

PROFESSOR & HOD
BLDE (DEEMED TO BE UNIVERSITY'S)
Shri B.M. Patil
Medical College, Vijaypura

Date:

Place: Vijayapur

**Dr.S.P. GUGGARIGOUDAR**

PRINCIPAL
BLDE (DEEMED TO BE UNIVERSITY'S)
Shri B.M. Patil
Medical College, Vijaypura

Date:

Place: Vijayapur

**B.L.D.E (DEEMED TO BE UNIVERSITY'S)**

**SHRI.B.M.PATIL MEDICAL COLLEGE, HOSPITAL &**

**RESEARCH CENTRE, VIJAYAPUR.**

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Date: **DR SANJEEVANI MAHESHUMAR UMARANI**

Place: Vijayapur

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**Dr.SANJEEVANI MAHESHKUMAR UMARANI**

## LIST OF ABBREVIATIONS USED

| Sl no. | Abbreviation | Full form |
|---|---|---|
| **1** | AHA | American Heart Association |
| **2** | AMA | Against Medical Advice |
| **3** | ARI | Acute Respiratory Infections |
| **4** | ARTI | Acute Respiratory Tract Infections |
| **5** | CAP | Community Acquired Pneumonia |
| **6** | CPAP | Continuous Positive Pressure Airway |
| **7** | CLIA | Chemiluminescence Immunoassay |
| **8** | DBP | Vitamin D Binding Protein |
| **9** | DBS | Direct Blood Spot |
| **10** | DHC | Dihydrocholecalciferol |
| **11** | DNA | Deoxyribonucleic acid |
| **12** | $FEV_1$ | Forced Expiratory Volume in $1^{st}$ second |
| **13** | HCAP | Human Cathelicidin Protein |
| **14** | ICU | Intensive care unit |
| **15** | IL | Interleukin |
| **16** | LC-MS | Liquid chromatography-Mass Spectrometry |
| **17** | MS | Mass Spectrometry |
| **18** | nm | nanometer |
| **19** | PICU | Pediatric Intensive Care Unit |
| **20** | PIM | Pediatric Index of Mortality |
| **21** | PRESS | Pediatric Respiratory Severity Score |
| **22** | PRISM | Pediatric Risk of Mortality Score |
| **23** | PTH | Parathyroid Harmone |

| | | |
|---|---|---|
| **24** | RSV | Respiratory syncytial virus |
| **25** | SD | Standard Deviation |
| **26** | SOFA | Sepsis related Organ Failure Assessment |
| **27** | $SP0_2$ | Saturation of peripheral oxygen |
| **28** | SPSS | Statistical Package for statistical sciences |
| **29** | TLRs | Toll Like Receptors |
| **30** | TNF-α | Tumor Necrosis Factor-α |
| **31** | URTI | Upper respiratory tract infection |
| **32** | UVA | Ultra violet A rays |
| **33** | UVB | Ultra violet B rays |
| **34** | VDD | Vitamin D Deficiency |
| **35** | VDR | Vitamin D Receptors |
| **36** | VDRE | Vitamin D Response Element |
| **37** | VDSP | Vitamin D Standardization Program |

ABSTRACT

## BACKGROUND

Acute respiratory infectious diseases are one of the most important respiratory diseases in children and is the main cause for hospitalizing children in intensive care unit. More than 40 million annual deaths in the developing countries are estimated to be due to acute respiratory infections like pneumonia, bronchitis, bronchiolitis or could be a combination of these. Vitamin D deficiency and insufficiency have been shown to be associated with increased susceptibility to and increased severity of respiratory illness in children .Low serum levels of 25hydroxy vitamin D is proposed to be risk factor for lower respiratory tract infections and its severity. Whether low levels of vitamin D affects severity of illness and its clinical outcomes has been the subject of debate in pediatrics as well as adult population

**Objectives of the study:**

1. To determine the vitamin D status in critically ill children with respiratory illness admitted to paediatric intensive care unit
2. To correlate the vitamin d status with clinical outcomes and length of stay in children with respiratory illness admitted in PICU.

**Methodology**

Hospital based prospective cross sectional observational study was performed in 50 cases of critically ill children with respiratory infectious disease admitted to the pediatric intensive care unit of Shri B M Patil Medical College and Research Centre

The severity of respiratory illness was assessed using Pediatric respiratory severity score (PRESS). Serum vitamin D levels, serum calcium, serum phosphorous and alkaline phosphatase was assessed. Evidence of duration of PICU stay, hospital stay, need for mechanical ventilation and duration of mechanical ventilation was also recorded.

**Results:**

Among the 50 critically ill cases with respiratory illness 52% were males and 48% were females. According to Pediatric respiratory severity score 28% had mild illness, 32% had moderate illness and 40% had severe illness. Severe Vitamin D deficiency (<20mg/ml) was noted in 64% of total cases admitted with respiratory illness in PICU. Among these 62.5% cases had severe respiratory illness and 37.5% with moderate respiratory illness. In this study, the severity of respiratory illness was found to be highly significant with Serum vitamin D values ($p<0.01$). Serum vitamin D levels were also significant with length of PICU stay ($p<0.01$), length of hospital stay ($p=0.014$), type of respiratory support ($<0.001$) and duration of respiratory support ($p<0.001$)

**Conclusion:**

A high prevalence of Vitamin D deficiency and insufficiency was found in critically ill children admitted with Respiratory infection as strong statistical correlation was noted .Vitamin D deficiency was also associated with prolonged PICU care, respiratory support and hospitalization.

**KEYWORD:** Vitamin D deficiency, respiratory infection, pediatric respiratory severity score

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# INTRODUCTION

# INTRODUCTION

Pediatric respiratory tract infections are among the most common reasons for physician visits and hospitalization, and are associated with significant morbidity and mortality**.** (1) The acute lower respiratory infections are the major cause of hospitalizing children in pediatric intensive care unit (PICU)(**2)** and is an important cause of childhood death globally . "It has been estimated that more than 40 million annual deaths in the developing countries are due to acute respiratory infections, including bronchitis, pneumonia and bronchiolitis as well as a combination of these".(3). In developing countries, seven out of 10 deaths in children under 5 years of age occur due to acute respiratory tract infection (ARTI). In India , ARTI contributes to 15-30% of all under five deaths and most of these deaths are preventable (4)

Although micronutrient deficiencies may increase the risk of ALRI ; Nutritional Vitamin D deficiency in Indian children was observed and reported as a significant risk factor for severe ARTI (1,4) Vitamin D deficiency have been associated with increased susceptibility to and severity of respiratory infections and is a modifiable risk factor in the severity of respiratory illnesses(5) .

Growing evidence suggests that in vitamin D not only plays a role in calcium homeostasis but also a key role in innate and adaptive immunity and thus vitamin D deficiency has been hypothesized to be a culprit in the risk and severity of acute respiratory infection (ARI) in both adults and children. The cells of the innate and adaptive immune system widely express vitamin D receptors. "When stimulated, these cells produce Human cathelicidin protein (HCAP-18), which augments the microbial killing capacity of phagocytes and activates anaphylactoid factors that promote neutrophil and monocyte migration to the site of infection” (2). “In addition to its immunologic activating effects, vitamin D also suppresses the release of potentially damaging pro-inflammatory cytokines and chemokines, to include IL-1β, IL-6, IL-8, and TNF-α” (6)

Vitamin D regulates more than 200 genes including genes for cellular proliferation differentiation and apoptosis (7). Many studies have been carried out on the physiological importance of vitamin D as this field is rapidly expanding and giving us an insight that vitamin D has many new roles. “In addition, a recent meta-analysis of randomized controlled trials concluded that use of vitamin D supplements is associated with a decrease in total mortality rates” (8). Specifically vitamin D deficiency has been seen to increase the risk of upper respiratory tract infections and tuberculosis. It is also known to decrease the forced expiratory volume in 1 s (FEV1) in asthma and wheezing diseases (5)

“ Vitamin D deficiency has been reported to be widely prevalent in critically ill children from ICUs worldwide”.(8) There is evidence from few studies that vitamin D deficiency also contribute to or prolongs critical care pathophysiology (7, 10). There are many adult-based critical care studies that support this idea,which report severe deficiency of vitamin D and its association with higher illness severity scores, and longer ICU length of stay.(11–13, 9) . There are also several studies which have now shown that there is an increased incidence of ARI in subjects with vitamin D deficiency (4-9) but very is little known regarding their association with severity of ARI .Whether low levels of serum Vitamin D affects the illness severity of illness and its outcome has been the subject of debate in pediatrics as well as adult population.

Due to the limited data available in the pediatric population and lack of interventional studies to show that administration of vitamin D indeed improves clinical outcomes, opinion is still divided as to whether it is just an innocent bystander or a marker of severe disease.

There may, therefore ne an important role for Vitamin D in the prevention and/or treatment of respiratory infections in critically ill children. Given an evolving role of Vitamin D in respiratory health and its association with severity, our objective was therefore to estimate the levels of vitamin D in children admitted to intensive care unit (ICU) with respiratory illness and to correlate its association with duration of ICU stay and other key clinical outcome.

# AIMS AND OBJECTIVES

# AIMS AND OBJECTIVES:

- To determine the vitamin D status in critically ill patients admitted to the paediatric intensive care unit.
- To correlate the serum vitamin D status with clinical outcomes and the length of stay in critically ill children admitted in PICU

# REVIEW OF LITERATURE

# REVIEW OF LITERATURE

In 1903, a Nobel Prize recipient, Dr. Niels Finsen, discovered sunlight as the novel and effective treatment for skin tuberculosis. He cured patients with lupus vulgaris through phototherapy (10). Later, in 1920s, sun exposure was a popular treatment for tuberculosis (11) the success of this therapy is that sunlight increases vitamin D levels. Eventually, with the advent of antibiotics, phototherapy as a treatment was forgotten. However, again after a century later, the possibilities of vitamin D as treatment for and an aid in prevention of respiratory illnesses have come up. (12, 13)

**Vitamin D Physiology**

Vitamin D is steroid hormone that is essential in the mineralization of bones (14). Humans meet the requirement of vitamin D by two sources, the majority of it is produced in the skin after sunlight exposure and the remaining from dietary sources. Few foods that are naturally rich with vitamin D are available, although fortified products are also available (15).

There are two forms of Vitamin D, vitamin D2 (ergocalciferol) which is generated from ergosterol in plants and vitamin D3 (cholecalciferol) which is produced in the skin of humans from 7-dehydrocholecalceferol (7DHC), (16).

In the skin 7DHC under the impact of UVB radiation with the wavelengths 290-315 nm undergoes isomerisation and generates previtamin D3, which is transformed into vitamin D3 with the help of membrane fatty acids. Then vitamin D3 is shifted from the skin to the circulation by vitamin D binding protein (DBP). The excess of vitamin D is destroyed by photo degradation in the skin by UVA and thus maintains homeostasis to provide tissues and organs with essential amount of vitamin D (17).

Subsequent metabolism of vitamin D takes place in the liver and kidneys. Vitamin D is converted to 25-hydroxyvitamin D (25(OH) D) in the liver by cytochrome P450s (18). 25(OH) D is the main circulated form of vitamin D metabolites and half-life is two-three weeks. Therefore 25(OH) D is most appropriate for the assessment of vitamin D status, which reflects well with secondary hyperparathyroidism, rickets and osteoporosis (18). Later, in the kidneys 25(OH) D is metabolized by 1 – alpha hydroxylase to the biologically most active form is 1,25dihydroxyvitamin D (1, 25(OH) 2D).Vitamin D effects on the health of humans occurs through the action of 1,25dihydroxyvitamin D (19).

**Effect on the skeletal system**

1, 25 (OH)2D plays an important role in maintaining stable circulatory levels of calcium and phosphorus which is regulated by vitamin D receptors (VDR) in osteoblasts of skeletal system and cells of small intestine. 1, 25 (OH) 2D interacts with VDR to increase the reabsorption of calcium and phosphorus in the small intestine. Insufficient dietary intake of calcium, brings out the stored calcium from the bones by activating the proliferation process of osteoclasts when 1, 25 (OH) 2D interacts with VDR. (19).

Deficiency of Vitamin D may decrease the absorption of calcium and phosphorus in small intestine up to 85-90% and 40% respectively (18). It further decreases the level of ionized calcium in serum and causes stimulation of calcium sensors in the parathyroid glandules.in response, more parathyroid hormone (PTH) is produced because of which the reabsorption of calcium in the kidneys' tubular system is elevated, while phosphorous is lost with urine. In addition, PTH releases calcium from bones to maintain normal Calcium level in the serum. In the state of secondary hyperparathyroidism the conversion of 25(OH) D into 1, 25(OH) 2D is further increased. Therefore, by measuring the levels of 1, 25(OH) 2D or calcium does not give enough information, because its remains normal while person might have deep deficiency of vitamin D (19).

Vitamin D deficiency leads to failure in the mineralization of the bones and development of osteomalacia for children. when skeletal system is immature, it manifests in form of rickets and osteoporosis in adults(19) .Additionally, vitamin D deficiency in early life causes growth retardation, which may impair the child' s ability to achieve genetically inherent height (16).

**Extra skeletal effects of vitamin D**

In the recent years, the part of vitamin D for human wellbeing is reappraised. There are several review articles which have been published to summarize the extra skeletal effects of vitamin D (20-25). It has an important role in the prevention of autoimmune, neoplastic and cardiovascular diseases (20). Furthermore, vitamin D deficiency contributes to the incidence and the severity of acute low respiratory tract infections as well as progression of tuberculosis to its active form (25-27).

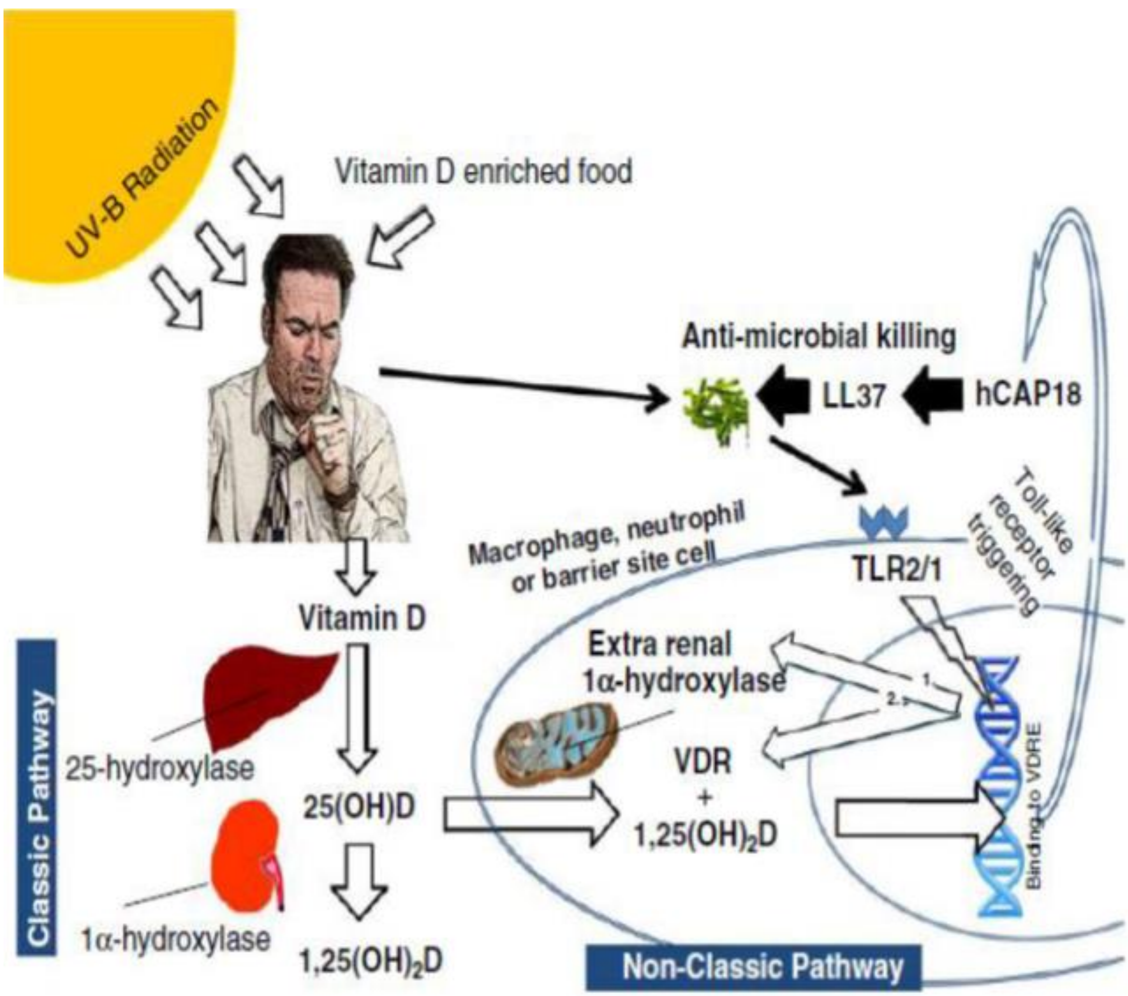
Due to discovery that majority of the human tissue has the nuclear VDR (20), and understanding that the most type of cells are able to transform vitamin D into the it's active form 1, 25(OH) 2D, the focus to non-skeletal effects of vitamin D appears (28).

1, 25(OH) 2D is recognized as a steroid hormone that acts as a gene expression factor.

1, 25(OH) 2D gets attached to the VDR in association with ligand-activated transcriptional factors and displaces into the nucleus. Inside of nucleus 1, 25(OH) 2D binds to the special DNA sequences recognized as the vitamin D response elements (VDRE) (20). Hereby, vitamin D regulates expression of more than 200 genes with transcription of various proteins. These proteins adjust cellular differentiation, proliferation and apoptosis with consequent effects on the function of many organs and systems (27, 29).

For pediatric group the potential effect of vitamin D on immune system and risk of acquiring respiratory infections is more crucial and influential on public health indicators.

**Figure 1: Potential effects of vitamin D on the Immune system**



Regarding immune system, the skin, gastrointestinal tract and respiratory tract serve as an ordinary portal of infections entry. Epithelial barrier (a part of innate immunity) along with macrophages and neutrophils protect against infection (30).

Circulated 25(OH) D is absorbed by macrophages, neutrophils and epithelial cells. In the cellular level, 25(OH) D converted into the active form 1, 25 (OH) 2D under the impact of extra renal 1 alpha hydroxylase. Subsequently, active vitamin D binds to VDR, translocate into the nucleus and attaches to the VDRE (29). It is known that the gene which encodes cathelicidin contains VDRE (31). Cathelecidin is antimicrobial peptides produced by epithelial cells and neutrophils and so relates to the function of innate immune systems (28). (See figures1, vitamin D's pathways)

1, 25(OH) 2D-VDRE complex turn on the gene responsible for the synthesis of cathelicidin (hCAP18). Cathelicidin undergoes segmentation and is transformed into the active form IL37 (16). In fact, IL37 manifests antimicrobial activities against bacteria, virus and fungi(28) .Additionally, on the surface of macrophages there are Toll-like receptors (TLRs) that play role of sensors to recognize bacterial lipoprotein and forward signal to macrophage for synthesis of –cathelicidin. As a part of this signaling system, when Toll-like receptors are triggered by bacteria's lipoprotein, it boosts VDR and extra renal 1 alpha hydroxylase that leads to the enhancement of the cathelicidin's production (29).

The recent immunological data indicates that conversion of vitamin D into the active form 1, 25(OH) 2D is permanent process in the epithelial cells of respiratory tract and it accelerates during the viral infection (32). Therefore, sufficient levels of vitamin D is essential for the adequate cathelicidin production for defense against respiratory infections (28).

Numbers of epidemiological studies have been conducted that have looked into possible association of vitamin D deficiency and acute low respiratory tract infections among pediatric group (33, 34). Results from case-control studies conducted in India (35), Bangladesh (36) indicated strong association between vitamin D deficiencies with acute low respiratory tract infections (ARTI). However, this association has not been proved for Canadian children with bronchiolitis, studied by Roth et al. in 2005 (37); although, the authors suggested that it could be due to different etiological factors that cause ALRI in developing countries and in developed one such as Canada(37). Subsequently another case control study by McNally et al. in Canada, has compared serum vitamin D levels between healthy children and those with pneumonia(38).The result suggested that vitamin D deficiency is not associated with incidence of ALRI, but with severity of respiratory infections among pediatric group (38). Similar conclusion has been confirmed by hospital based retrospective case study from Japan (39). Furthermore, complementary analysis of the Canadian study by Roth et al. from 2005 (37), identified association between genotype ff with less active VDR in the epithelial cells of respiratory tract (25). It has been show that children with genotype ff are susceptible to ARTI particularly towards RSV (respiratory syncytial virus) bronchiolitis, because of inability of vitamin D to implement immunomodulatory and antimicrobial effects (25, 40). Additionally, data from study conducted in a vitro model suggested that vitamin D diminishes inflammation in respiratory tract caused by RSV (32), with the evidence that vitamin D is able to suppress release of pro inflammatory cytokines by macrophages (31).

To know the effect of vitamin D on the susceptibility of ARI in high risk pediatric age group, many randomized interventional control trial were done. (41-43). The results have varied from positive effect on the reduction of incidence of repeated cases to no effect of intervention. It has been suggested that dose adjustment may be required for the different age groups and further research is needed (44).

"As regards to the association of vitamin D status and tuberculosis, the meta-analysis and systematic review published in 2008, concluded that there is a strong correlation between vitamin D insufficiency and risk of development active tuberculosis" (21). Also the study suggests that vitamin D deficiency increases the chances of developing acute tuberculosis by five times among healthy household contacts (45). This is due to the fact that due to low levels of vitamin D, there is decreased production of cathelicidin by macrophages, which is an antimicrobial peptide and respiratory epithelial cells. This increase susceptibility towards Mycobacterium Tuberculosis (21, 45, and 46).

Determination of vitamin D status

It is recommended to measure 25(OH) D for the assessment of vitamin D status, which has a half-life of 2-3 weeks. It is considered as the most reliable metabolite that reflects the body's vitamin D stores. In contrast as it was discussed above the measurement of its active metabolite 1, 25(OH) 2D is not informative, and is recommended only if there is suspicion on impaired production of 1, 25(OH) 2D by kidneys in terms of rare inherit or acquired disorders (47).

As regards to the measurements techniques, various methods are available such as radioimmunoassay and high-performance liquid chromatography. However, liquid chromatography– tandem mass spectrometry (LC-MS/MS) has been the most accurate method to quantify 25(OH) D as it allows measuring 25(OH) D2 and 25(OH) D3 separately and is considered as a gold standard (48).

In addition, during recent years the dried blood spot (DBS) sampling methods along with LC-MS/MS has been suggested as a new approach for the clinical testing and screening (49). This novel method of sampling brings better opportunities for the assessment of vitamin D status. First of all it is less invasive and so reduces the risk of infection's transmission; secondly, the amount of blood required for the assessment is remarkably less, what makes it convenient for pediatric patients. Also, it can be used for field research and in the resource poor settings as it does not require sophisticated equipment shipping materials (49).Most important, it has shown good correlation between LC-MS/MS method using DBS with serum. As a result LC-MS/MS method using DBS is considered to be highly sensitive with good correlation for the assessment of vitamin D (50-52).

As regards to the evaluation of vitamin D status, so far there is no unified agreement for the definition of vitamin D sufficiency and insufficiency. Various methods have been suggested to determine the cut off level. The most common way of determining normal level of vitamin D is to identify the minimum level of 25(OH) D which maximally suppresses the secretion of PTH, and this (plateau of PTH) was observed at level 30ng/ml (47). However, there is some discrepancies. It was identified that for some individuals there is no correlation between level of 25(OH) D and PTH. Moreover, the deviation in the level of PTH does not always relate to the changes in the vitamin D status during childhood, because of elevated calcium absorption in the period of active growth (53).

There are also different suggestion regarding the normal range of vitamin D, such as determine the level of 25(OH) D that ensures maximal absorption of calcium in the intestinal, or the level when the majority does not have any manifestation of diseases associated with vitamin D metabolism. However, both of these suggestions are also debatable (53).

In fact, until recently the most widely accepted definition of vitamin D status was the one suggested by Lips P. (54), where vitamin D deficiency subdivided on mild, moderate and sever deficiency.

Table 1: Definition of Vitamin D status

| **Vitamin D status** | **Level of 25(OH)D** |
|---|---|
| Severe deficiency | 0-12.5 nmol/l |
| Moderate deficiency | 12.6-25 nmol/l |
| Mild deficiency | 25.1-49.9 nmol/l |
| Sufficient | ≥ 50 nmol/l |

Although, these criteria still are widely accepted by clinicians (see table above), the Endocrine Society's Clinical Practice Guidelines suggested the new criteria for both children and adults (see table below)

Table 2: Definition of vitamin D status by Endocrine Society's Clinical Practice Guidelines

| Vitamin D status | Level of 25(OH)D(ng/ml) |
|---|---|
| Deficiency | 20 |
| Insufficiency | 21-29 |
| Sufficient | 30 |
| Ideal | 30-60 |
| Safe | <100 |

Suggestions have been made that the level of 25(OH) D of 10ng/ml is needed to maintain the bone metabolism (40), although the level of vitamin D that requires to perform extra skeletal effects is greater and more likely is 30ng/ml (31).

Additionally, it is recommended to measure the serum values of calcium, phosphorus and alkaline phosphatase for the determination of vitamin D status. Alkaline phosphatase is marker of bone turn over and the level of calcium will be deviated when the bone stores are depleted. So, these indicators are only informative when child has severe deficiency of vitamin D and bone metabolism is involved (53).

**Risk factors for developing hypovitaminosis D**

**Geographical determinants:** It is known that living above 350N latitude increases the possibility of vitamin D deficiency in winter months. This is due to considerably less UVB photons are able to reach the Earth's surface in that latitude; the UVB photons are absorbed by the ozone layer in the stratosphere when the zenith angle is oblique as it is happening during winter months (16). Moreover, it has been recently proved by Holick et al. (56) in vitro models even the height above sea level matters along with the altitude having considerable effect on the production of vitamin D from 7DHC.

**Pollution:** atmospheric pollution may have great impact on the levels of vitamin D, through enhancement of UBV photons absorption. Although it is more essential for inhabitant of big industrialized cities with high level of emission (57).

**Skin pigmentation and use of sunscreen:** melanin determines the skin pigmentation and works as photo protector. It is produced in the basal layer of epidermis by melanocytes and has great capacities to absorb UVB and decrease syntheses of vitamin D (43). Proper use of sunscreen with protection factor 8, consumes up to 95% of UBV photons thus decreasing the synthesis of vitamin D in the skin (56).

**Restriction of sunlight exposure**: it could be due to clothing habits or limitation of outdoor activities. Also, scarcities of products in the diet and absents of food fortification policy in the country would have certain impact on the populations' vitamin D status(58).

**Exclusively breastfeeding:** It is a predisposal factor in the development of low levels of vitamin D. It is known that the breast milk does not contain enough vitamin D to provide child with daily requirement, it consist even less when women is vitamin D insufficient. Consequently it is recommended to ensure sun exposure for infants when it is possible, or provide supplementation (14).

**Malabsorption:** Yet other risk factors for the developing of vitamin D insufficiency or deficiency are the conditions that cause malabsorption, hence decrease the intake of vitamin D from intestine. Also, the important role plays the treatment with medication that is likely to interfere with vitamin D metabolism (Phenytoin, Phenobarbital, Carbamazepine, Isoniazid, Theophylline, and Rifampin) (14).

Obesity: It has been shown that people with obesity at the risk of vitamin D insufficiency due to reduced bioavailability of vitamin D. In other words they develop relative insufficiency because vitamin D deeply sequesters in the fatty tissue and cannot replenish the circulating pool of vitamin D (59).

Each of these factors may contribute to the development of vitamin D deficiency in a certain extent. For South Asian region, skin pigmentation, clothing style, traditional diet and exclusively breastfeeding are the major factors. Additionally for the industrial population it is account pollution and time spend outdoor (58).

1.1.7 Recommendations for vitamin D testing

According to the resent scientific data it is advised to test those who are at risk of development insufficiency or deficiency (14, 53, and 55):

- Individuals with darker skin and living at high latitude
- Individuals with chronic diseases that leads to the malabsorption or those who are on the long lasting medication that interferes with vitamin D metabolism
- Infants with symptoms of rickets
- Individuals with frequent fractures

There is not data on the benefits of testing general population (55).

1.1.8 Recommendation for vitamin D supplementation

In the recent past the recommendation for vitamin D supplementation regarding infants was 200 IU/daily, the dosage was calculated based on the evidence that 200 IU/d allows to keep the level of 25(OH) D on the level of 11ng/ml (14). However, in connection with recent knowledge of normal vitamin D status, the recommendation was revised. The most updated recommendations based on the suggestion of maintaining the level of vitamin D equal to 30ng/ml. The Endocrine Society's Clinical Practice Guidelines suggested the following dosage for the prevention (table 4) and for the treatment (table 5) of vitamin D deficiency (55).

Table 3: Recommendation regarding vitamin D intake for the prevention of deficiency

| Group of Individuals | Vitamin D3 or Vitamin D2 |
|---|---|
| Children 0-12 moths | 400- 1000 IU |
| Children 1-8 years | 600-1000 IU |
| Children (males) 9-18 y | 600-1000 IU |
| Children (females) 9-18 y | 400-2000IU |
| Adults | 1500-2000 IU |
| Pregnancy, and lactation period | 1500-2000 IU |
| Mother's requirement during exclusively breastfeeding, if child does not take supplementation | 2000 - 4000 IU |

Table 4: Recommendation regarding vitamin D intake for treatment of deficiency

| Group of individuals | Vitamin D3 or Vitamin D2 |
|---|---|
| Children 0-12 months | 2000 IU/daily during 6 weeks, after reaching level of 30ng/ml 400 IU/daily |
| Children 1-18 year | 2000 IU/daily during 6 weeks, after reaching the target level is 30ng/ml 600 IU/ daily |
| Adults | 50,000 IU/weekly during 8 weeks, after reaching target level is 30ng/ml 1500 IU/daily |

Additionally, for obese individuals (BMI 30 kg/m2 or more) as well as for those who are on the continuing medication that interferes with vitamin D metabolism it is recommended augment the dosage twice (55).

In fact, the Endocrine Society's Clinical Practice Guidelines, stated clear that there is no evidence regarding differences in outcomes of vitamin D2 or vitamin D3 supplementation; and in addition there is not significant differences whether to comply daily, weekly or quarterly regiment (55)

Table 5: Main studies of Vitamin D deficiency or insufficiency in children with respiratory tract infection

| **AUTHOR** | **AGE GROUP** | **RESPIRATORY TRACT INFECTION** | **REPORT** |
|---|---|---|---|
| Ginde *et al. (7)* | >12 years | URTI | • Association of Serum 25(OH)D with URTI;<br>• association present in patients with asthma and chronic obstructive pulmonary disease |
| Reid *et al* (59) | 4-16 years | Pharyngo-tonsillitis | • association between Serum 25(OH)D levels and darker skin , BMI and larger tonsils were seen |
| Aydin *et al.(60)* | 2-12 years | Pharyngo-tonsillitis | • comparison of Serum 25(OH)D levels and |

| | | | |
|---|---|---|---|
| | | | receptor gene polymorphisms in tonsillectomised children and healthy controls was done<br>• low 25(OH)D levels were more frequent in the former |
| Yildiz et al(61) | 2-10 years | Pharyngo-tonsillitis | • Serum 25(OH)D levels were lower in the group with recurrent pharyngotonsillitis than in healthy children,<br>• no difference in the incidence of VitOR gene polymorphisms. |
| **AUTHOR** | **AGE GROUP** | **RESPIRATORY TRACT INFECTION** | **REPORT** |
| Mulligan et al (62) | <18 years | Rhinosinusitis | • vitamin D deficiency was seen in Children with allergic fungal rhinosinusitis or chronic rhinosinusitis and nasal polyposis |

| | | | |
|---|---|---|---|
| | | | • this could be related to increased dendritic cell infiltrate |
| Elemraid *et al.(63)* | <18 years | Chronic supportive otitis media | • Children with chronic suppurative otitis media were more undernourished than Controls.<br>• The Vitamin D-deficient and iron-depleted children had longer-lasting infection. |
| Muhe *et al (64).* | <5 years | CAP | • VDD may be important predisposing factor for CAP |
| Oduwole *et al.(65)* | <18 years | Community acquired pneumonia | • Vitamin D insufficiency plays important role in the immune and hemopoetic system. |
| **AUTHOR** | **AGE GROUP** | **RESPIRATORY TRACT INFECTION** | **REPORT** |
| Haider *et al.(66)* | <5 years | Community acquired pneumonia | CAP was a very common presentation of rickets |

| | | | |
|---|---|---|---|
| Wayse *et al. (35 )* | <5 years | LRTI | Sub-clinical Vitamin D deficiency and non-exclusive breastfeeding in the first 4 months of life are significant risk factors for severe LRTI in Indian children |
| McNally *et al.(38)* | <5 years | Community acquired pneumonia | Serum 25(OH)D levels seem to influence the severity of LRTI |
| Inamo *et al.(39)* | <5 years | Community acquired pneumonia | Significantly more of the children with CAP who needed supplementary oxygen and ventilator management were Vitamin D deficient |
| Banajeh *et al (67).* | <5 years | Community acquired pneumonia | In cases of severe CAP, rickets was significantly associated with treatment outcome and Vitamin D deficiency significantly predicted reduced circulating neutrophil levels and dav-5 hypoxemia |
| **AUTHOR** | **AGE GROUP** | **RESPIRATORY TRACT INFECTION** | **REPORT** |
| Roth *et al. (37)* | 1-25 months | LRTI | No correlation between risk of hospitalization and serum vitamin D |

| | | | |
|---|---|---|---|
| | | | levels |
| Sita-Lumsden *et al(68)* | less than 18 years | TB | Patients with active TB had lower serum Vitamin D concentrations than contacts from similar ethnic and social backgrounds with comparable dietary intake and sun exposure, and did not show the expected seasonal variation |
| Gray *et al.* *(69)* | Less than 18 years | TB | Refugee children with TB had reduced vitamin D levels |
| Ganmaa *et al* *(70).* | Less than 18 years | TB | High serum 25(OH)D concentrations correlated with fewer cases of tuberculin skin test conversion |
| Williams *et al.(71)* | Less than 18 years | TB | Serum 25(OH)D levels were lower in children with latent TB and TB infection than in healthy controls |

**Vitamin D deficiency in critical illness**

"Recent studies involving critically ill children demonstrated that VDD is common and a few of them also identified that VDD is associated with greater severity of illness and a longer stay in the paediatric intensive care unit (PICU)" (38, 72, and 73).

Whether low levels of serum vitamin D deficiency affects the illness severity and its clinical outcome, has been the subject of debate in the paediatric as well as the adult population. "It has been associated with greater illness, severity presentation, increased need of mechanical ventilation, duration of stay and even mortality".(8) Although Vitamin D deficiency is reported to be common in India(74,75,76), and vitamin D supplementation has been shown to improve outcome in Chronically ill Indian children with moderate to severe asthma(8),.(2)

- Hebbar et al., in their study titled "Vitamin D Deficiency in Pediatric Critical Illness" which was performed in the pediatric intensive care unit (PICU) at Children's Healthcare of Atlanta at Eagleton from January 2010 to March 2012. On 61 PICU patients and 46 control patients found that Over 60% of the PICU cases were found to be vitamin D insufficient while less than 1/3 of the controls were insufficient ($p < 0.0001$). And suggested that overall finding of profound vitamin D deficiency in the pediatric critical care population is an important finding.(77)
- Rippel et al., in their study titled "Vitamin D status in critically ill children" in 2012 performed a prospective study to determine the prevalence of hypovitaminosis D in 316 concluded the association between hypovitaminosis D

with higher inotropes in the postoperative cardiac population, but not with PICU length of stay or hospital survival.(72)

- McNally et al., in their prospective cohort study conducted on 326 critically ill children upto 17 years of age, from 2005-2008 which was titled as "The Association of Vitamin D Status With Pediatric Critical Illness" in Canada , observed that the prevalence of 25(OH)D <50 nmol/L was 69% (95% confidence interval, 64–74), and 23% (95% confidence interval, 19–28) for 25(OH)D between 50 to 75 nmol/L. Through this study it is evident that vitamin D deficiency is seen among critically ill children and is associated with greater severity of critical illness.(38)
- Madden K et al., in their study titled " Vitamin D deficiency in critically ill children" conducted on 511 critically ill children admitted to PICU from November 2009 to November 2010, taking into consideration PRISM III as severity scoring for critical illness, found that 40.1% had vitamin D deficiency (<20ng/dl) and found high rate of vitamin D deficiency in critically ill children.(73)
- Ebenezer K et al., in their prospective observational study titled "serum vitamin D status and outcome among critically ill children admitted to paediatric intensive care unit in south India", among 54 critically ill Vitamin D deficiency was seen in 40.3% of the children. Also higher PIM score or SOFA score were associated with low levels of Vitamin D. Their study concluded that Vitamin D deficiency is common among Paediatric patients admitted to PICU patients in South India and low serum Vitamin D levels were associated with higher severity

of illness, need for mechanical ventilation , more vasopressor use and lower serum calcium levels(78).

- Ponnarmeni et al., in their retrospective study which was performed at PICU in north India during January to December 2012 , titled as "Vitamin D deficiency in critically ill children with sepsis" involving 124 critically ill children with sepsis concluded that Prevalence of VDD [25(OH) D level v 50 nmol/L] was higher among critically ill children with sepsis compared to healthy controls (50.8% vs. 40.2%, P50.04).(79)
- Rey C et al., in their prospective observational study titled "Vitamin D deficiency at pediatric intensive care admission" has measured vitamin D levels in 156 critically ill patients and 289 healthy children as control were compared with pediatric risk of mortality III (PRISM III) or pediatric index of mortality 2 (PIM II) and found that prevalence of vitamin D <20ng/dl was 29.5%. They concluded that hypovitaminosis D incidence was high in PICU patients. Hypovitaminosis D was not associated with higher prediction of risk mortality scores.(80)

There are limited studies on the association between vitamin D status and outcome in critically ill hospitalized children and none pertaining to the respiratory illness in PICU , though it is most common indication for admission to PICU.(2) Due to limitation of the data available especially in the pediatric population and lack of interventional studies to know the role of vitamin D, its deficiency, insufficiency and its relation with critically ill children with respiratory infections , further evidence from the pediatric population is therefore needed. Thus this study is being conducted.

# METHODOLOGY

# METHODOLOGY

**Study design:**

- Study type :Prospective Observational Cross sectional study
- Study approval**:** the study was approved by Institutional Ethics Committee of Shri B.M. Patil Medical College & Research Centre, Vijayapur
- Study site : Pediatric Intensive Care Unit
- Study period: 1.5years (2-Nov-2016 to 31-July-2018).

**Sample size**:

50 cases in span of 1.5 years

Among children with respiratory illness with anticipated SD as 18.1 and 95% confidence level and margin of error ±5%, a sample size of 50 subjects was calculated to be allowed for the stud to determine the levels of Vitamin D among these children.

By the formula

$N=Z^2\sigma^2/e^2$

$N= (1.96*1.96) (18.1*18.1)/ (5*5)$

$= 50.3$

Where Z= z statistics at 5% level of significance (1.96)

e = margin of error

σ= anticipated SD

**Source of data:**

This is prospective study conducted in children admitted with respiratory infection in PICU of Shri B M Patil Medical College & Research Centre fulfilling the inclusion criteria were included in the study .

**Selection criteria**

**INCLUSION CRITERIA**

All children admitted to PICU aged 1 month to 15 years with respiratory infection disease ( bronchitis, bronchiolitis , bronchopneumonia , tuberculosis or combination of these ) were included in the study .

**EXCLUSION CRITERIA:**

- Known or suspected adrenal, pituitary or hypothalamic diseases.
- Use of systemic steroids in the past one week
- Known cases of hypoparathyroidism, rickets, renal tubular acidosis, CKD, AKI
- Respiratory illness due to poisoning
- Chronic lung disease like asthma
- Lack of consent to participate by parents or by children older than 12 years

**Method of study:**

Consent:

Before enrolling the child in the study an informed consent of the parents was taken after explaining in detail about the methods and procedures involved in the study in their vernacular language.

Enrolment and Laboratory analysis:

On admission, respiratory case fulfilling the inclusion criteria were assessed for their severity using paediatric respiratory severity score (PRESS). Variables at baseline for each patient were age, gender, reason for admission, anthropometry and documentation of past respiratory illness and family history of respiratory illness were documented. Evidence of need and type of respiratory support, duration of respiratory support, duration of PICU stay and hospital stay and clinical outcome was recorded.

Within 12 hours of admission to critical care unit, blood was drawn for investigation of Serum Calcium, serum phosphorus, ALP and serum Vitamin D.

Blood samples were collected in clot activator vials were sent to laboratory where serum was separated and vitamin D levels are estimated

**ESTIMATION OF LEVELS OF SERUM VITAMIN D**

The levels of Serum Vitamin D was estimated by CLIA (Chemiluminescence immunoassay)

PRINCIPLE: specific antibody to vitamin D is used and vitamin D is linked to an isoluminol derivative. During incubation 25-hydroxy vitamin D is dissociated from its binding protein and competes with labelled vitamin D for binding sites on antibody .After the incubation the unbound material is removed with the wash cycle. The starter reagents are added and flash chemiluminescent reaction is initiated. The light signal is measured by a photomultiplier as relative light units and is inversely proportional to the concentration of 25-hydroxy vitamin D present in the sample.

Vitamin D Total test is analysed on Siemens ADVIA Centaur, standardized against ID-LC/MS/MS, as per Vitamin D Standardisation Program (VDSP)


Figure 2: Siemens ADVIA Centaur immunoassay system.

Patients with serum Vitamin D levels were categorised as follows

Table no 6: classification of vitamin D deficiency in our study based on Vitamin D levels. Levels of serum vitamin D were be correlated with the severity of illness , the length of PICU stay and total hospital stay , type of respiratory support and duration of respiratory support .

| Vitamin D status | Level of 25(OH)D(ng/ml) |
|---|---|
| Deficiency | 20 |
| Insufficiency | 21-29 |
| Sufficient | 30 - 100 |

**Description of terms used in the study**:

1. **Paediatric respiratory severity score (PRESS)** **:**

The PRESS scoring system is used for the assessment of respiratory tract infections in children admitted in Paediatric intensive care unit.

Table 7: PRESS scoring system

| Score component | Operational definition | | Scoring |
|---|---|---|---|
| Respiratory rate | Respiratory rate at rest, on room air* | | 0 or 1 |
| Wheezing | High pitched expiratory sound heard by auscultation | | 0 or 1 |
| Accessory muscle use | Any visible use of accessory muscles | | 0 or 1 |
| SPO2 | Oxygen saturation less than 95% on room air | | 0 or 1 |
| Feeding difficulties | Refusing feedings | | 0 or 1 |
| | Sum of five components | | |
| PRESS SCORE | 0-1: mild; 2-3: moderate; 4-5: severe | | 0-5 |
| | Month | Respiratory rate | |
| Criteria for tachypnea | <12 | >60 | 1 |
| | 12-35 | >40 | 1 |
| | 36-156 | >30 | 1 |
| | >156 | >20 | 1 |

“The PRESS assessed tachypnea, wheezing, retraction (accessory muscle use), $SpO_2$, and feeding difficulties, with each component given a score of 0 or 1, and total scores were classified as mild (0–1), moderate (2–3), or severe (4–5)”(81).

*Respiratory rate was evaluated according to American heart association (AHA) guidelines

## STATISTICAL ANALYSIS:

All characteristics were summarized descriptively. Date was presented using diagrams, scattered charts, mean and standard deviation. Association between the qualitative data was performed using .chi – square test and correlation between continuous variables was performed using Spearmen’s correlation. To examine factors associated with vitamin D levels logistic regression was used. Tests with p<0.05(2 sided) were considered statistically significant. Analysis was performed using SPSS version 17.

# RESULTS

# RESULTS

**AGE**

Table 8: -DISTRIBUTION OF PATIENTS ACCORDING TO AGE (MONTHS)

| **Age(Months)** | No. of patients | Percent |
|---|---|---|
| <= 3 | 10 | 20.0 |
| 4 – 12 | 12 | 24.0 |
| 13+ | 28 | 56.0 |
| Total | 50 | 100.0 |

Out of 50 patients, 28 patients (56%) were in the age group above 13 months, 12 patients (24%) were in the age group between 4 – 12 months and 10 patients were in the age group 1-3 months.

GRAPH 1: DISTRIBUTION OF CASES ACCORDING TO AGE

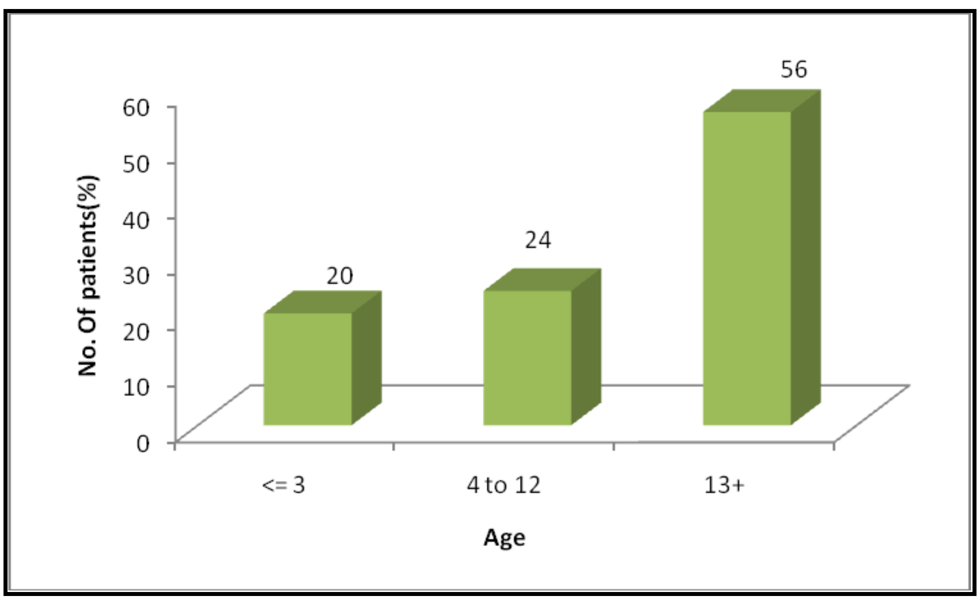


Table 9:-Association between Age and Serum vitamin D level

| Age (months ) | Vitamin D level | | | Total | Chi square test |
|---|---|---|---|---|---|
| | <20 | 20-30 | 30-100 | | |
| <= 3 | 9(28.1%) | 1(10.0%) | 0(.0%) | 10(20.0%) | P=0.353 NS |
| 4 – 12 | 7(21.9%) | 2(20.0%) | 3(37.5%) | 12(24.0%) | |
| 13+ | 16(50.0%) | 7(70.0%) | 5(62.5%) | 28(56.0%) | |
| Total | 32(100%) | 10(100%) | 8(100%) | 50(100%) | |

In the study, severe Vitamin D deficiency was found 32 cases, out of which 28.1% cases belonged to 1-3 months age group, 21.9% belonged to 4-12 months age group and > 13 months had 50% of the cases. Vitamin D insufficiency was found in total of 10 cases , out of which 70% of cases belonged to >13 months age group , 20% cases in 4-12 months age group and 10% cases in < 3 months age group . Sufficient level of Vitamin d was noted in only in 8 cases, and majority62.5% cases were noted in > 13 months age group and remaining (37.5%) were found in 4-12 months age group. However, there was no statistical signifance (p=0.353) between the age group and vitamin D levels

Table 10:-Distribution of patients according Gender

| **Gender** | No. of patients | Percent |
|---|---|---|
| Male | 26 | 52.0 |
| Female | 24 | 48.0 |
| Total | 50 | 100.0 |

In our study, a total of 50 patients were included, and in that, 26(52%) were males and 24(48%) were females.

GRAPH 2: DISTRIBUTION OF CASES ACCORDING TO GENDER

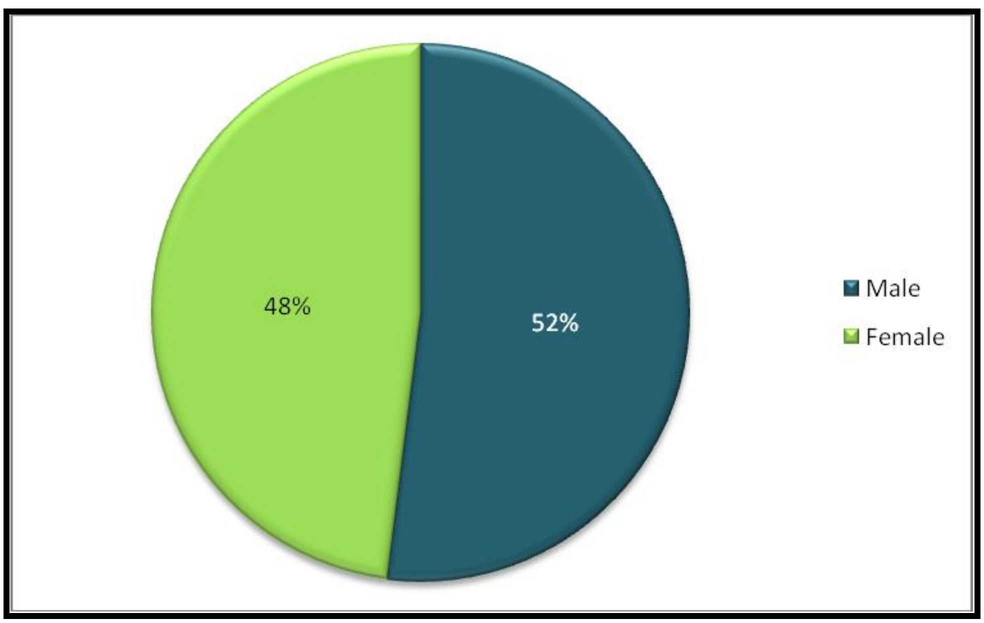


Table 11:-Association between Gender and Serum vitamin D level

| Gender | Vitamin D level | | | Total | Chi square test |
|---|---|---|---|---|---|
| | <20 | 20-30 | 30-100 | | P=0.918 NS |
| Male | 16(50%) | 6(60.0%) | 4(50%) | 26(52. %) | |
| Female | 16(50%) | 4(40.0%) | 4(50%) | 24(48.0%) | |
| Total | 32(100%) | 10(100%) | 8(100%) | 50(100%) | |

In the study, out of 32 cases severe Vitamin D deficiency cases, 50% were males and 50 % were females. Vitamin D insufficiency was found in total of 10 cases, out of which 60% were males and 40% were females. Sufficient level of Vitamin d was noted in only in 8 cases in which 50% were males and 50% were females. However, there was no statistical signifance (p=0.918) between the gender distribution and vitamin D levels.

Graph 3: association of vitamin D levels and gender

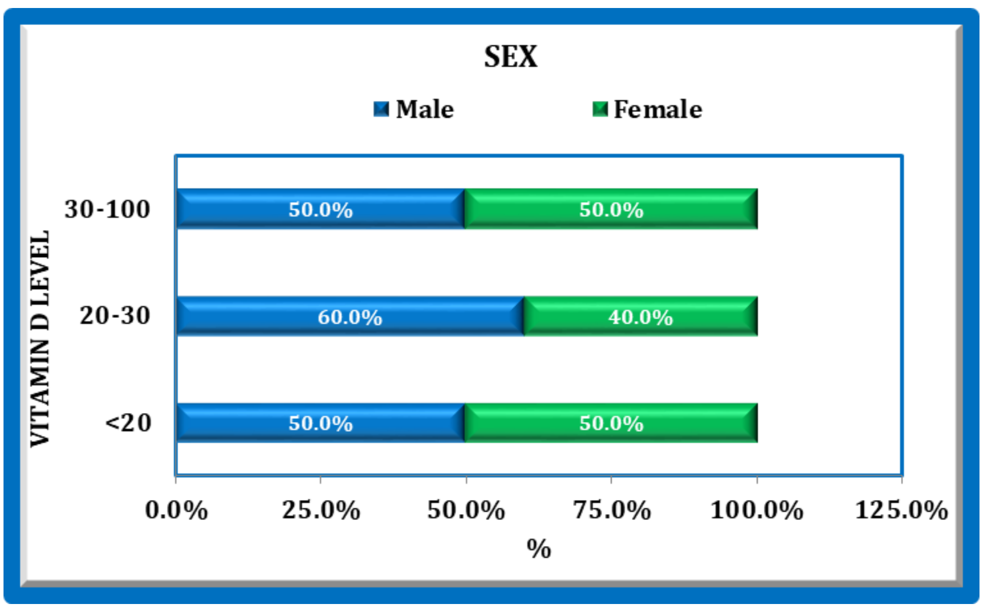


Table 12:Distribution of patients according to Diagnosis

| **Diagnosis** | No. of patients | Percent |
|---|---|---|
| Bronchitis | 4 | 8.0 |
| Bronchiolitis | 7 | 14.0 |
| Bronchopneumonia | 17 | 34.0 |
| Tuberculosis | 2 | 4.0 |
| Pneumonia | 16 | 32.0 |
| Croup | 3 | 6.0 |
| Empyema | 1 | 2.0 |
| Total | 50 | 100.0 |

In our study out of 50 patients, 17 (34%) suffered from bronchopneumonia, 16(32%) had pneumonia, 7(14%) were diagnosed as bronchiolitis, 4(8%) had bronchiolitis, 3(6%) had croup, 2(4%) suffered from tuberculosis and 1(2%) had empyema.

GRAPH 4: DISTRIBUTION OF CASES ACCORDING TO DIAGNOSIS

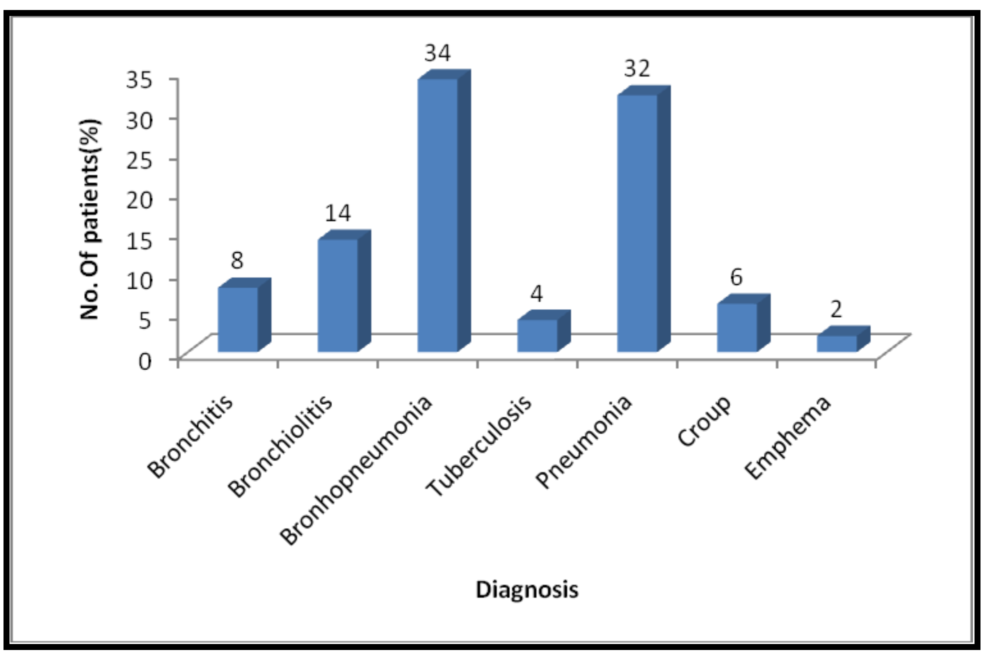


Table 13:-Distribution of patients according to **Immunization Status**

| **Immunization Status** | No. of patients | Percent |
|---|---|---|
| Immunized till date | 24 | 48.0 |
| Not Immunized | 5 | 10.0 |
| Partially Immunized | 21 | 42.0 |
| Total | 50 | 100.0 |

Out of 50 cases, 24(48%) were fully immunized till date according to national immunization schedule, 21(42%) were partially immunized and remaining 5(10%) were not immunized.

GRAPH 4: DISTRIBUTION OF CASES ACCORDING TO IMMUNSATON STATUS

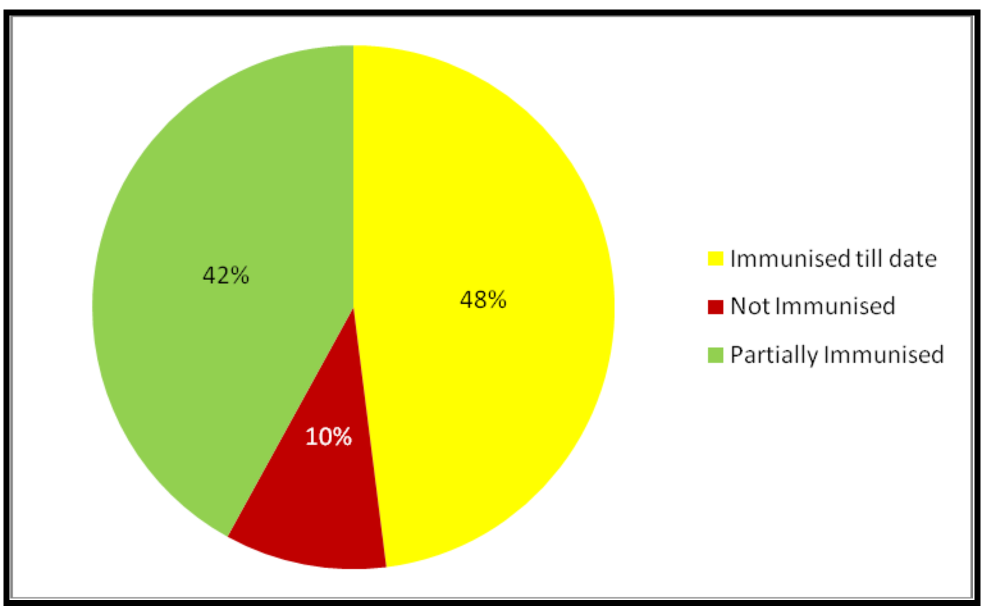


Table 14:-Distribution of patients according to Season of presentation

| Season of presentation | No. of patients | Percent |
|---|---|---|
| Summer | 23 | 46.0 |
| Monsoon | 5 | 10.0 |
| Winter | 22 | 44.0 |
| Total | 50 | 100.0 |

In this study among the total 50 patients, 23(46%) had their illness presented during summer, 22(44%) in winter, 5(10%) in monsoon

GRAPH 6: DISTRIBUTION OF PATIENTS ACCORDING TO THE SEASON OF PRESENTATION

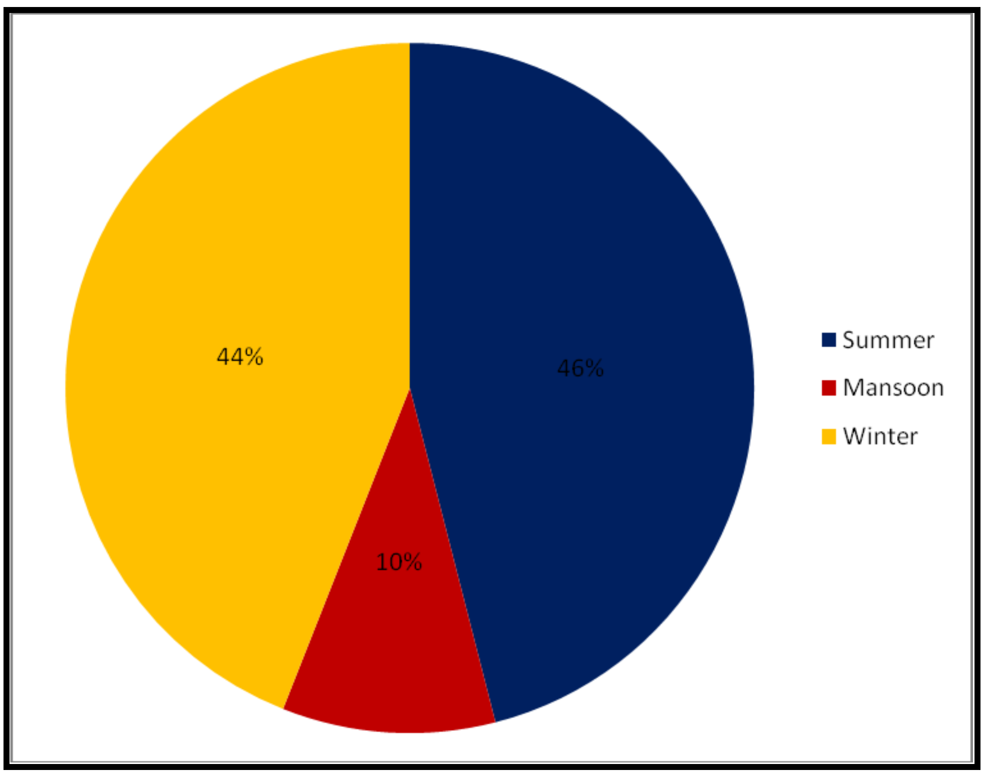


Table 15:-Association between Season of presentation and Serum vitamin D level

| Season | Vitamin D level | | | Total | Chi square test |
|---|---|---|---|---|---|
| | <20 | 20-30 | 30-100 | | |
| Summer | 14(43.8%) | 5(50.0%) | 4(50.0%) | 23(46.0%) | P=0.969 NS |
| Monsoon | 3(9.4%) | 1(10.0%) | 1(12.5%) | 5(10.0%) | |
| Winter | 15(46.9%) | 4(40.0%) | 3(37.5%) | 22(44.0%) | |
| Total | 32(100%) | 10(100%) | 8(100%) | 50(100%) | |

In the study, 46.9% cases of severe vitamin D deficiency presented in the winter, 43.8% cases presented in the summer and 9.4% cases presented in the winter months. Out of total 10 cases of Vitamin D insufficiency, 50% of cases presented during summer, 40% during winter and 10% during monsoon. Out of 8 sufficient level of Vitamin d 50% presented summer, 37.5% cases presented during winter and 12.5% cases presented in monsoon. But, there was no statistical signifance (p=0.969) between the season of presentation and vitamin D levels.

Graph 7: Association between Season of presentation and Serum vitamin D level

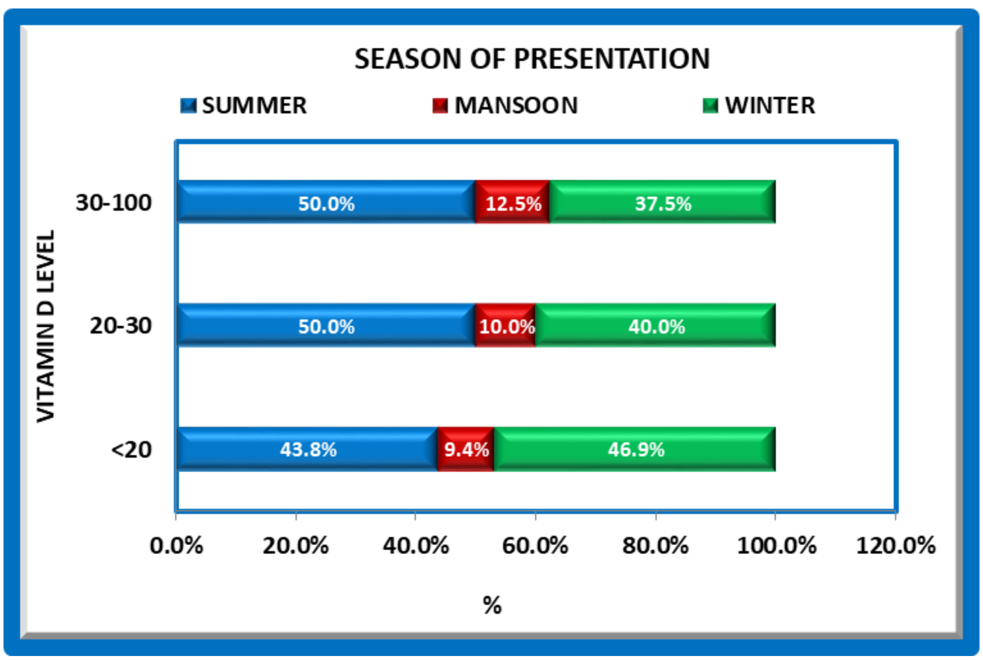


Table 16:-Distribution of patients according to No. of previous respiratory Illness

| No. of previous respiratory Illness | No. of patients | Percent |
|---|---|---|
| No past illness | 43 | 86.0 |
| 1-2 | 5 | 10.0 |
| >2 | 2 | 4.0 |
| Total | 50 | 100.0 |

In this study, 43 (84%) of cases had past history of respiratory illness and 5(10%) had 1-2 past history of respiratory illness and 2 (4%) cases had more than two past illness.

Graph 8:-Distribution of patients according to No. of previous respiratory Illness

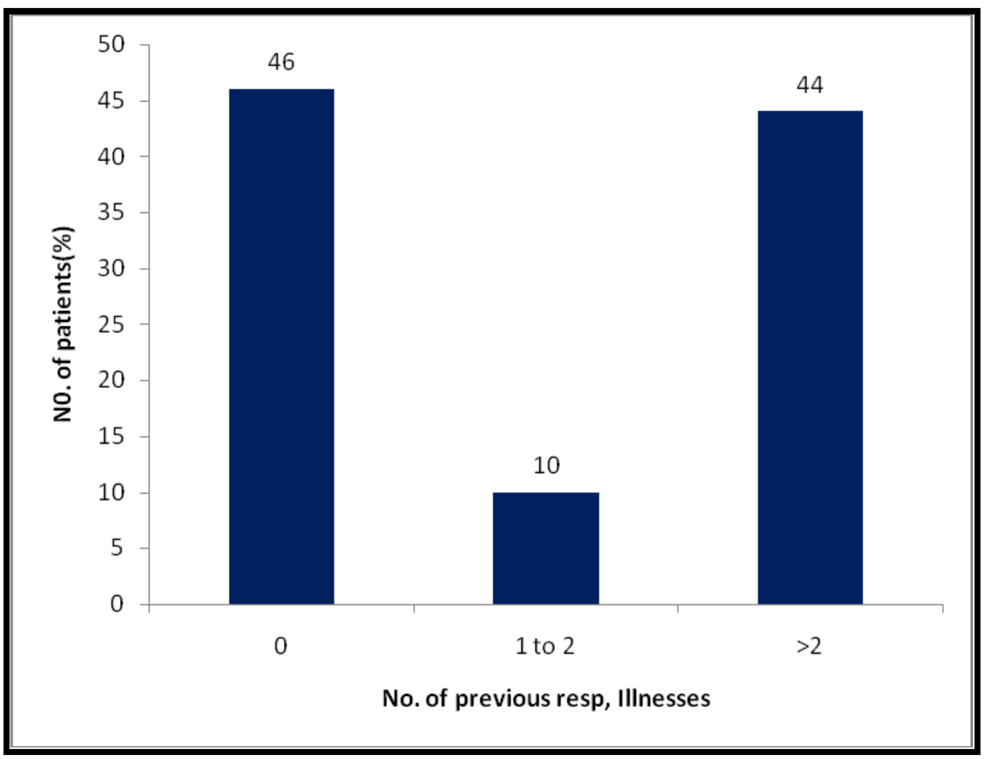


Table17 :-Association between No. Of previous respiratory illnesses and Serum vitamin D level

| No. Of previous respiratory illnesses | Vitamin D level | | | Total | Chi square test |
|---|---|---|---|---|---|
| | <20 | 20-30 | 30-100 | | |
| 0 | 26(81.3%) | 10(100.0%) | 7(87.5%) | 43(86.0%) | P=0.652 NS |
| 1-2 | 4(12.5%) | 0(.0%) | 1(12.5%) | 5(10.0%) | |
| >2 | 2(6.3%) | 0(.0%) | 0(.0%) | 2(4.0%) | |
| Total | 32(100%) | 10(100%) | 8(100%) | 50(100%) | |

From the above table, it is noted that p=0.652 which is not statistically significant. Hence there is no association between no.of respiratory illness and serum vitamin d levels which implies that respiratory illness occurs independent of Vitamin D levels in children.

Graph 9: Association between Number Of previous respiratory illnesses and Serum vitamin D level

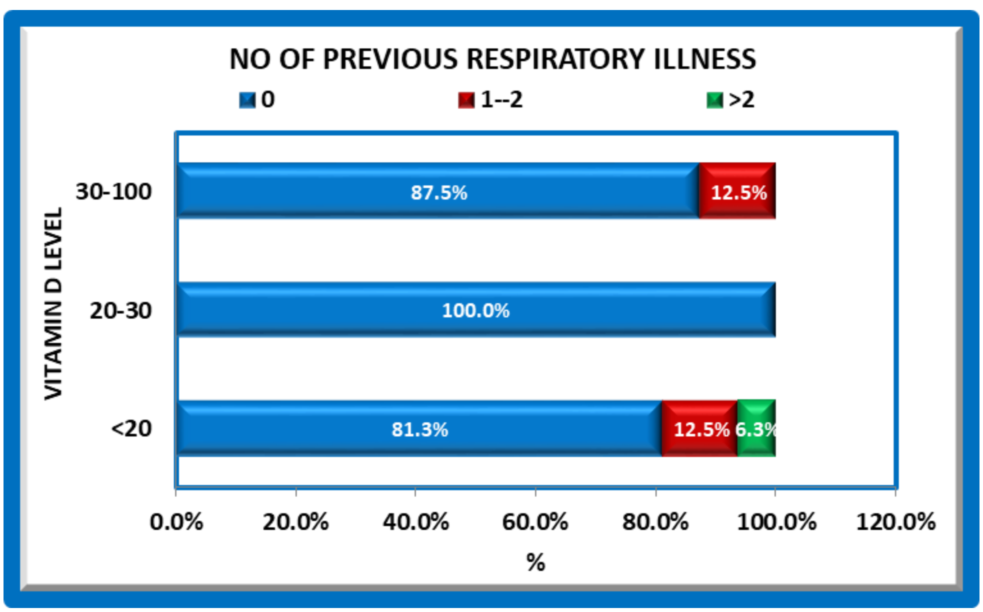


Table 18:-Distribution of patients according to Family history of respiratory Illness

| Family history of respiratory Illness | No. of patients | Percent |
|---|---|---|
| Yes | 1 | 2.0 |
| No | 49 | 98.0 |
| Total | 50 | 100.0 |

In the study population, only one case (2%) had family history of respiratory illness and 49 cases (98%) have no family history of respiratory illness.

Graph 10:-Distribution of patients according to Family history of respiratory Illness

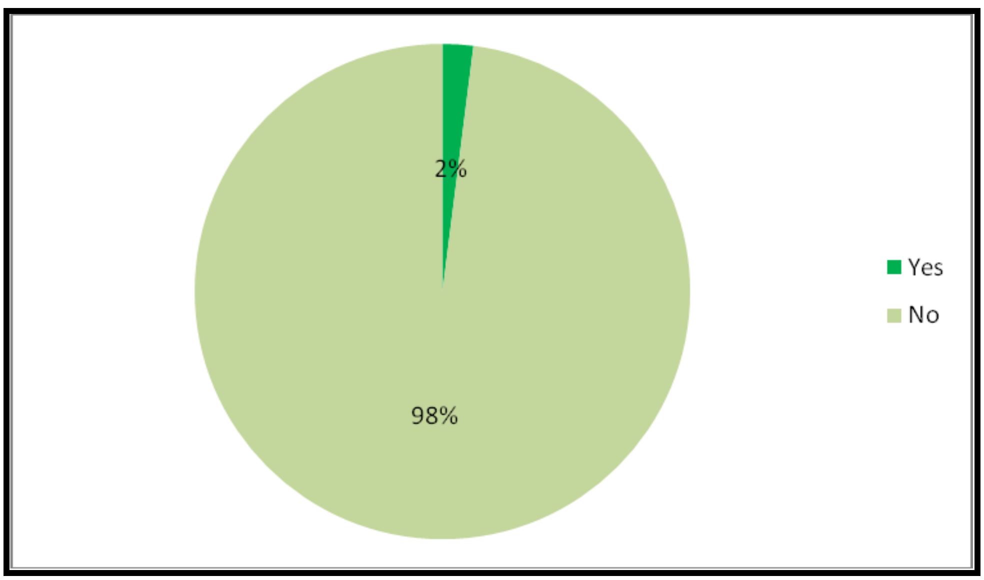


Table 19:-Association between Family H/O of Respiratory Illness and Serum vitamin D level

| Family H/O of Respiratory Illness | Vitamin D level | | | Total | Chi square test |
|---|---|---|---|---|---|
| | <20 | 20-30 | 30-100 | | |
| Yes | 1(3.1%) | 0(.0%) | 0(.0%) | 1(2.0%) | P=1.000 NS |
| No | 31(96.9%) | 10(100.0%) | 8(100.0%) | 49(98%) | |
| Total | 32(100%) | 10(100%) | 8(100%) | 50(100%) | |

From the above table, it is noted that p=1.000 which is not statistically significant. Hence there is no association between family history of respiratory illness and serum vitamin d levels.

Graph 11: Association between Family H/O of Respiratory Illness and Serum vitamin D level

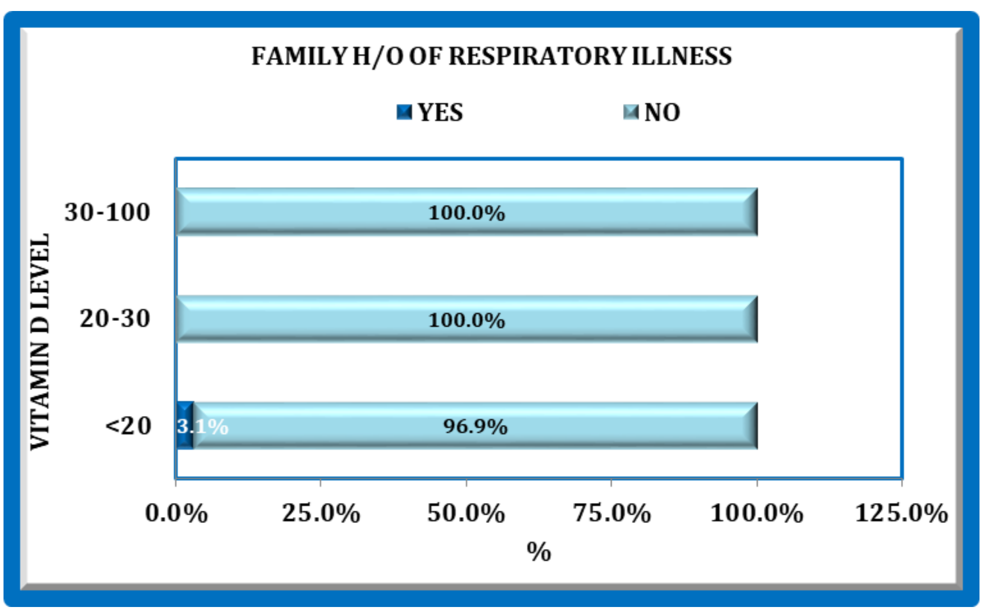


Table 20 :-Distribution of patients according to Socio Economic status

| Socio Economic status | No. of patients | Percent |
|---|---|---|
| Upper middle | 6 | 12.0 |
| Lower middle | 40 | 80.0 |
| Upper lower | 4 | 8.0 |
| Total | 50 | 100.0 |

The study population was divided on the basis of Kuppuswamy classification, the total of 6 (12%) of the cases in the upper middle socioeconomic strata,40 cases(80%) belonged to lower middle and 4 cases (8%) belonged to upper lower socioeconomic strata .

Graph 12: Distribution of patients according to Socio Economic status

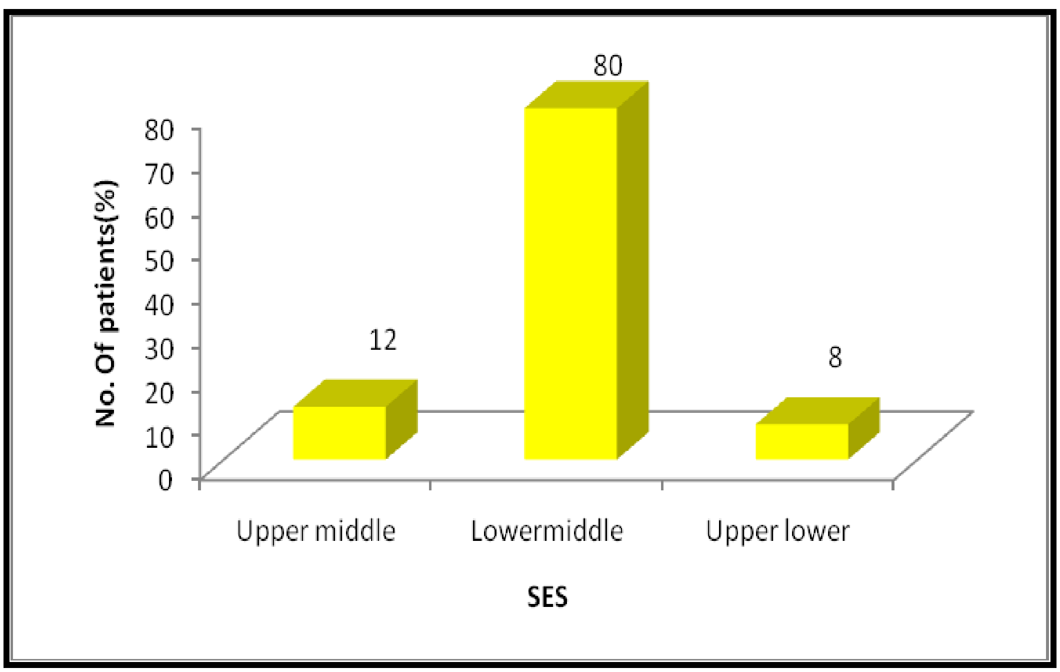


Table 21:-Association between Socio Economic Status and Serum vitamin D level

| Socio Economic Status | Vitamin D level | | | Total | Chi square test |
|---|---|---|---|---|---|
| | <20 | 20-30 | 30-100 | | |
| Upper middle | 5(15.6%) | 1(10.0%) | 0(.0%) | 6(12.0%) | P=0.690 NS |
| Lower middle | 24(75.0%) | 8(80.0%) | 8(100.0%) | 40(80.0%) | |
| Upper lower | 3(9.4%) | 1(10.0%) | 0(.0%) | 4(8.0%) | |
| Total | 32(100%) | 10(100%) | 8(100%) | 50(100%) | |

In the study, out of 32 cases severe Vitamin D deficiency cases, 75% of the children belonged to lower middle socioeconomic strata , while 15.6% in upper middle and 9.4% in upper lower class. In total of 10 cases of Vitamin D insufficiency, 80% belonged to lower middle and 10% each o upper middle and upper lower. Out of 8 cases in which vitamin D sufficiency was noted 80% belonged to lower middle, 12% belonged to upper middle and 8% belonged to upper lower. There was no statistical signifance (p=0.690) between the socioeconomic status distribution and vitamin D levels.

Graph 13:-Association between Socio Economic Status and Serum vitamin D level

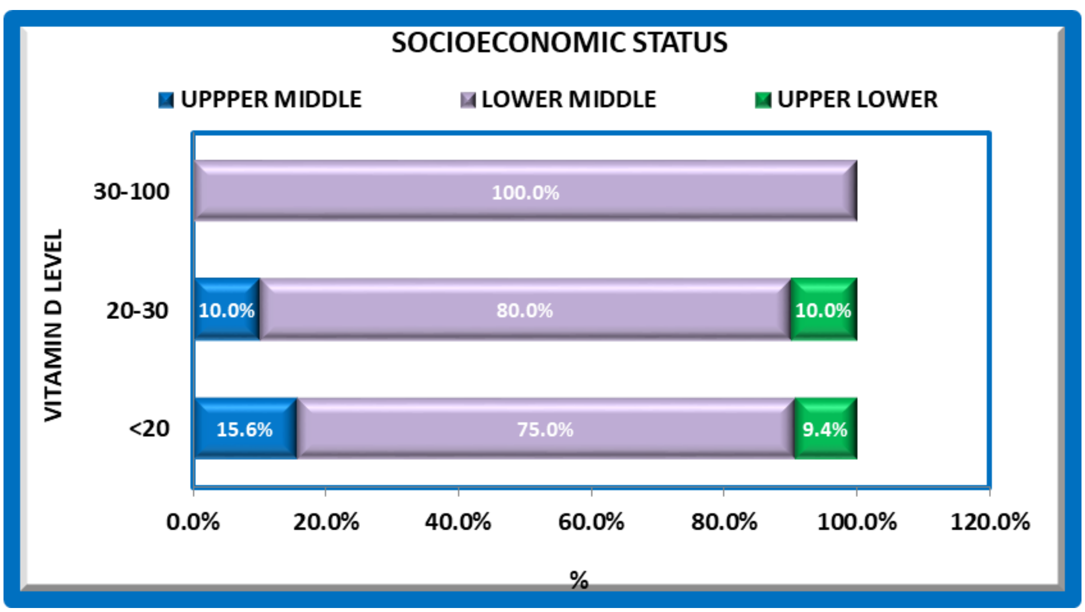


Table 22:-Distribution of patients according to Overcrowding

| Overcrowding | No. of patients | Percent |
|---|---|---|
| Yes | 7 | 14.0 |
| No | 43 | 86.0 |
| Total | 50 | 100.0 |

In the study population, 7 patients (14%) were living with overcrowding while rest cases, 43 patients (86%) had no overcrowded surroundings.

Graph 14: Distribution of patients according to Overcrowding

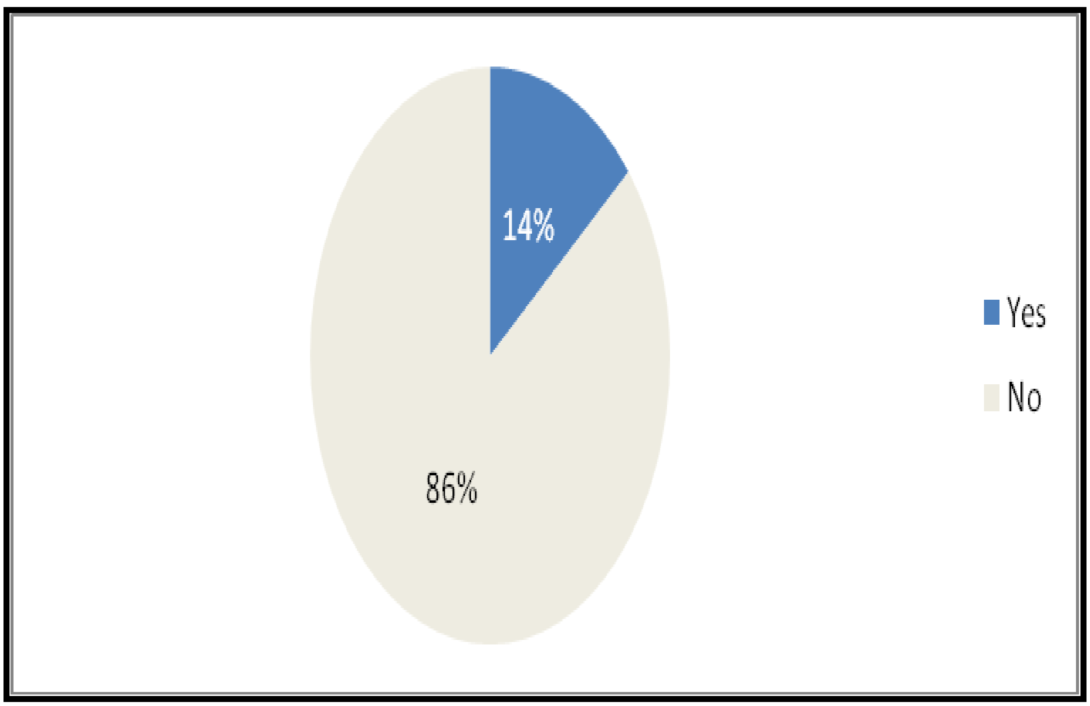


Table 23:-Association between Overcrowding and Serum vitamin D level

| Overcrowding | Vitamin D level | | | Total | Chi square test |
|---|---|---|---|---|---|
| | <20 | 20-30 | 30-100 | | |
| Yes | 7(21.9%) | 0(.0)0 | 0(.0%) | 7(14.0%) | P=1.000 |
| No | 25(78.1%) | 10(100.0%) | 8(100.0%) | 43(86.0%) | NS |
| Total | 32(100%) | 10(100%) | 8(100%) | 50(100%) | |

From the above table, it is noted that p=1.000 which is not statistically significant. Hence there is no association between Overcrowding and Serum vitamin D level

Graph 15:-Association between Overcrowding and Serum vitamin D level

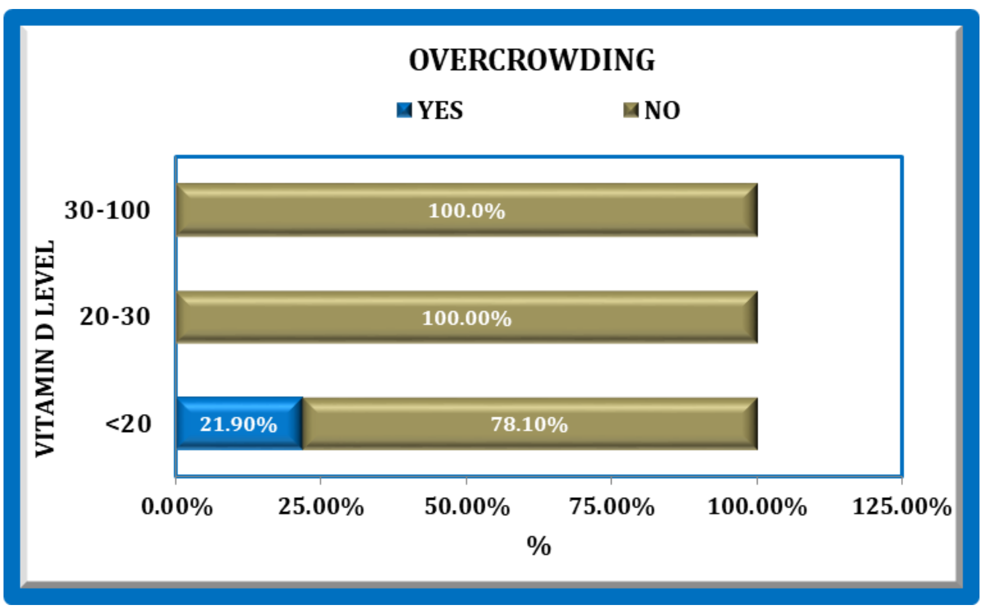


Table 24:-Distribution of patients according to Severity of respiratory illness.

| Severity | No. of patients | Percent |
|---|---|---|
| Mild | 14 | 28.0 |
| Moderate | 16 | 32.0 |
| Severe | 20 | 40.0 |
| Total | 50 | 100.0 |

Severity of respiratory illness for study population was graded according to Pediatric respiratory severity score, and according to this 14 patients (28%) had mild illness, 16 patients (32%) had moderate illness and remaining 20 patients (40 %) had severe illness.

Graph 16: Distribution of patients according to Severity

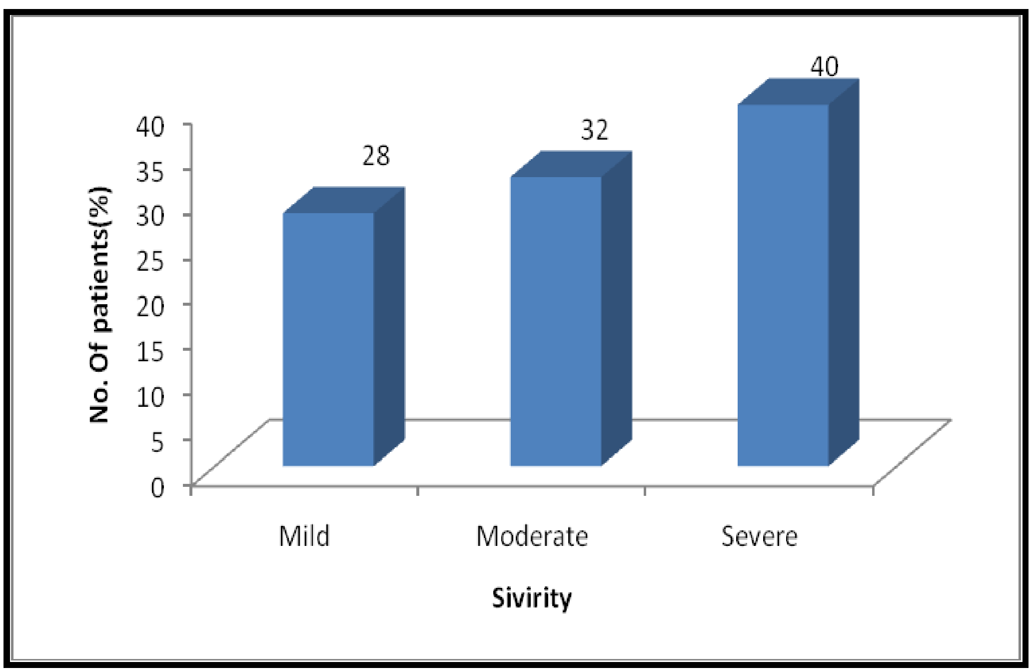


Table 25:-Association between Severity of respiratory illness and Serum vitamin D level

| Severity | Vitamin D level | | | Total | Chi square test |
|---|---|---|---|---|---|
| | <20 | 20-30 | 30-100 | | |
| Mild | 0(0%) | 8(80.0%) | 6(75.0%) | 14(28.0%) | P=0.0001* |
| Moderate | 12(37.5%) | 2(20.0%0 | 2(25.0%) | 16(32.0%) | |
| Sever | 20(62.5%) | 0(.0%) | 0(.0%) | 0(40.0%) | |
| Total | 32(100%) | 10(100%) | 8(100%) | 50(100%0 | |

Out of 32 severe Vitamin D deficiency was found , 62.5% had severe respiratory illness , 37.5% had moderate in severity respiratory illness while no cases had mild respiratory illness .Vitamin D insufficiency was found in total of 10 cases , out of which 80% of cases belonged to mild respiratory illness group and 20% cases belonged to moderate respiratory illness group with no severe respiratory cases .With Vitamin D sufficiency while only 25% cases had moderate illness and 75% cases had mild illness . There was very strong statistical signifance(p=0.0001 ) between severity and Vitamin D levels which highlights severe vitamin D deficiency patients have very severe respiratory illness. Hence the immunomodulatory effect of Vitamin D can be made out in our study.

Graph 17:-Association between Severity and Serum vitamin D level

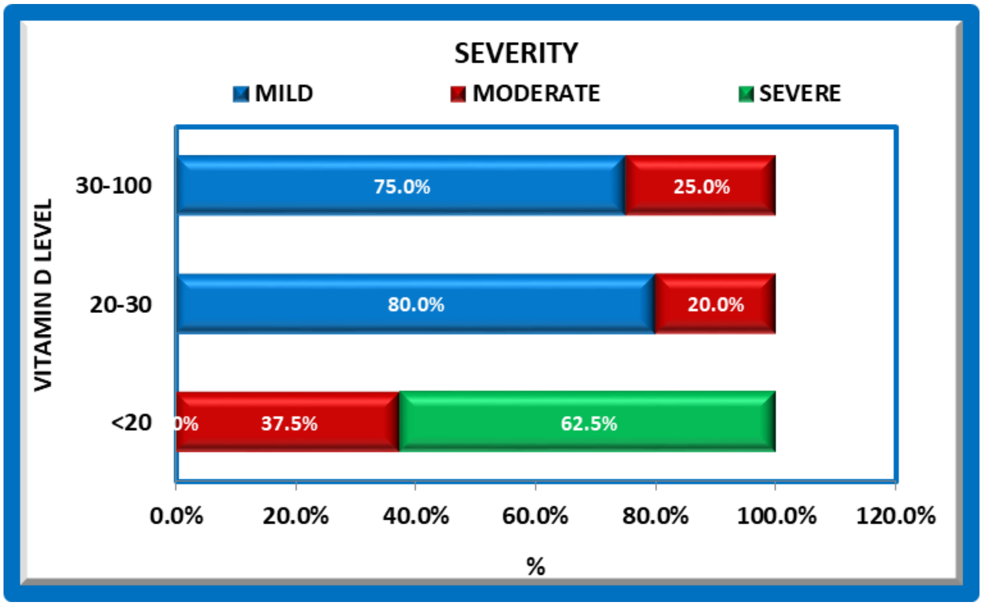


Table 26:-Distribution of patients according to Outcome

| **Outcome** | No. of patients | Percent |
|---|---|---|
| Improved | 45 | 90.0 |
| Death | 1 | 2.0 |
| AMA | 3 | 6.0 |
| Refer | 1 | 2.0 |
| Total | 50 | 100.0 |

Among the total number of cases admitted, 45patients (90%) improved, 3 cases (6%) had been discharged against medical advice. But these 3 cases (6%) had respiratory illness being completely cured. 1 case (2%) which was referred also had respiratory component being cured.

Total deaths noted in the study was only one (2%) which had severe respiratory illness and also deficiency of vitamin D levels.

Graph 18: Distribution of patients according to Outcome

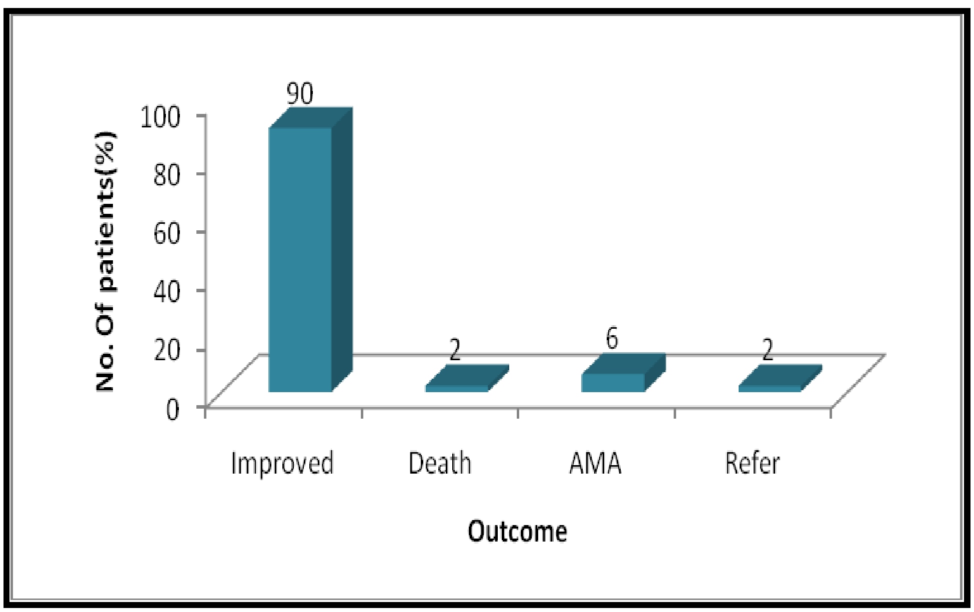
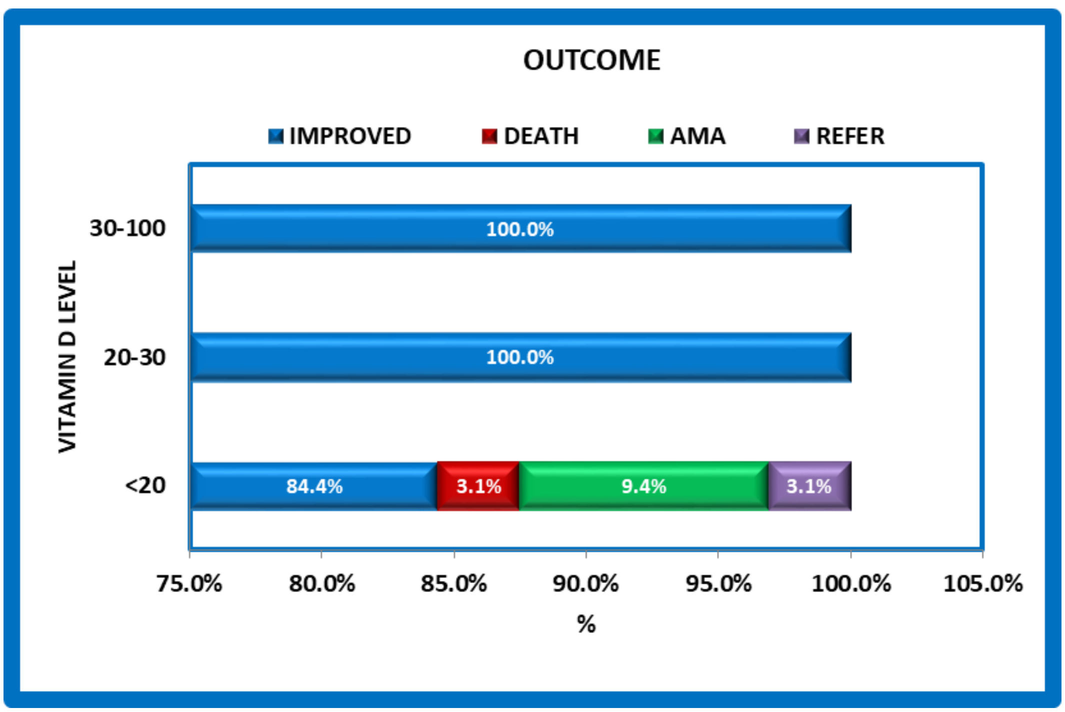


Table 27:-Association between Outcome and Serum vitamin D level

| Outcome | Vitamin D level | | | Total | Chi square test |
|---|---|---|---|---|---|
| | <20 | 20-30 | 30-100 | | |
| Improved | 27(84.4%) | 10(100.0%) | 8(100.0%) | 45(90.0%) | P=0.761 NS |
| Death | 1(3.1%) | 0(.0%) | 0(.0%) | 1(2.0%) | |
| AMA | 3(9.4%) | 0(.0%) | 0(.0%) | 3(6.0%) | |
| Refer | 1(3.1%) | 0(.0%) | 0(.0%) | 1(2.0%) | |
| Total | 32(100%) | 10(100%) | 8(100%) | 50(100%0 | |

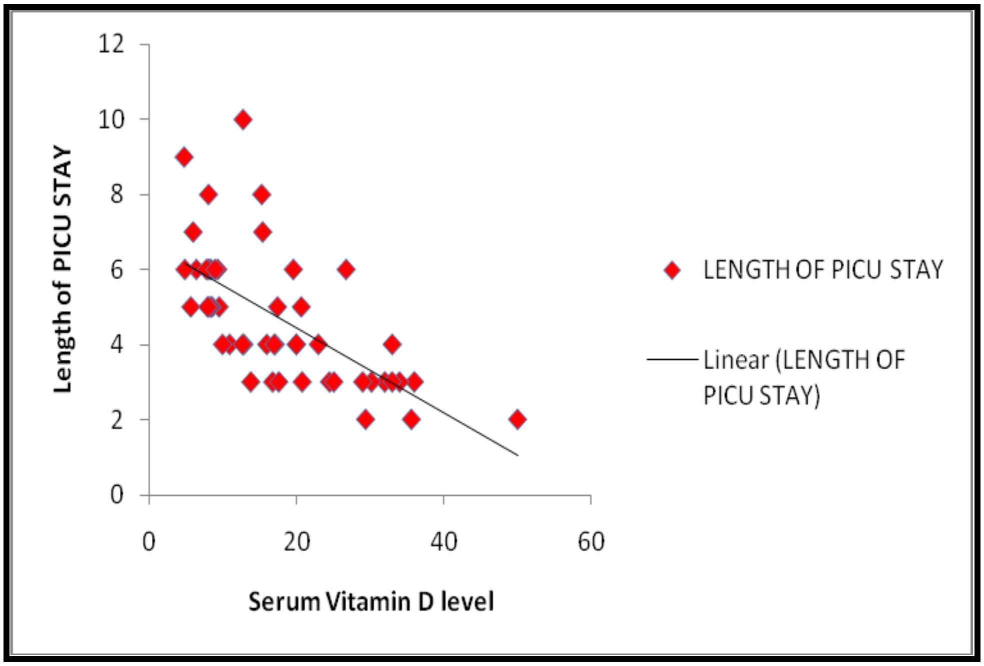
However it was found that there was no statistical significance (p=0.761) between the vitamin D levels and outcome.

Graph 19 :-Association between Outcome and Serum vitamin D level



## LENGTH OF PICU STAY

Graph 20 : Plot of length of PICU stay with serum levels of Vitamin D




The minimum duration of PICU stay is 2 days and maximum is10 days with mean duration of 4.70 with standard deviation of 1.799.

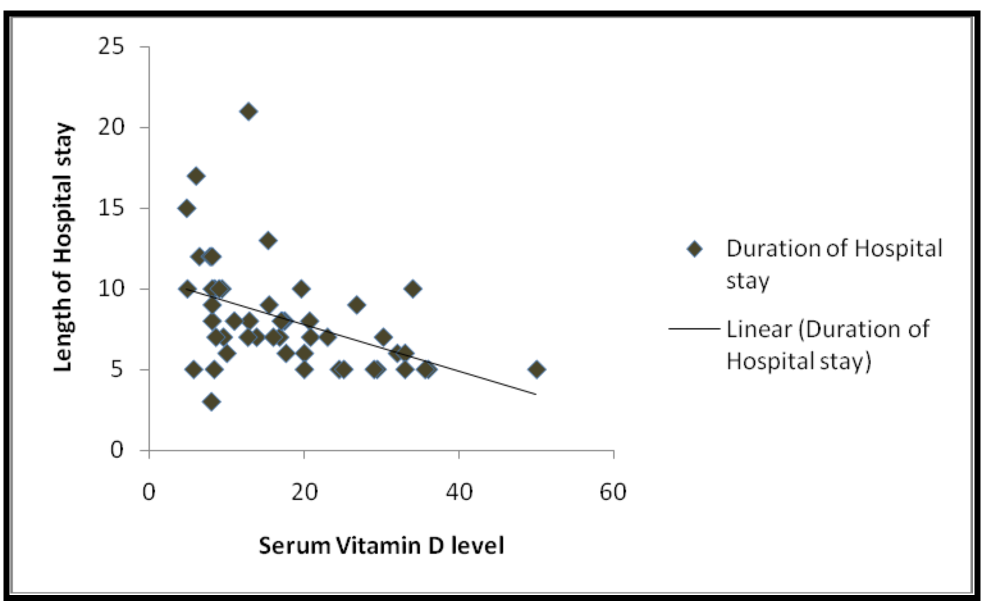
Table 28: Association between length of PICU stay and Serum vitamin D level

| LENGTH OF PICU STAY | VITAMIN D LEVEL CLASSIFICATION | | | | | |
|---|---|---|---|---|---|---|
| | <20 | | 20-30 | | 30-100 | |
| | Count | % | Count | % | Count | % |
| ≤5 | 17 | 53.1% | 9 | 90.0% | 8 | 100.0% |
| >5 | 15 | 46.9% | 1 | 10.0% | 0 | 0.00% |
| Total | 32 | 100.0% | 10 | 100.0% | 8 | 100.0% |
| Chi-square value = 9.24; **P= 0.01** | | | | | | |

Also with the grouping of above data, into of length of PICU stay into ≤5 days and >5 days, There was statistical significance (p=0.01) noted between the length of PICU stay and Vitamin D levels of the patient.

Length of Hospital Stay

Graph 21:association between length of hospital stay and serum vitamin D levels.



The minimum duration of hospital stay is 3 days and maximum is 21 days with mean duration of 8.12 with standard deviation of 3.366.

Table 29: Association between length of PICU stay and Serum vitamin D level

| LENGTH OF HOSPITAL STAY | VITAMIN D LEVEL CLASSIFICATION | | | | | |
|---|---|---|---|---|---|---|
| | <20 | | 20-30 | | 30-100 | |
| | Count | % | Count | % | Count | % |
| ≤ 5 | 3 | 9.4% | 5 | 50.0% | 4 | 50.0% |
| 6--10 | 22 | 68.8% | 5 | 50.0% | 4 | 50.0% |
| >10 | 7 | 21.9% | 0 | 0.00% | 0 | 0.00% |
| Total | 32 | 100.0% | 10 | 100.0% | 8 | 100.0% |
| Chi-square value = 12.51; **P= 0.014** | | | | | | |

Also with the grouping of above data, into of length of hospital stay into ≤5 days, 6-10 days and > 10 days, there was statistical significance (p=0.014) noted between the length of hospital stay and Vitamin D levels of the patient

Table 30:-Distribution of patients according to Type of Respiratory support

| **Type of Respiratory support** | No. of patients | Percent |
|---|---|---|
| Room Air | 10 | 20.0 |
| Oxygen therapy | 21 | 42.0 |
| CPAP | 15 | 30.0 |
| Ventilator | 4 | 8.0 |
| Total | 50 | 100.0 |

Among the total number of cases admitted, 10 (20%) cases did not require any respiratory support , while 21 cases ( 42%) required oxygen therapy , 15 cases (30%) were managed on CPAP and 4 cases (8%) required ventilator support

GRAPH 22: Distribution of patients according to type of respiratory support used

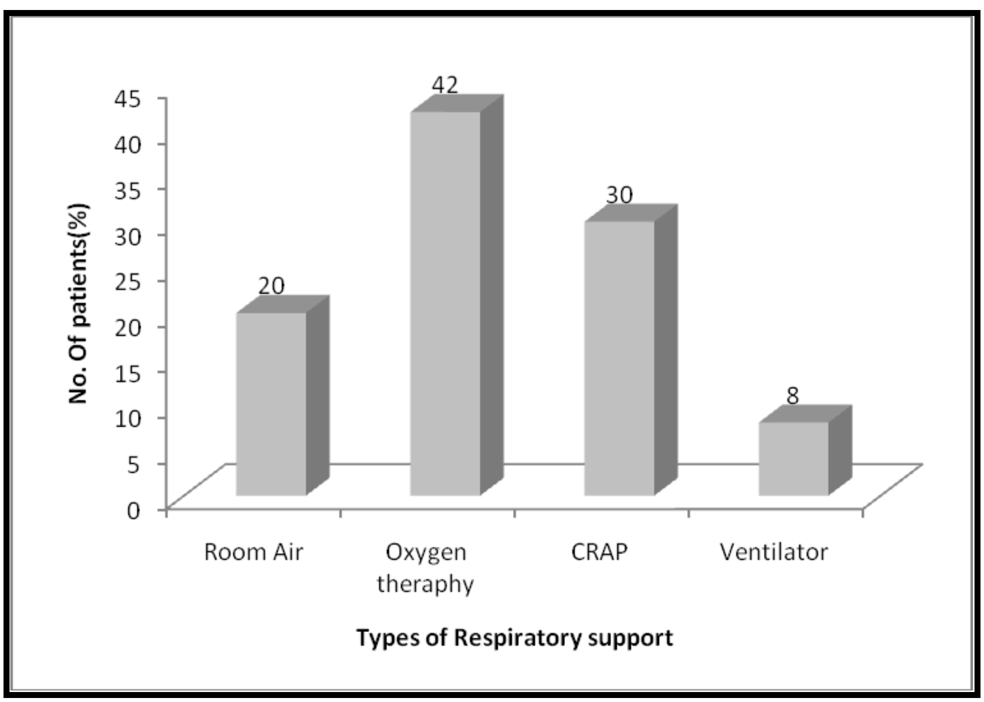


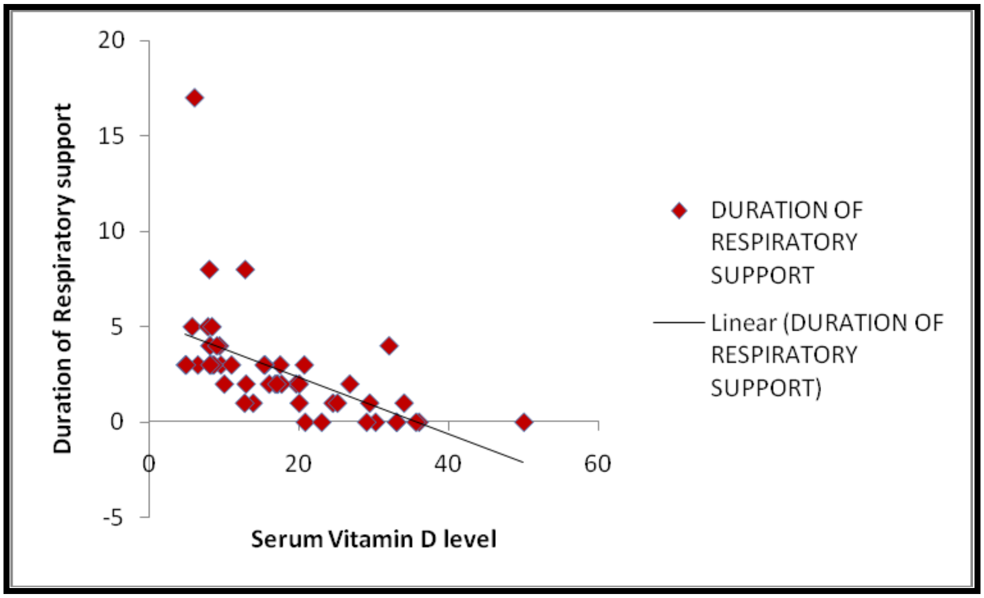
Table 31: association of type of respiratory support with Vitamin D levels

| TYPE OF RESPIRATORY SUPPPORT | VITAMIN D LEVEL CLASSIFICATION | | | | | |
|---|---|---|---|---|---|---|
| | <20ng/ml | | 20-30ng/ml | | 30-100ng/ml | |
| | Count | % | Count | % | Count | % |
| ROOM AIR | 0 | 0.00% | 4 | 40.0% | 6 | 75.0% |
| OYGEN THERAPHY | 15 | 46.9% | 4 | 40.0% | 2 | 25.0% |
| CPAP | 14 | 43.8% | 1 | 10.0% | 0 | 0.00% |
| VENTILATOR | 3 | 9.4% | 1 | 10.0% | 0 | 0.00% |
| Total | 32 | 100.0% | 10 | 100.0% | 8 | 100.0% |
| Chi-square value = 27.76; **P<0.001** | | | | | | |

Out of 32 severe Vitamin D deficiency was found, 9.4% required ventilator .43.8% cases required CPAP, 46.9% cases required oxygen therapy and none required room air. With Vitamin D sufficiency while only 10 % cases required ventilator, 10 % cases required CPAP, 40% cases required oxygen therapy and 40% cases required no respiratory support. In Vitamin D sufficiency group 75% cases required no respiratory support while only 25% cases required oxygen therapy and none required CPAP and ventilator.

Hence there was very strong statistical signifance ($p < 0.001$) between type of respiratory support and Vitamin D levels which highlights severe vitamin D deficiency patients have more requirement of respiratory support in the management of these patients.

Graph 23:-Distribution of patients according to Duration of Respiratory support




The minimum duration of respiratory support is 0 days and maximum is 17 days with mean duration of 2.68 days with standard deviation of 2.773.

Table 32: association between serum vitamin D levels and duration of respiratory support

Also with the grouping of above data , duration of respiratory support into 0 days, 1-3 days and > 3 days ,there was statistical significance (p<0.001) noted between the duration of respiratory support and Vitamin D levels of the patient

| DURATION OF RESPIRATORY SUPPORT | VITAMIN D LEVEL CLASSIFICATION | | | | | |
|---|---|---|---|---|---|---|
| | <20 | | 20-30 | | 30-100 | |
| | Count | % | Count | % | Count | % |
| 0 | 0 | 0.00% | 4 | 40.0% | 6 | 75.0% |
| 1—3 | 22 | 68.8% | 6 | 60.0% | 1 | 12.5% |
| >3 | 10 | 31.3% | 0 | 0.00% | 1 | 12.5% |
| Total | 32 | 100.0% | 10 | 100.0% | 8 | 100.0% |
| Chi-square value = 28.36; **P<0.001** | | | | | | |

# Non parametric correlations

Table 33: Correlation between length of PICU stay, length of Hospital stay and duration of respiratory support with Serum Vitamin D

| Correlation between | Spearman's Correlation coefficient (r) | P value |
|---|---|---|
| Serum vitamin D and Length of PICU stay | r=-0.738 | P=0.0001* |
| Serum vitamin D and Length of hospital stay | r=-0.512 | P=0.0001* |
| Serum vitamin D and Duration of Respiratory support | r=-0.784 | P=0.0001* |

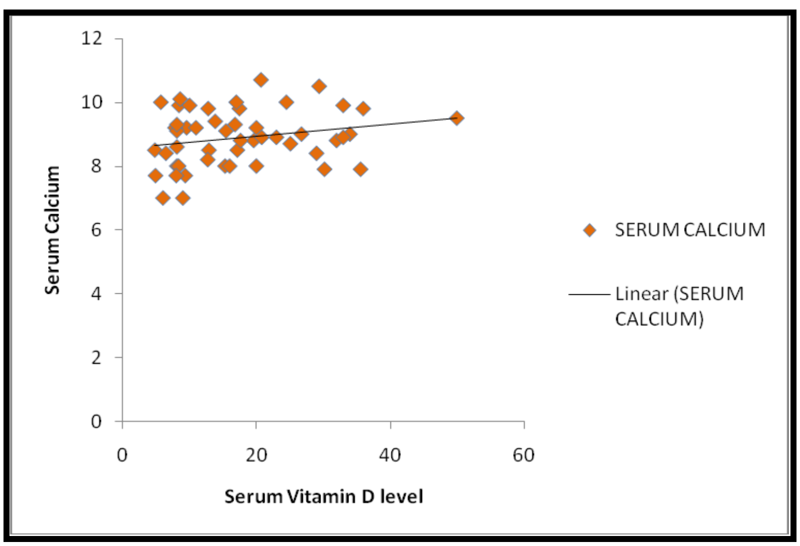
As with above Nonparametric Correlations table, applying Spearmen correlation coefficient (r), p values were seen significant with length of PICU stay ($p>0.01$), length of hospital stay ($p=0.014$), type of respiratory support ($<0.001$) and duration of respiratory support ($p<0.001$)

Table 34: Correlation between levels of serum calcium, serum phosphorous and serum alkaline phosphate with serum vitamin D.

| **Correlation between** | **Spearman's Correlation coefficient (r)** | **P value** |
|---|---|---|
| Serum vitamin D and Serum calcium | r=0.212 | P=0.140 NS |
| Serum vitamin D and Serum Phosphorous | r=-0.235 | P=0.101 NS |
| Serum vitamin D and Serum ALP | r=-0.318 | P=0.006* |

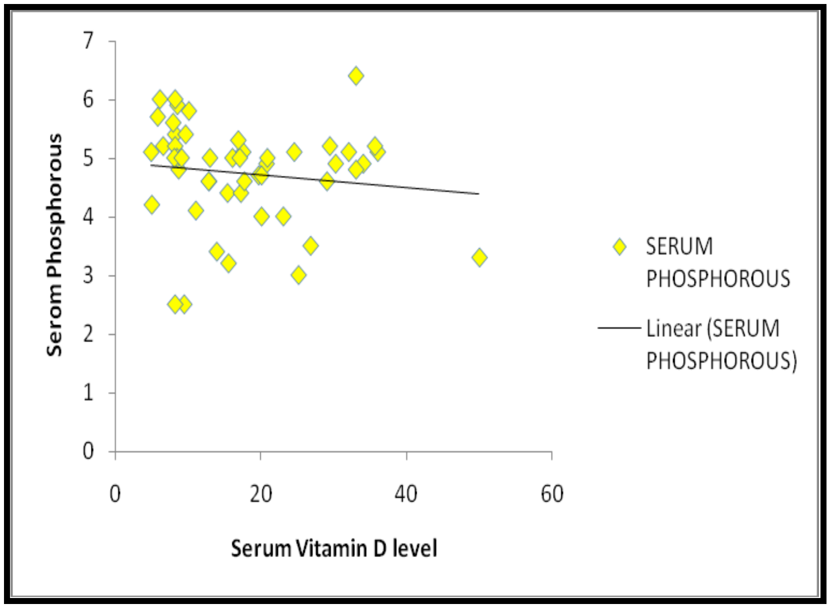
As with above Nonparametric Correlations table, applying Spearmen correlation coefficient (r), p values were seen significant with only serum alkaline phosphate (p=0.006) while serum calcium (p=0.140) and serum phosphorous (p=0.101) had no statistical significance.

Graph 24 :-Correlation between Serum Vitamin D level and Serum Calcium [r=0.212]



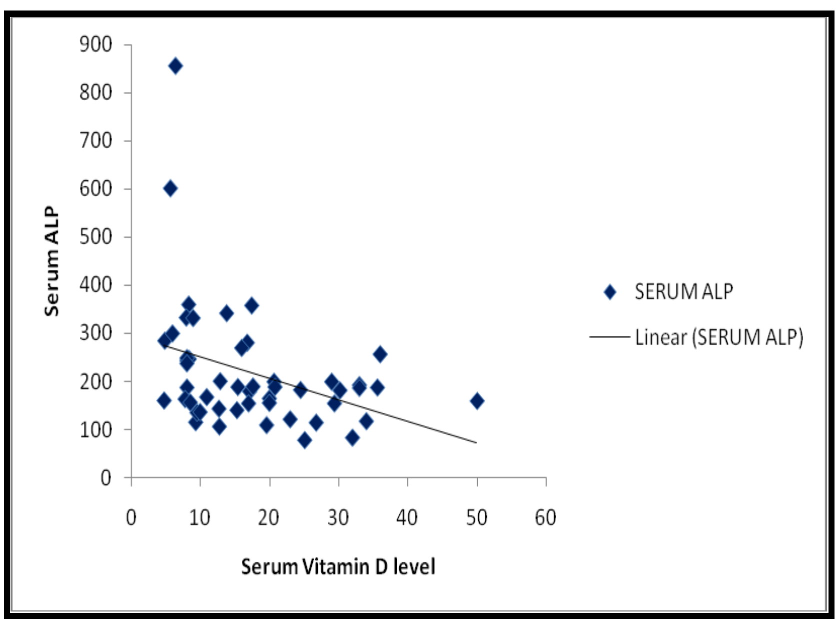
Graph 25:-Correlation between Serum Vitamin D level and Serum Phosphorous

r=-0.235




Graph 26:-Correlation between Serum Vitamin D level and Serum ALP

r=-0.318



## Multivariate analysis of confounders

Table 35: Multivariate analysis of confounders and Vitamin D deficiency among Respiratory Illnesses Children

| **Confounders** | **Vitamin D level** | |
|---|---|---|
| | **<30ng/ml** | **>30ng/ml** |
| | **OR** | **95% CI** |
| **Severity** | | |
| Mild | Ref | |
| Moderate | 1.333 | 0.463-3.843 |
| Severe | 7.00 | 1.591-30.800 |
| **Length of PICU stay** | | |
| <5 | Ref | |
| 5+ | 4.010 | 2.119-7.588 |
| **Length of Hospital stay** | | |
| <10 | ref | |
| 10+ | 4.143 | 1.815-9.457 |
| **Duration of Respiratory support** | | |
| <10 | ref | |
| 10+ | 5.125 | 2.403-10.932 |
| | | |

Multivariable log-transformed linear regression analysis verified that VDI patients had more severity ( 7 times more severe compared to milder group ; 95% CI: 1.591-30.800) longer duration of intensive care management ( more than 5 days longer 4 times ref, 95% CI: 2.119-7.588) and hospital stay (more than 10 days longer in 4.14 times ref , 95% CI: 1.815-9.457) and duration of respiratory support (more than 10 days longer in 5.12 times ref , 95% CI: 2.403-10.932) compared to Vitamin d sufficient subjects

# DISCUSSION

# DISCUSSION

There is paucity of published studies in the Indian literature related to serum vitamin D deficiency prevalence among children less than 15 years with acute respiratory illness admitted to pediatric intensive care unit (PICU).In our study out of 50 respiratory cases, 64 % cases had severe Vitamin D deficiency (<20 ng/ml) and 20 % had Vitamin D (insufficiency) with total prevalence being 84% which was comparable to case group of other studies.

| Sl no. | Study | %Prevalence |
|---|---|---|
| 1 | Wayse et al[35] | 80% |
| 2 | Roth et al[36] | 84% |
| 3 | Albanna et al[82] | 77.5% |
| 4 | Karatekin et al[83] | 92% |
| 5 | Our study | 84% |

Similarly mean Vitamin D noted in our study was 17.56 ng/ml which is comparable with other studies

| Sl no. | Study | Mean Vitamin D(ng/ml) |
|---|---|---|
| 1 | Wayse et al[35] | 16.8 |
| 2 | Roth et al[36] | 11.6 |
| 3 | Albanna et al[82] | 15.2 |
| 4 | Karatekin et al[83] | 9.2 |
| 5 | Our study | 17.56 |

The present study was planned to determine the serum vitamin D status in critically ill patients with respiratory illness admitted to PICU and to correlate the serum vitamin D status with clinical outcomes, length of PICU stay, and total length of hospital stay, type and duration of respiratory support. Though some other factors like season of presentation, history of past respiratory illness, family history of respiratory illness, overcrowding and socioeconomic details were also considered in the study a total of 50 children were studied with age group from 1 month to 14 years.

**Season of presentation and Serum vitamin D level**

The season during presentation can also be the factor for variation in serum vitamin D levels. Belderbos et al [84] reported that 25(OH) D levels had a seasonal distribution. They noticed a positive correlation between cord blood 25(OH)D level and monthly sun hours exposure (r = 0.196, p = .01). Differing seasons could also explain differences in their finding . For example, four studies were conducted during winter months ( Karatekin et al.,[83]; Roth et al [36]; Roth et al.[37]). During the winter, cases' vitamin D levels were likely affected by the lack of sunlight. This situation could be a confounding factor but it was not observed in our study as our study was done over span of one and half year where presentation during all seasons were reported .But still season of presentation have statistical significance with serum Vitamin D levels ,

Similarly other factors like of past respiratory illness, family history of respiratory illness, overcrowding and socioeconomic details had no Statistical significance with serum Vitamin D

**Vitamin D status and severity of respiratory illness:**

From the above table(25), it was found that association between serum levels of vitamin D and Severity of respiratory illness according to Pediatric respiratory severity score was statistically highly significant. Our study involved the children who were admitted in pediatric intensive care unit with respiratory illness like bronchiolitis, croup, bronchopneumonia, empyema, tuberculosis (table 11).

**Studies which investigated the role of vitamin D in the severity of respiratory illness in children.**

- In a case-control study in India, Wayse et al (2004) found that low serum 25(OH)D levels was associated with a significantly lower risk of severe ALRI.[35]
- In a study of 152 children younger than 59 months of age with pneumonia at Al-Sabeen hospital in Sana'a, Yemen,VDD was an independent predictor of persistent hypoxemia for children admitted with pneumonia ($p = .021$)[67].
- Inamo and colleagues (2011) studied 28 infants in Tokyo, Japan, and found that, compared with infants who had 25(OH)D levels of 6 ng/ml or more, infants with 25(OH)D levels of < 4 ng/ml were significantly more likely to need supplementary oxygen and ventilator management ($p < .01$)[39].
- McNally and colleagues (2009), found that children with ALRI in a Canadian paediatric intensive care unit had significantly lower vitamin D levels than did control subjects, who were children hospitalized for something other than ALRI. These studies suggest that VDD might increase the severity of a respiratory

infection and that infants and children with VDD and ALRI might require higher levels of care than children with sufficient vitamin D levels [38].

**Serum vitamin D level and length of PICU stay**

The mean duration of PICU stay in this study is 4.70 days with total hospital stay duration being 8.12 days. There is statistical significance between length of PICU stay, duration of total hospital stay and serum vitamin D levels of the patient with p value being 0.014 and 0.01 respectively.

In the study done by Sankar at all, similar observations were seen with the length of PICU stay being longer in children with vitamin D deficiency with a mean difference in PICU stay of 3.5 days as compared to those who were no deficient [8]. On the other hand, the study done by Rippel et al concluded that hypovitaminosis D is associated with higher morbidity but not with the length of hospital stay.[72]

**Serum vitamin D levels and type of respiratory support:**

In our study, among the 50 patients, 80% of the cases required respiratory support in the form of oxygen by nasal prongs, CPAP or invasive ventilation. The mean duration of respiratory support was 2.78 days. A strong statistical significance was noted with $p<0.001$. In the study done by inamo et al, children with acute lower respiratory infections who needed oxygen and ventilator management were significantly vitamin D deficient [39].

Ebenezer K et al., in their prospective observational study done in south India among 54 critically ill Vitamin D deficient children concluded that Vitamin D deficiency was associated with higher severity of illness, need for mechanical ventilation and more vasopressor use (78).

**Serum Vitamin D and other biochemical parameters**

In our study we also assessed for serum calcium, serum phosphorus and serum alkaline phosphate, but it was found that serum vitamin D levels did not have statistical significant correlation with serum calcium and serum phosphorous. This was inconsistent with other studies like Geng et al where a positive correlation was found between the serum concentration of calcium and 25(OH) D, revealing that Vitamin D deficiency can reduce the absorption of calcium. Vitamin D has also been reported to promote the absorption of phosphorous in the gastrointestinal tract.[85] However, no significant associations of the 25(OH)D concentration with the levels of phosphorous also was found in this study. The result was consistent with other studies conducted in New Zealand and California. [86, 87]

In our study Serum Vitamin D levels significant correlation with Serum alkaline phosphate which was similar in the study by Khan et al ,in their study , high levels of serum alkaline phosphatase were found in children who had wheezing and was inversely correlated with serum vitamin D levels [88]

# **CONCLUSION**

## CONCLUSION

- This study shows that there is a strong correlation between the severity of respiratory illness and serum vitamin D status.
- There is a positive correlation between the duration of hospital stay with serum vitamin D levels.
- The need and duration of respiratory support is seen to be higher among children with low levels of serum vitamin D.

**Limitation of the study:**

- Wide range of age of the study group could have affected the results of serum vitamin D levels.
- The factors affecting the vitamin D levels were not addressed.
- Several other factors which affect the length of PICU stay like sepsis, requirement of inotrophes were not taken into consideration.

# SUMMARY

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# SUMMARY

- This is a hospital based cross sectional study
- Mean age group of this study is 38 months.
- Mean serum vitamin d levels among the study group is 17.56 ng/ml
- Mean length of PICU stay is 4.7 days and mean total hospital stay being 8.12 days
- In this study, the mean duration of respiratory support is 2.68 days
- Among the total number of study group , 64% of them have severe vitamin D deficiency, 20% have insufficient vitamin D levels and only 16% of cases have normal vitamin D levels.
- Vitamin D levels have strong statistical significance with severity of respiratory illness
- Also, vitamin D levels have statistical significance with length of hospital stay and type and duration of respiratory support
- Vitamin D levels have significant correlation with serum alkaline phosphatase levels.

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# REFERENCES


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# ANNEXURES

**ANNEXURE-I**

Institutional Ethical Committee
BIJAPUR-586 103.
OUTWARD
No. 63/17
Date 27/2/17
B.L.D.E. U's Shri B.M. Patil Medical College

*B.L.D.E. UNIVERSITY'S*

**SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103**

INSTITUTIONAL ETHICAL COMMITTEE

***INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE***

*The Ethical Committee of this college met on* 22-02-2017 *at* 3:30pm *to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.*

*Title* Serum Vitamin D status and out-come among critically ill children with respiratory infectious disease admitted to the pediatric ~~[illegible]~~ intensive care unit.

*Name of P.G. student* Dr Sanjeevani Mahesh Kumar Umarani

*Name of Guide/Co-investigator Dr* Dr. S.S. Kalyanshettar
Professor, Dept of Pediatrics.

DR.TEJASWINI. VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR

Institutional Ethical Committee
BLDEU's Shri B.M. Patil
Medical College, BIJAPUR-586103.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

**Modified Kuppuswamy classification**** : socioeconomic classification was done according to modified Kuppuswamy classification .

| | | | | |
|---|---|---|---|---|
| **(A) Education Score** | | | | |
| 1 | Professional or Honors | 4 | | |
| 2 | Graduate or Post Graduate | 3 | | |
| 3 | High school or Intermediate or Diploma | 2 | | |
| 4 | Illiterate or Primary school | 1 | | |
| **(B)** | **Occupation Score** | | | |
| 1 | Legislators, Senior Officials, and Managers | 13 | | |
| 2 | Professionals | 11 | | |
| 3 | Technicians and Associate Professionals | 9 | | |
| 4 | Clerks | 7 | | |
| 5 | Service Workers and Shop and Market Sales Workers | 6 | | |
| 6 | Skilled Agricultural and Fishery Workers | 5 | | |
| 7 | Craft and Related Trades Workers | 4 | | |
| 8 | Plant and Machine Operators and Assemblers | 3 | | |
| 9 | Unskilled worker | 2 | | |
| 10 | Unemployed | 1 | | |
| **(C) Monthly family income in ₹** | | **Score** | **Modified for 1998[3] in ₹** | **Modified for 2012 in ₹** |
| 1 | ≥2,000 | 12 | ≥13,500 | ≥32,050 |
| 2 | 1,000-1,999 | 10 | 6,750-13,499 | 16,020-32,049 |
| 3 | 750-999 | 6 | 5,050-6,749 | 12,020-16,019 |
| 4 | 500-749 | 4 | 3,375-5,049 | 8,010-12,019 |
| 5 | 300-499 | 3 | 2,025-3,374 | 4,810-8,009 |
| 6 | 101-299 | 2 | 676-2,024 | 1,601-4,809 |
| 7 | ≤100 | 1 | ≤675 | ≤1,600 |
| **Total Score** | | | **Socioeconomic class** | |
| 26-29 | | | Upper (I) | |
| 16-25 | | | Upper Middle (II) | |
| 11-15 | | | Middle/Lower middle (III) | |
| 5-10 | | | Lower/Upper lower (IV) | |
| <5 | | | Lower (V) | |

**Overcrowding****: overcrowding is considered to exist if two over age of 9 years (not husband and wife) of opposite are obliged to sleep in the same room.

**ANNEXURE-II**

**RESEARCH INFORMED CONSENT FORM**

**BLDEA's Shri B.M.PATIL Medical College, Hospital & Research Centre, VIJAYAPURA-586103.**

**TITLE OF THE PROJECT : "SERUM VITAMIN D STATUS AND OUTCOME AMONG CRITICALLY ILL CHILDREN ADMITTED TO THE PEDIATRIC INTENSIVE CARE UNIT"**

**GUIDE : Dr. S. S KALYANSHETTAR, MD**
**PROFESSOR**
**DEPARTMENT OF PEDIATRICS.**

**PG STUDENT : DR. SANJEEVANI M UMARANI**

**PURPOSE OF RESEARCH:**

I have been informed that the present study will help in estimating the levels of vitamin d and correlation with the clinical outcomes of all the cases admitted in PICU

**PROCEDURE:**

I understand that after having obtained a detailed clinical history, thorough clinical examination and relevant investigations, the role of vitamin D in critically ill children is established.

**RISK AND DISCOMFORTS:**

Since this study is a observational study and no an interventional study, it involves no harms, risks and discomforts.

**BENEFITS:**

I understand that my participation in the study will have no direct benefit to me other than the potential benefit for the research.

**CONFIDENTIALITY:**

I understand that the medical information produced by this study will become a part of hospital records and will be subject to the confidentiality. Information of sensitive personal nature will not be part of the medical record, but will be stored in the investigations research file.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs will be used only with special written permission. I understand that I may see the photograph before giving the permission.

**REQUEST FOR MORE INFORMATION:**

I understand that I may ask more questions about the study at any time;
Dr.Sanjeevani maheshkumar umarani at the department of Pediatrics is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation. A copy of this consent form will be given to me to keep for careful reading.

**REFUSAL FOR WITHDRAWAL OF PARTICIPATION:**

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice. I also understand that Dr.Sanjeevani Maheshkumar umarani may terminate my participation in the study after he has explained the reasons for doing so.

**INJURY STATEMENT:**

I understand that in the unlikely event of injury to my baby resulting directly from baby's participation in this study, if such injury were reported promptly, the appropriate treatment would be available to the baby. But, no further compensation would be provided by the hospital. I understand that by my agreements to participate in this study and not waiving any of my legal rights.

I have explained to ______________________________the purpose of the research, the procedures required and the possible risks to the best of my ability.

_____________________ _____________________

Dr. Sanjeevani Maheshkumar umarani

Date

(Investigator)

**PARENTS / GUARDIAN CONSENT STATEMENT:**

We confirm that Dr. Sanjeevani Maheshkumar Umarani, is doing a study on "Serum vitamin D status and outcome among children admitted to the Pediatric Intensive Care Unit in Shri B. M patil Medical College and Hospital". I Dr Sanjeevani

Maheshkumar Umarani, has explained to us the purpose of research and the study procedure. We are willing to give as much as information required for the study and consent for investigations and the possible discomforts as well as benefits. We have been explained all the above in detail in our own language and we understand the same. Therefore we agree to give consent for child's participate as a subject in this research project.

____________________________ __________________________

( Parents / Guardian) Date

_______________________________ ___________________________

(Witness to signature) Date

**ಪಾಲಕರು / ಪೋಷಕರು ಒಪ್ಪಿಗೆಯನ್ನು ಸೂಚಿಸುವ ಹೇಳಿಕೆ:**

ನಾನು/ನಾವು ಈ ಮೂಲಕ ಧೃಡ ಪಡಿಸುವುದೇನೆಂದರೆ, ಡಾ. ಸಂಜೀವಿನಿ ಉಮರಾನಿ ಅವರು **"SERUM VITAMIN D STATUS AND OUTCOME AMONG CRITICALLY ILL CHILDREN WITH RESPIRATORY INFECTIOUS DISEASE ADMITTED TO THE PEDIATRIC INTENSIVE CARE UNIT"** ವಿಷಯದ ಮೇಲೆ ಅಧ್ಯಯನಮಾಡುತಿದ್ದಾರೆ.

ಡಾ. ಸಂಜೀವಿನಿ ಉಮರಾನಿ ರವರು ನಮಗೆ ಈ ವಿಷಯದ ಕುರಿತು ಸಂಶೋಧನೆ ನಡೆಸುವ ಉದ್ದೇಶ ಹಾಗು ಅಧ್ಯಯನದ ಕಾರ್ಯಪದ್ಧತಿ ಬಗ್ಗೆ ವಿವತಿಸಿರುತ್ತಾರೆ. ನಾನು / ನಾವು ಈ ಅಧ್ಯಯನದಸಲುವಾಗಿ ಅವಶ್ಯಕವಿರುವ ಮಾಹಿತಿಗಳನ್ನು ಎಷ್ಟು ಸಾಧ್ಯವೋ ಅಷ್ಟೂ ಮಾಹಿತಿ ನೀಡಲು ಹಾಗು ಈ ಅಧ್ಯಯನದಿಂದ ಆಗಬುಹುದಾದ ತೊಂದರೆಗಳು ಹಾಗು ಲಾಭಗಳ ಕುರಿತು ಪತ್ತೆ ಹಚ್ಚಲು ಅವಶ್ಯಕ ಮಾಹಿತಿಗಳನ್ನು ನೀಡಲು ನಮ್ಮ ಸಮ್ಮತಿ ಇರುತ್ತದೆ. ನನಗೆ /ನಮಗೆ ಮೇಲೆ ತಿಳಿಸಿದ ಅಧ್ಯಯನದ ಕುರಿತು ಎಲ್ಲ ಮಾಹಿತಿಗಳನ್ನು ನಮ್ಮ ಮಾತೃಭಾಷೆಯಲ್ಲಿ ವಿವರಿಸಿದ್ದು, ನಾವು ಇದನ್ನು ಅರ್ಥಮಾಡಿ ಕೊಂಡಿದ್ದೇವೆ. ಆದ್ದರಿಂದ ನಾವು ಈ ಸಂಶೋಧನೆಯಲ್ಲಿನ ಒಂದು ವಿಷಯವಾಗಿ ನಮ್ಮ ಮಗುವಿನ ಭಾಗವಹಿಸುವಿಕೆಯ ಕುರಿತು ಸಮ್ಮತಿಯನ್ನು ನೀಡಿರುತ್ತೇವೆ.

____________________ ____________________

(ತಂದೆತಾಯಿಗಳು / ಪೋಷಕರು) ದಿನಾಂಕ

____________________ ____________________

ಸಾಕ್ಷಿದಾರರ ಸಹಿ ದಿನಾಂಕ

**ANNEXURE-III**

# PROFORMA

NAME:

AGE/SEX:

IP NO:

ADDRESS AND PHONE NUMBER:

DATE OF ADMISSION:

DATE OF DISCHARE/ DEATH:

PRESENTATION AT ADMISSION:

SIGNIFICANT PAST HISTORY:

FAMILY HISTORY OF RESPIRATORY ILLNESS:

IMMUNISATION STATUS:

SOCIOECONOMIC STATUS:

ANTHROPOMETRY:

PRESS SCORE:

| Score component | Operational definition | | Scoring |
|---|---|---|---|
| Respiratory rate | Respiratory rate at rest, on room air* | | 0 or 1 |
| Wheezing | High pitched expiratory sound heard by auscultation | | 0 or 1 |
| Accessory muscle use | Any visible use of accessory muscles | | 0 or 1 |
| SPO2 | Oxygen saturation less than 95% on room air | | 0 or 1 |
| Feeding difficulties | Refusing feedings | | 0 or 1 |
| | Sum of five components | | |
| PRESS SCORE | 0-1: mild; 2-3: moderate; 4-5: severe | | 0-5 |
| | Month | Respiratory rate | |
| Criteria for tachypnea | <12 | >60 | 1 |
| | 12-35 | >40 | 1 |
| | 36-156 | >30 | 1 |
| | >156 | >20 | 1 |

LENGTH OF PICU STAY:

DURATION OF HOSPITAL STAY:

TYPR OF RESPIRATORY SUPPORT:

DURATION OF RESPIRATORY SUPPORT:

INVESTIGATION:

SERUM CALCIUM:

SERUM PHOSPHOROUS:

SERUM ALKALINE PHOSPHATASE:

SERUM VITAMIN D:

CLINICAL OUTCOME:

# MASTER CHART

| SL NO | IP NO | NAME | AGE | SEX | ADDRESS | DIAGNOSIS | IMMUNISATION STATUS | SEASON OF PRESENTATION | PAST H/O RESPIRATORY ILLNESS | NO OF PREVIOUS RESPIRATORY ILLNESS | FAMILY H/O OF RESPIRATORY ILLNESS | SOCIOECONOMIC STATUS | OVERCROWDING | WEIGHT | HEIGHT | SEVERITY | SERUM VIT D LEVELS | VITAMIN D LEVEL CLASSIFICATION | SERUM CALCIUM | SERUM PHOSPHOROUS | SERUM ALP | OUTCOME | LENGTH OF PICU STAY | LENGTH OF HOSPITAL STAY | TYPE OF RESPIRATORY SUPPPORT | DURATION OF RESPIRATORY SUPPORT |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 38629 | SANGAMESH | 4 | 1 | INDI | 3 | 1 | 3 | 1 | 2 | 2 | 3 | 2 | 7 | 64 | 3 | 17.5 | 1 | 10 | 5.1 | 358 | 1 | 5 | 8 | 2 | 3 |
| 2 | 35231 | FAYAZ | 72 | 1 | BAGEWADI | 6 | 3 | 3 | 2 | 1 | 2 | 3 | 1 | 17 | 110 | 3 | 15.5 | 1 | 9 | 3.2 | 189 | 1 | 7 | 9 | 2 | 3 |
| 3 | 35263 | PRAJWAL | 84 | 1 | BAGEWADI | 6 | 3 | 3 | 2 | 1 | 2 | 2 | 2 | 15 | 102 | 2 | 26.8 | 2 | 9 | 3.5 | 115 | 1 | 6 | 9 | 1 | 2 |
| 4 | 35550 | PRATIKSHA | 48 | 2 | BIJAPUR | 4 | 1 | 3 | 2 | 1 | 1 | 4 | 1 | 14 | 100 | 2 | 19.6 | 1 | 9 | 4.7 | 110 | 1 | 6 | 10 | 2 | 2 |
| 5 | 38869 | SOMALING | 24 | 1 | INDI | 5 | 3 | 3 | 1 | 2 | 2 | 3 | 1 | 9 | 77 | 3 | 12.8 | 1 | 10 | 4.6 | 107 | 4 | 10 | 21 | 2 | 8 |
| 6 | 37669 | KAJOL | 144 | 2 | BIJAPUR | 5 | 3 | 3 | 1 | 3 | 2 | 3 | 2 | 24 | 128 | 2 | 13.8 | 1 | 9 | 3.4 | 342 | 1 | 3 | 7 | 2 | 1 |
| 7 | 39000 | PREETAM | 2 | 1 | SANGLI | 2 | 1 | 3 | 2 | 1 | 2 | 3 | 2 | 5 | 50 | 3 | 5.71 | 1 | 10 | 5.7 | 601 | 3 | 5 | 5 | 4 | 5 |
| 8 | 39110 | RAMESH | 144 | 1 | YADGIRI | 1 | 3 | 3 | 2 | 1 | 2 | 2 | 2 | 43 | 140 | 3 | 4.81 | 1 | 9 | 5.1 | 161 | 1 | 9 | 15 | 3 | 3 |
| 9 | 39811 | ASHOK | 120 | 1 | BIJAPUR | 5 | 1 | 1 | 2 | 1 | 2 | 4 | 1 | 20 | 130 | 2 | 9.36 | 1 | 8 | 2.5 | 116 | 1 | 6 | 10 | 3 | 4 |
| 10 | 41011 | DEEPIKA | 84 | 2 | BABLESHWAR | 5 | 1 | 3 | 1 | 2 | 2 | 3 | 2 | 15 | 120 | 2 | 32 | 3 | 9 | 5.1 | 84 | 1 | 3 | 6 | 2 | 4 |
| 11 | 40948 | CHANDANA | 48 | 2 | VIJAYAPUR | 5 | 1 | 3 | 1 | 1 | 2 | 4 | 2 | 10 | 90 | 3 | 15.3 | 1 | 8 | 4.4 | 141 | 1 | 8 | 13 | 2 | 3 |
| 12 | 204/2017 | AMRUTA | 2 | 2 | MUDDEBIHAL | 3 | 3 | 1 | 1 | 3 | 2 | 3 | 2 | 4 | 54 | 3 | 8.1 | 1 | 8 | 5.4 | 244 | 1 | 6 | 8 | 2 | 3 |
| 13 | 3099 | MOH INAMDAR | 12 | 1 | BIJAPUR | 1 | 3 | 1 | 2 | 1 | 2 | 3 | 2 | 9 | 74 | 1 | 24.5 | 2 | 10 | 5.1 | 183 | 1 | 3 | 5 | 2 | 1 |
| 14 | 42454 | HABIBA | 11 | 1 | BIJAPUR | 5 | 1 | 1 | 2 | 1 | 2 | 3 | 2 | 8 | 71 | 1 | 36 | 3 | 10 | 5.1 | 257 | 1 | 3 | 5 | 1 | 0 |
| 15 | 10141 | MEHBOOBI | 1 | 2 | ATHANI | 5 | 2 | 1 | 2 | 1 | 2 | 3 | 2 | 3 | 60 | 2 | 20.7 | 2 | 11 | 4.9 | 200 | 1 | 5 | 8 | 4 | 3 |
| 16 | 30473 | ZAIBUN | 2 | 1 | BIJAPUR | 1 | 1 | 2 | 2 | 1 | 2 | 3 | 2 | 3 | 52 | 2 | 16.8 | 1 | 9 | 5.3 | 281 | 1 | 3 | 7 | 3 | 2 |
| 17 | 29770 | KRUTIKA | 7 | 2 | BABLESHWAR | 5 | 2 | 2 | 2 | 1 | 2 | 3 | 2 | 5 | 62 | 3 | 9.55 | 1 | 9 | 5.4 | 136 | 1 | 5 | 7 | 3 | 3 |
| 18 | 29376 | SIDDARTH | 9 | 1 | INDI | 6 | 1 | 2 | 2 | 1 | 2 | 3 | 2 | 8 | 63 | 2 | 34 | 3 | 9 | 4.9 | 118 | 1 | 3 | 10 | 2 | 1 |
| 19 | 34658 | RAKSHITA | 3 | 2 | BIJAPUR | 3 | 1 | 3 | 2 | 1 | 2 | 3 | 2 | 5 | 60 | 3 | 6.46 | 1 | 8 | 5.2 | 855 | 1 | 6 | 12 | 3 | 3 |
| 20 | 38463 | RAMESH | 2 | 2 | BIJAPUR | 2 | 2 | 2 | 2 | 1 | 2 | 3 | 2 | 4 | 58 | 2 | 12.9 | 1 | 9 | 5 | 201 | 1 | 4 | 8 | 3 | 2 |
| 21 | 38648 | SOUJANYA | 30 | 2 | BIJAPUR | 5 | 1 | 2 | 2 | 1 | 2 | 3 | 2 | 10 | 82 | 1 | 29.4 | 2 | 11 | 5.2 | 155 | 1 | 2 | 5 | 2 | 1 |
| 22 | 35544 | SUVARNA | 1 | 2 | BIJAPUR | 2 | 1 | 3 | 2 | 1 | 2 | 3 | 2 | 4 | 55 | 2 | 8.42 | 1 | 10 | 5.9 | 247 | 1 | 6 | 10 | 3 | 3 |

| | | | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 23 | 35533 | REKHA | 9 | 2 | MUDDEBIHAL | 3 | 1 | 3 | 2 | 1 | 2 | 2 | 1 | 8 | 72 | 2 | 17.2 | 1 | 9 | 4.4 | 180 | 1 | 4 | 8 | 3 | 2 |
| 24 | 35831 | PREETAM | 4 | 1 | BIJAPUR | 3 | 3 | 3 | 2 | 1 | 2 | 3 | 2 | 7 | 60 | 3 | 11 | 1 | 9 | 4.1 | 168 | 1 | 4 | 8 | 3 | 3 |
| 25 | 747 | NINGRAJ | 18 | 1 | YADGIRI | 3 | 1 | 1 | 2 | 1 | 2 | 3 | 2 | 7 | 78 | 1 | 33 | 3 | 10 | 6.4 | 193 | 1 | 4 | 6 | 1 | 0 |
| 26 | 502 | DEEPTI | 24 | 2 | BAGALKOT | 3 | 1 | 1 | 2 | 1 | 2 | 3 | 2 | 7 | 78 | 1 | 50 | 3 | 10 | 3.3 | 160 | 1 | 2 | 5 | 1 | 0 |
| 27 | 1956 | SANVI | 9 | 2 | BIJAPUR | 3 | 3 | 1 | 2 | 1 | 2 | 2 | 2 | 6 | 70 | 3 | 10 | 1 | 10 | 5.8 | 137 | 1 | 4 | 6 | 2 | 2 |
| 28 | 1814 | SHRAVAN | 18 | 1 | SANGLI | 3 | 1 | 1 | 2 | 1 | 2 | 3 | 2 | 8 | 76 | 3 | 8.1 | 1 | 9 | 2.5 | 188 | 1 | 6 | 10 | 3 | 4 |
| 29 | 3747 | SAMARTH | 36 | 1 | MUDHOL | 5 | 3 | 1 | 2 | 1 | 2 | 3 | 2 | 12 | 84 | 1 | 25.1 | 2 | 9 | 3 | 79 | 1 | 3 | 5 | 3 | 1 |
| 30 | 3418 | MAHADEVI | 60 | 2 | INDI | 7 | 1 | 1 | 2 | 1 | 2 | 3 | 2 | 15 | 108 | 3 | 7.83 | 1 | 9 | 5.6 | 164 | 1 | 6 | 12 | 2 | 5 |
| 31 | 3149 | BASAVANT | 84 | 1 | BIJAPUR | 5 | 3 | 1 | 2 | 1 | 2 | 3 | 2 | 18 | 118 | 1 | 20 | 2 | 9 | 4 | 165 | 1 | 4 | 6 | 2 | 1 |
| 32 | 4936 | SAMARTH | 3 | 1 | YADGIRI | 3 | 3 | 1 | 1 | 2 | 2 | 3 | 2 | 4 | 54 | 3 | 4.9 | 1 | 8 | 4.2 | 285 | 1 | 6 | 10 | 4 | 3 |
| 33 | 4916 | PREETAM | 8 | 1 | SINDAGI | 5 | 1 | 1 | 2 | 1 | 2 | 3 | 2 | 7 | 70 | 2 | 8.59 | 1 | 10 | 4.8 | 157 | 1 | 5 | 7 | 3 | 3 |
| 34 | 5623 | ISHWAR | 3 | 1 | BIJAPUR | 5 | 3 | 1 | 2 | 1 | 2 | 2 | 2 | 5 | 56 | 3 | 8.1 | 1 | 9 | 5.2 | 249 | 1 | 8 | 12 | 3 | 4 |
| 35 | 8464 | GOUTAMI | 48 | 2 | BIJAPUR | 2 | 1 | 1 | 2 | 1 | 2 | 3 | 2 | 12 | 100 | 1 | 30.2 | 3 | 8 | 4.9 | 182 | 1 | 3 | 7 | 1 | 0 |
| 36 | 8545 | SAKSHI | 2 | 2 | INDI | 3 | 3 | 1 | 2 | 1 | 2 | 3 | 2 | 5 | 55 | 3 | 8.1 | 1 | 9 | 6 | 238 | 1 | 5 | 9 | 4 | 3 |
| 37 | 5313 | NINGAWWA | 23 | 2 | SANGLI | 2 | 3 | 1 | 2 | 1 | 2 | 3 | 2 | 10 | 82 | 2 | 17.6 | 1 | 9 | 4.6 | 190 | 1 | 3 | 6 | 2 | 2 |
| 38 | 5882 | GODAWARI | 160 | 2 | MIRAJ | 4 | 3 | 1 | 2 | 1 | 2 | 3 | 1 | 20 | 130 | 3 | 8.36 | 1 | 8 | 5 | 360 | 3 | 5 | 5 | 2 | 5 |
| 39 | 8184 | VISHAL | 24 | 1 | BIJAPUR | 3 | 1 | 1 | 2 | 1 | 2 | 3 | 2 | 8 | 80 | 2 | 12.7 | 1 | 8 | 4.6 | 144 | 1 | 4 | 7 | 2 | 1 |
| 40 | 8288 | AHMED ALI | 36 | 1 | BIJAPUR | 1 | 3 | 1 | 2 | 1 | 2 | 3 | 2 | 14 | 90 | 1 | 20.8 | 2 | 9 | 5 | 189 | 1 | 3 | 7 | 1 | 0 |
| 41 | 12445 | RAJKUMAR | 150 | 1 | SINDAGI | 5 | 2 | 1 | 1 | 2 | 2 | 3 | 1 | 30 | 140 | 3 | 6.02 | 1 | 7 | 6 | 300 | 2 | 7 | 17 | 2 | 17 |