

Association between Vitamin D Status and Asthma Course and Severity among Iraqi Children: Evaluating its Role as a Predictive Biomarker

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ABSTRACT

Childhood asthma is one of the significant health problems, beside vitamin D deficiency is currently the most common nutritional deficiency worldwide. Several studies assessed the association between vitamin D and pathophysiology of many diseases. However, few studies on the national and international levels evaluate the utility of vitamin D as predictor of asthma severity and control. The present study aimed to assess the performance of serum vitamin D level in prediction of asthma severity and its association with asthma control. Hence, a cross-sectional study was conducted during the between June 2024 to March 2026 included 118 Iraqi Asthmatic children aged 10-15 years and were proved diagnosed according to the clinical criteria of Global Initiative of Asthma (GINA) guideline 2024. Asthma control was assessed using two validated tests; the Asthma control test (ACT) used for children aged 12-15 years and the child Asthma control test (c-ACT) used for children aged 10-11 years. Our findings showed that Hypovitaminosis D is frequent in asthmatic children aged 10-15 years, deficient/insufficient levels reported in more than half, 55.1% of the asthmatic child patients. Lower vitamin D level was significantly associated with more severity of asthma and lower disease control. Vitamin D showed excellent performance in predicting asthma severity and it was strong predictor for asthma control. We recommended monitoring of serum vitamin D levels in asthmatic children as study participants of their management and follow-up plan. Normalizing vitamin D levels as part of therapeutic plan of asthmatic child can improve disease control as well as help to control the vitamin D deficiency in general

Keywords: Bronchial Asthma, Severity, Control, , Vitamin D, Children

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INTRODUCTION:

Bronchial asthma (BA) is one of the commonest chronic diseases that affect children in all age groups. It is an inflammatory respiratory disease characterized by increased hyperactivity of the tracheobronchial tree. Bronchial asthma manifests itself as repeated episodes of dyspnea, cough, and wheezing [1]. In recent years, the level of hospitalization and mortality from BA has significantly decreased globally, nonetheless, other clinical problems have emerged and worsened, one of which is the high proportion of uncontrolled and partially controlled BA. Scientists cite various reasons for this phenomenon: low adherence to treatment, insufficient awareness of patients about their condition, the presence of disease phenotypes resistant to therapy, genetic polymorphism, airway remodeling, etc. [2–4]. The modern concept of asthma diagnosis is based on the following components: inflammation and hypersensitivity of the airways, features of atopic status, the presence of characteristic respiratory symptoms. At the same time, the diversity of clinical characteristics (gender, age, race, onset of the disease, etc.) and prognostic factors (duration of remission), risks of exacerbation and mortality, lack of effect from standard preventive treatment (steroid resistance, toxicity of fast- and long-acting selective β_2 -adrenomimetics, sensitivity to anti-IgE) confirm the idea that asthma is a syndrome that combines several variants or phenotypes, and it is a heterogeneous chronic airway disease results due to interplay of several genetic and environmental factors. However, the pathophysiological features of childhood asthma remain not well identified but the key feature is the immune system dysregulation, mucus hypersecretion and structural airway remodeling [5–7].

The main tasks in the treatment of asthma are aimed at normalizing the patient's activity, ensuring the normal functioning of the bronchopulmonary system, and avoiding the harmful effects of drugs used to treat asthma. The choice of drugs depends on the frequency of exacerbations and the severity of the disease. According to modern recommendations, the use of inhaled anti-inflammatory drugs (corticosteroids and non-steroidal drugs) for the prevention of chronic asthma is necessary [8]. Based on the daytime symptoms, nighttime awakening, using rescue medications and interference with child's normal activity, as well as the lung function, the childhood asthma severity is classified into four levels; intermittent, mild

persistent, moderate persistent and severe persistent [9]. The high socioeconomic burden and steadily increasing prevalence of asthma prompt scientists to further explore the factors driving this trend. In recent years, interest has increased in studying the possible impact of micronutrient deficiencies on the course of asthma [10].

Vitamin D is a fat-soluble vitamin that plays an important role in regulating the immune system and maintaining bone health. In the years between 2000-2022, the prevalence of vitamin D deficiency among people aged 1 year and older was 15.7% [11]. Recent estimates in 2026, indicated that vitamin D deficiency affect almost half of the global population representing a worldwide public health challenge that required strategic action and intervention like food fortification and targeted supplementation [12]. On the other hand, the prevalence of vitamin D deficiency increasing with the age reaching up to 40% among children and adolescents aged 10-17 years [13]. In the Eastern Mediterranean region the prevalence reaches up to 80%, however, the prevalence of vitamin D deficiency varies depending on the cutoff values used to define deficient level, as well as latitude, the population studied, sex, age, and income level. There are several factors contribute to vitamin D deficiency or insufficiency, such as urbanization, less exposure to sun light, overweight/obesity, sedentary lifestyle and low physical activity, poor nutrition and unhealthy diet, smoking and using some therapeutic agents among the main factors in addition to non-modifiable factors such as age, sex and ethnicity [11,14].

Currently, it is well-known that the deficiency of vitamin D is linked to many chronic illnesses including asthma [15]. The genetic polymorphism of intracellular vitamin D receptors has been identified and in numerous cells of the immune system, vitamin D receptors (VDRs) can be found. These include macrophages, dendritic cells, monocytes, activated B and T lymphocytes [16]. Therefore, vitamin D is essential for immunomodulation throughout the body [17]. Furthermore, the regulation of the inflammatory response and the immune response in the respiratory epithelium is governed by many genes. Transcription of these genes is managed by VDRs. [18]. The IL-17 and IL-13 pro-inflammatory cytokines are suppressed whereas the anti-inflammatory cytokine IL-10 is enhanced by vitamin D [19]. Furthermore, vitamin D alters the balance of T cell responsiveness from the Th1 phenotype to the Th2 phenotype [20]. Although there are no reviews or analyses done systematically, there is evidence which links

low vitamin D levels to asthma in children. Therefore, innovation in the identification of potential biomarkers to guide diagnosis and progression of asthma and even in the differentiation of inflammatory endotypes of the disease for the appropriate treatment and control of asthma, is of great importance within international health strategies. Keeping all these in mind, the purpose of our study is to determine the levels of vitamin D in Iraqi children with asthma and to assess the relationship, if any, between vitamin D levels with severity, frequency of attacks and exacerbation of asthma. Given the high prevalence of hypovitaminosis D in the population of the Republic of Belarus, it can be assumed that the problem of vitamin D deficiency is also relevant for patients with asthma. Regional-level studies of serum vitamin D levels in children with asthma could provide valuable information on the potential role of vitamin D in modifying clinical symptoms and facilitate the development of targeted interventions to improve treatment outcomes. The aim of the study was to determine the vitamin D status of children with bronchial asthma

PATIENTS AND METHODS:

A Cross-sectional observational clinical study conducted over 20 months at Karbala city, middle of Iraq, during the period between June 2024 and March 2026. The study included 118 children aged 10-15 years of both genders. The rationale for choosing this age group is to facilitate reliable performance of spirometry as the children at this age group can perform the spirometry maneuvers [17]. The enrolled children presented with bronchial asthma and have a history of at least one attack of shortness of breath in the past 12 months and were visited the outpatient department or admitted to the inpatient wards, as well as those who were followed up in the private clinics of the authors.

The sample size was calculated according to Mandeville and Roscoe, where the sample size for studies in which the magnitude of the effect/problem is unknown is 15 to 20 replicates of measurement for each classification group and variable. These groups must possess the attributes to be measured in the target population. This quantity would be sufficient to obtain a normality curve in the case of continuous or ratio variables.

Inclusion criteria

1. Iraqi children aged 10 -15 years at time of enrollment
2. Both genders sexes.
3. Diagnosed according to the Global Initiative of Asthma (GINA) guideline [8]
4. Participation in the study confirmed by their parents , caregivers or child's guardian and provide a verbal informed consent at the time of sample collection,

Exclusion criteria:

1. Having chronic respiratory diseases other than asthma
2. Children with co-existing other chronic non- respiratory diseases; like endocrine diseases, kidney disease, liver disease , malignancy, severe anemia and heart diseases
3. Having signs and /or symptoms of an acute infection at time of enrollment or respiratory infection in the past 30 days.
4. Using inhaled corticosteroids or antihistamines in the past 24 hours before performing spirometry tests.
5. Children who used vitamin D supplementation in the past three months
6. Known cases of vitamin D metabolism disorders or malabsorption syndrome.
7. Children who were unable to perform spirometry and those whose spirometry results did not meet the American Thoracic Society (ATS) / European Respiratory Society (ERS) standardized criteria [18]
8. Children who were having primary immunodeficiency or systemic autoimmune disease.
9. Children with cognitive and/or motor disabilities or unable to respond to the questionnaire.

Case definition:

Asthma was diagnosed when the child met the GINA 2024 [19] guideline criteria where he/ or she had respiratory symptoms; wheeze, shortness of breath, chest tightness, cough and documented limitation of expiratory air flow as well as response to bronchodilator and excluding other differential diagnoses

Asthma severity classification:

For purpose of this study, we take a full medical history and performed a thorough clinical examination. The severity of Asthma was categorized in accordance with the GINA guideline. Severity categorized into 4 categories; intermittent, mild persistent, moderate persistent and severe persistent.

Asthma control:

The asthma control was assessed using two validated questionnaires, the first was that used for children aged 4-11 year, it was used to our patients aged 10-11 years, this questionnaire is the Childhood Asthma Control Test (c-ACT) and composed of 7 questions, (4 items for the child and 3 items answered by the parent/caregiver), the total score ranged 0- 27 with higher value indicated better control.

The second questionnaire used to children aged 12 and older, in our study we used this questionnaire for children aged 12-15 years. The Asthma Control Test (ACT) composed of 5 self-reported items scored 1-5, inquire about asthma status during the past 4 weeks, total score ranged 5-25, with 5 for uncontrolled and 25 for completely controlled [20,21]. According to the results of this test, the patients were sub grouped according to the status of asthma control into 3 subgroups; well-controlled, partially controlled and poorly / or uncontrolled.

Vitamin D measurement and categorization

A sample of venous blood was collected from each participant and send to the laboratory for vitamin D level and other requested investigations. Vitamin D was measured using standard laboratory procedures and protocols followed at our setting laboratory based on the Kit's manufacturer instructions that available in the leaflet attached with the testing kit. The measurement was done using the electrochemiluminescence immunoassay by an autoanalyzer. Vitamin D level was categorized according to most commonly used classification for children and adolescents in the literature as: Deficient (<20 ng/mL), Insufficient (20-29.9 ng/mL) and Sufficient (≥ 30 ng/mL) [22].

Ethical considerations.

All ethical issues were in accordance with the Declaration of Helsinki of the World Medical Association on the Ethical Principles for Medical Research Involving Human Subjects, in its 2024 revision. This study did not represent any risk to the health of the participants because it was a cross-sectional study with the collection of 5 ml of whole blood on only one occasion and the performance of non-invasive pulmonary function tests. Participation was voluntary. In this context, the patient's parent/ guardian agreed a verbal informed consent that clearly specified the benefits of participating in the study, with the freedom to withdraw at any time without coercion or detriment to medical care. Patients' data were kept anonymous and confidentially.

Data management and analysis

Data were collected using a pre-constructed data collection form, transformed into computerized database and analyzed using the statistical package for social sciences (SPSS) software version 29. Statistical tests were applied accordingly; Analysis of variances (ANOVA) used to compare mean vitamin D levels across asthma severity and asthma control categories. Receiver operating characteristic (ROC) curve analysis used to assess the performance of vitamin D as predictor of asthma severity. Regression analysis used to assess the validity of vitamin D as independent predictor for asthma severity and asthma control. Level of significance, set at ≤ 0.05 .

RESULTS:

A total of 118 asthmatic children were enrolled in this study, age and sex distribution of the studied group showed that 60.2% of patients aged between 12-15 years. Males were relatively dominant and contributed for 55.9% of the studied group. Majority, (79.7%), of the child patients were of urban residence, (**Table 1**). Among the studied group, intermittent asthma found in 39.8%, mild persistent in 35.6%, moderate persistent in 16.9% and severe persistent in 7.6%. From other point of view, 33.1% of patients had good control, 43.2% partially while in 23.7% asthma was poorly controlled, (**Table 2**). Regarding the levels of vitamin D, deficiency (<20 ng/ml) reported in 26 patients (22%), insufficiency (20.1-29.99 ng/ml) in 33.1% of patients

while 53 patients (44.9%) had sufficient levels of vitamin D (≥ 30 ng/ml). However, the mean vitamin D level was 27.8 (range: 11.4-44.2) ng/ml, (**Table 3**). Moreover, we combined patients with deficient and insufficient status in one group and compared against those with sufficient levels of vitamin D, we found the patients with deficient and insufficient levels were 65 contributed for 55.1% of the studied group (**Figure 1**), this distribution used later in receiver operating characteristic (ROC) curve analysis and regression analysis. Comparison of vitamin D levels across severity and control of asthma among the studied group revealed a dose-dependent correlation where the vitamin D levels decrease significantly with the increasing asthma severity, the mean vitamin D level in patients with intermittent was the highest (34.33 ng/ml) compared to 27.32 ng/ml in mild persistent asthma group, 19.37 ng/ml in those with moderate persistent and the lowest mean vitamin D level of 14.41 ng/ml reported in those with severe persistent asthma, (P. value < 0.001 , significant), so as for the correlation with asthma control; patients with good controlled disease had the higher vitamin D levels compared to those with poorly controlled disease, 33.33 vs. 17.24 ng/ml, respectively, (P. value < 0.001), as shown in (**Table 4 and Figures 2 & 3**). To assess the performance of vitamin D as predictor of asthma severity, Receiver operating characteristic (ROC) curve analysis was conducted (**Figure 4**) and revealed that at an optimal cutoff value of ≤ 21.8 ng/ml (Identified according to Youden's index), vitamin D level was good predictor of asthma severity with a Sensitivity (96.4%), Specificity (91.1%), Accuracy (92.7%), positive predictive value (PPV) of (87.8%) and negative predictive value (NPV) of 97.4%, (**Table 5**). Further analysis was performed to assess the significance of correlation of vitamin D with the severity of asthma independent of other variables including age and sex of the patients, we performed logistic regression analysis which revealed that vitamin D was strong predictor of severe asthma independent of age and sex, where patients with lower vitamin D level less than 22 ng/ml about 1.22-fold more likely to have severe asthma (Odds ratio= 1.22, $P < 0.001$) and that 64.3% of severity of asthma can be explained by lower vitamin D levels. Similar analysis was performed against asthma control and revealed that vitamin D was strong predictor of asthma control where patients with higher levels of vitamin D were about 1.6-fold more likely to have good controlled asthma (Odds ratio= 1.578, $P < 0.001$), (**Table 7**).

Table 1. Age and sex distribution of the studied group (N=118)

Variable	No.	%
Age (year)		
10 – 11	47	39.8
12 - 15	71	60.2
Mean (SD)	12.2 (1.4)	-
Median (IQR)	12 (11-13)	-
Sex		
Male	66	55.9
Female	52	44.1
Residence		
Urban	94	79.7
Rural	24	20.3
SD: standard deviation; IQR: Interquartile range		

Table 2. Distribution of severity and control of asthma among the studied group (N=118)

Variable	No.	%
Asthma severity		
Intermittent	47	39.8
Mild Persistent	42	35.6
Moderate Persistent	20	16.9
Severe persistent	9	7.6
Asthma control		
Good controlled	39	33.1
Partially controlled	51	43.2
Poorly controlled	28	23.7

Table 3. Vitamin D status and serum levels of the studied asthmatic children (N=118)

Vitamin D	No.	%
Deficient	26	22.0
Insufficient	39	33.1
Sufficient	53	44.9
Mean (SD)	27.8 (8.4)	-
Median (IQR)	28.6 (19-34)	-
Range	11.4 – 44.2	-

SD: standard deviation, IQR: Interquartile range

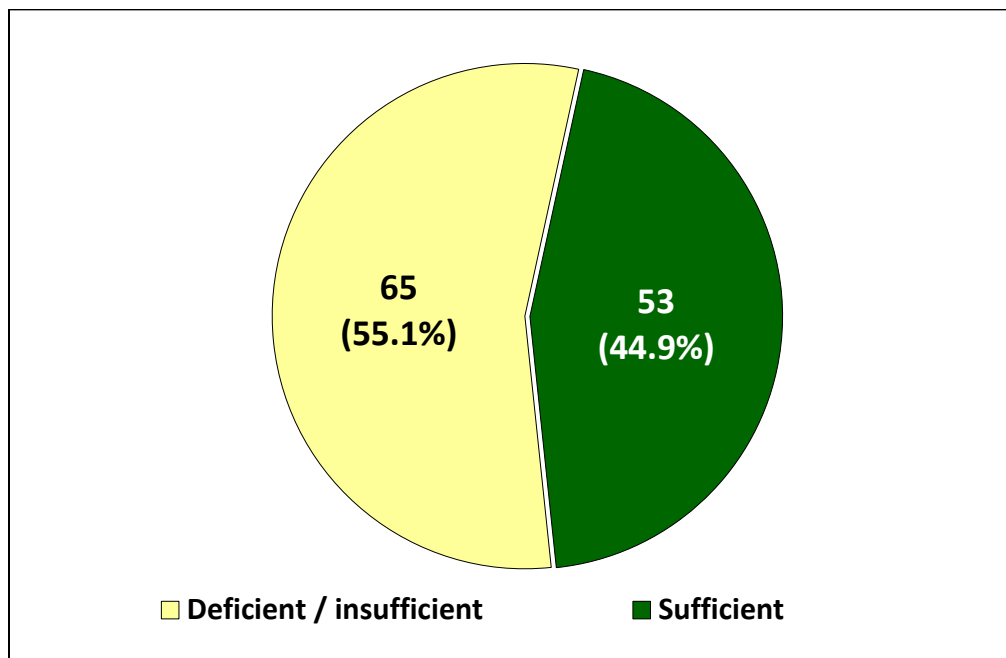
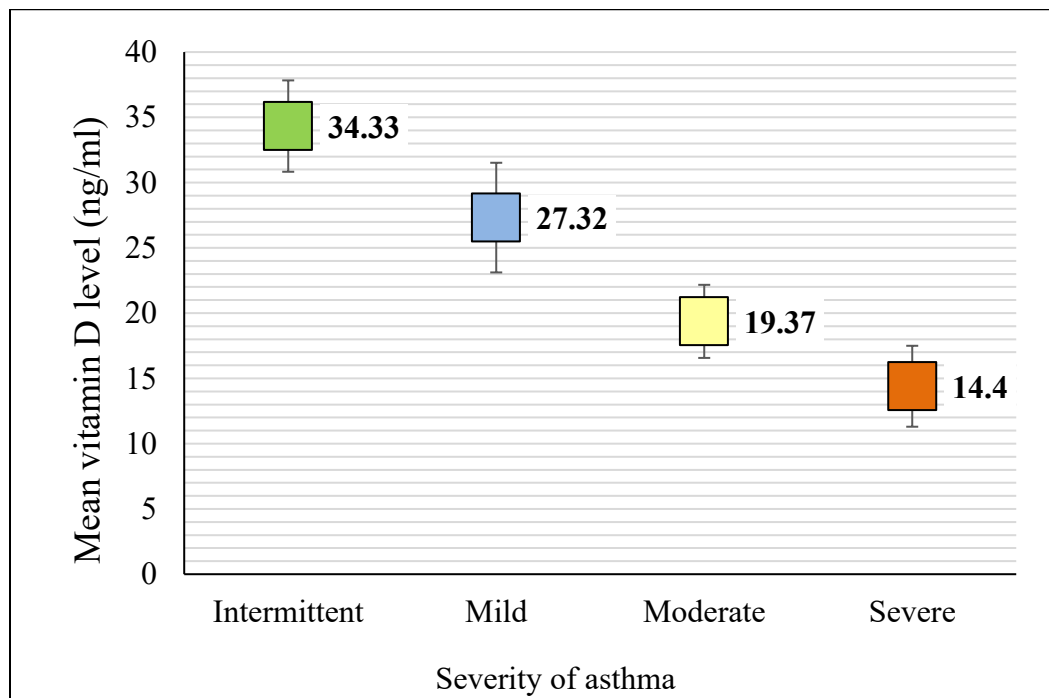
**Figure 1. Distribution of asthmatic children according to vitamin D status deficient / insufficient against sufficient levels**

Table 4. Comparison of vitamin D levels across severity and control of asthma among the studied group (N=118)

Category	Vitamin D level (ng/ml)			P. value
	Mean	SD	Range	
Asthma severity				
Intermittent	34.33	6.21	19.5- 47.4	< 0.001
Mild Persistent	27.32	5.26	18- 38	
Moderate Persistent	19.37	4.93	13.6- 32.5	
Severe	14.41	2.99	11.4- 21.5	
Asthma control				
Good controlled	33.33	6.08	19.5- 45.1	< 0.001
Partially controlled	29.32	6.92	13.6- 47.4	
Poorly controlled	17.24	3.12	11.4- 23.1	

**Figure 2. Line-Marker plot showing the trend of change in vitamin D level across severity of asthma; Vitamin D tend to decrease with increasing severity of asthma (P. value<0.001).**

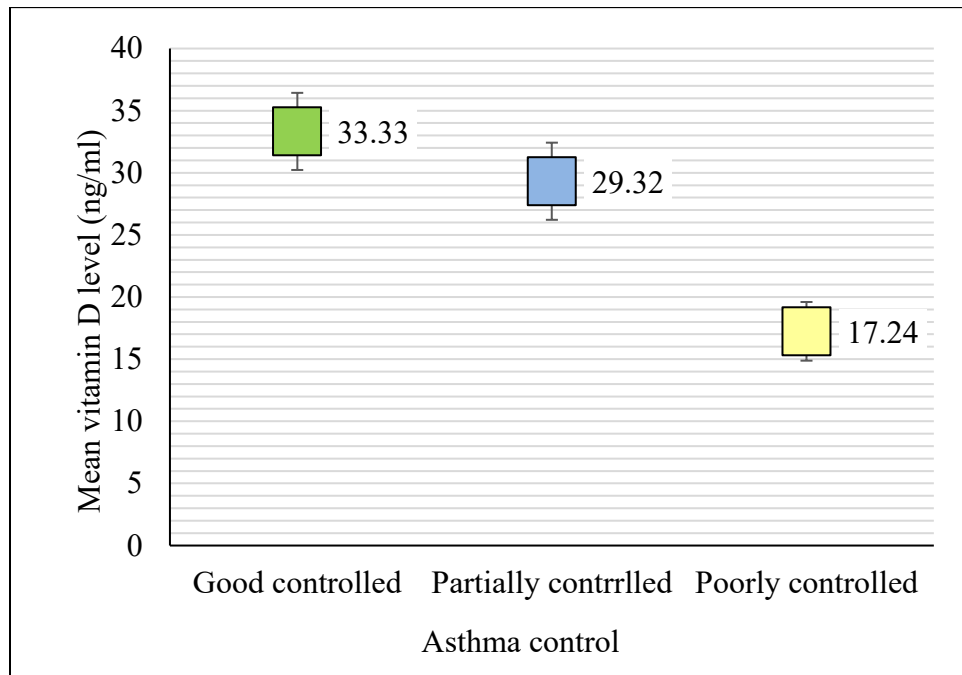


Figure 3. Line-Marker plot comparing mean vitamin D level across status of asthma control The Lowest Vitamin D is reported in poorly controlled group, (P. value<0.001).

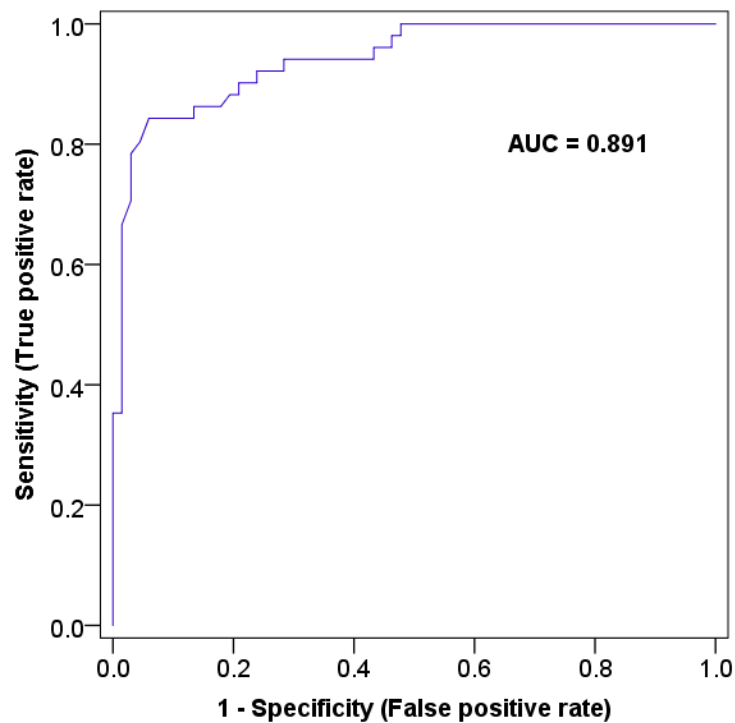


Figure 4. Receiver operating characteristic (ROC) curve for performance of vitamin D as predictor of asthma severity

Table 5. Parameters of performance of vitamin D as predictor of asthma severity among 118 asthmatic children

Youden's index	0.870
Optimal cutoff value	≤ 21.8
Sensitivity	96.4%
Specificity	91.1%
Accuracy	92.7%
PPV	87.8%
NPV	97.4%

Table 6. Results of binary logistic regression for the predictors of asthma severity

Variable	B	S.E.	Wald	P. value	OR	95% C.I. for OR
Age	-0.29	0.197	2.168	0.141	0.748	0.509 - 1.101
Sex	1.054	0.643	2.685	0.101	2.869	0.813 - 10.119
Vitamin D level	0.199	0.048	16.948	<0.001	1.22	1.11 - 1.341

Table 7. Results of binary logistic regression for the predictors of asthma control

Variable	B	S.E.	Wald	P. value	OR	95% C.I. for OR
Age	0.028	0.228	0.015	0.901	1.029	0.657 - 1.61
Sex	-0.022	0.718	0.844	0.358	0.978	0.125 - 1.37
Vitamin D level	0.456	0.088	26.896	<0.001	1.578	1.332 - 2.351

DISCUSSION:

Vitamin D deficiency is a condition characterized by a decrease in serum 25(OH)D concentrations below optimal values, which can potentially lead to suboptimal intestinal calcium absorption, the development of secondary hyperparathyroidism and an increased risk of fractures . Currently, vitamin D deficiency is the commonest nutritional deficiency all over the world and affect almost all age group, However, the definition of optimal serum level of vitamin D varied in literature according to the used source of definition. Nonetheless, there is a strong evidence-based consensus that serum level of vitamin D of less than 20 ng/ml is sub-optimal while levels above 30 ng/ml are recommended by many clinical guidelines and

specialist experts [23,24]. In this context, several etiological factors associated with vitamin D deficiency including less or avoidance of sun exposure, high pigmentation of skin, insufficient vitamin D intake (dietary or supplementation), endocrine diseases, malabsorption diseases, increased body weight, and using some therapeutic agents, as well as other factors, all can contribute to lower vitamin D levels, particularly in children with its adverse health consequences [25]. Several studies assessed the association between vitamin D and pathophysiology of many diseases as a biomarker, for instance, immunological, endocrinological and skin diseases [26,27]. However, few studies, particularly in our country, assessed the role of vitamin D as predictor of severity of asthma among children, therefore, our aim in this study was assessment of performance of vitamin D level in prediction of asthma severity, to ensure addressing this aim we considered some main objectives to assess the concentration of vitamin D level among 118 asthmatic Iraqi children of both gender; identify the frequency of each type of asthma (intermittent, mild, moderate and severe persistent); identify the status of asthma control among the studied group using standard c-ACT and ACT validated questionnaires [20,21] then assess the trend of vitamin D levels across the asthma severity and control categories and finally we tested the performance of vitamin D in predicting the severity and control of asthma among our cohort. Our findings showed relative dominance of male gender among the studied group; despite there is conflicting results in previous studies regarding the sex variation in the prevalence of asthma, our findings supported some previous studies in performance of male gender before puberty, these studies showed that boys are more frequently having asthma at this age and they attributed this male predominance to different factors such as smaller airway caliber prior to puberty, more liability to atopic sensitization, and sex-related immunological development[28][29]. Hence, our findings supported the existing evidence and confirmed this pattern among Iraqi children. Previous Iraqi studies documented predominance of males among asthmatic children under 14 years of age [30]. With regard to the severity of asthma reported in our study, it is consistent with the clinical profile of asthma among Iraqi children as reported by Ibraheem et al. [31] in Baghdad, who documented intermittent asthma in 52% of children, 24% mild persistent, 19% moderate persistent and 5% severe persistent asthma. So as for the asthma control where we found that 33.1% of patients had good control, 43.2% partially while in

23.7% asthma was poorly controlled, Hussein et al. [32] found in 2024, that 51% of the asthmatic children had well controlled diseases while 49% uncontrolled, based on the ACT. Hamawandi et al. [33] from Sulaimani, North of Iraq, reported a well-controlled asthma in 53.7%, partially controlled in 30.5% and uncontrolled in 15.9%. However, the control rates varied across the studies and affected by multiple factors. Our findings showed that 44.9% of our patients had sufficient and 55.1% had deficient or insufficient levels of vitamin D, this finding was not unexpected according to the epidemiological profile of vitamin D status in our population where the vitamin D sufficient levels less frequent. Mahmood et al. documented a mean vitamin D of 26.5 ng/ml, ranging 3-110 which reflected a wide range and variation among the Iraqi population, however, Mahmood et al. found deficient vitamin D in 39% [34] which is close to our finding. As a main objective in our study, we assessed the performance of vitamin D in predicting the severity of asthma and we found a negative dose-response relationship between vitamin D and asthma severity where the mean vitamin D levels decreases with the increasing severity. On the other hand Receiver operating characteristic analysis showed that vitamin D performed excellently in predicting asthma severity with high validity parameters; Sensitivity (96.4%), Specificity (91.1%), Accuracy (92.7%), positive predictive value (PPV) of (87.8%) and negative predictive value (NPV) of 97.4%. Furthermore the same trend of negative relationship was found between vitamin D levels and asthma control confirmed by logistic regression analysis. Iraqi studies that address similar relationship or concerned with the predictive performance of vitamin D among asthmatic children are scarce, however, recent Iraqi study from Karbala conducted by Aziz ZH and Mahmood TA [35] assessed the diagnostic utility of vitamin D3 as one of three biomarkers to differentiate asthma than non-asthma status, but they did not discussed the association between vitamin D and severity of disease, however, they documented that vitamin D produced an AUC of 0.819 yielded a sensitivity and specificity of 80% and 75%, respectively. Another Iraqi study conducted by Ali et al. [36] assessed the performance of vitamin D in classification asthmatic patients than healthy controls, they concluded that vitamin D had moderate diagnostic performance, at a cutoff value of ≤ 25 ng/ml, the sensitivity was 83.3% but low specificity of 55.5%, in discriminating asthmatic patients from controls. Nonetheless, international studies supported our findings; an Egyptian study El-Gamal et al. [37] evaluated the validity of vitamin

D in predicting asthma control status and they found that at vitamin D level threshold of ≤ 8.5 ng/ml it predicted uncontrolled disease with sensitivity of 69% and specificity of 66.7%. Kumar et al. from India [38] found a significant negative association between vitamin D levels and severity of asthma. So as, Jat et al. [39] reported a significant relationship between deficient vitamin D level and severe asthma where children with lower level of vitamin D were more likely to have exacerbations, lower lung functions and more severe disease. Another study conducted by Shebl et al. [40] concluded that vitamin D deficiency was significantly more prevalent in asthmatic patients and was significantly associated with more severe asthma and atopy. According to our findings and previous studies and literature, vitamin D may serve as a promising biomarker for monitoring asthma severity and its control. Therefore, further studies are required to validate these findings, further evaluation and get more precise conclusions.

CONCLUSION:

Hypovitaminosis D is frequent in asthmatic children aged 10-15 years, deficient/insufficient levels reported in more than half, 55.1% of the asthmatic child patients. Lower vitamin D level was significantly associated with more severity of asthma and lower disease control. Vitamin D showed excellent performance in predicting asthma severity and it was strong predictor for asthma control. We recommended monitoring of serum vitamin D levels in asthmatic children as study participants of their management and follow-up plan. Normalizing vitamin D levels as part of therapeutic plan of asthmatic child can improve disease control as well as help to control the vitamin D deficiency in general

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