e-ISSN:2602-2079

Volume 8
Issue 3
2024

JOURNAL of Surgery and Medicine

International Medical Journal

JOSAM

Editorial Team

Editor-in-Chief

Editors & Editorial Board

Prasenjit Das, Professor, MD, DNB, MNAMS, MNASc
Department of Pathology
All India Institute of Medical Sciences
New Delhi, India
Website

Seyed Vahid Hosseini, Professor
Shiraz University of Medical Sciences, Shiraz, Iran
Website

Vol. 8 No. 3 (2024):

Published: 2024-03-31

Research Article

Retrospective evaluation of patients with vitamin B12 deficiency in the pediatrics outpatient clinic

Vitamin B12 deficiency in the pediatrics

Sinan Yavuz, Huseyin Kaya , Abdullah Sert , Ozgül Yigit

51-54

PDF 30 33 Citations 0

HRCT severity score as a predictive biomarker in severity assessment of COVID-19 patients

HRCT severity score in severity assessment of COVID-19 patients

Dipesh Karki, Sundar Adhikari

55-58

PDF 30 25 Citations 0

Vitamin D distribution by month, sex, and season in Turkey, Niğde province: A retrospective cohort study

D vitamin status in Niğde, Turkey

Ergül Bayram, Durmuş Ayan, Tevfik Balcı, Kader Zeybek Aydoğan, Dogan Bahadır Inan, Umut Karabay

59-64

PDF 24 25 Citations 0

Case Report

Does sodium phosphate enema use cause electrolyte disorder?

Sodium-phosphate enema poisoning

Songül Tomar Güneysu, Okşan Derinöz Güleryüz , Nazmi Mutlu Karakaş , Özlem Çolak

65-68

PDF 27 28 Citations 0

J Surg Med. 2024;8(3):51-54.
https://doi.org/10.28982/josam.7587

Research article
https://jsurgmed.com/

JOSAM
Journal of Surgery and Medicine
e-ISSN: 2602-2079

Retrospective evaluation of patients with vitamin B12 deficiency in the pediatrics outpatient clinic

Sinan Yavuz [1], Huseyin Kaya [2], Abdullah Sert [3], Ozgül Yigit [4]

[1] Department of Pediatric Intensive Care, Batman Education and Research Hospital, Batman, Turkey
[2] Department of Neonatology, Dunya Hospital, Batman, Turkey
[3] Department of Pediatrics, Biruni University Hospital, Istanbul, Turkey
[4] Department of Pediatrics, Bagcilar Education and Research Hospital, Istanbul, Turkey

ORCID of the author(s)

SY: https://orcid.org/0000-0001-6159-8710
HK: https://orcid.org/0000-0002-6532-5661
AS: https://orcid.org/0000-0001-6330-9548
OY: https://orcid.org/0000-0002-9738-2388

Corresponding Author
Sinan Yavuz
Department of Pediatric Intensive Care, Batman Education and Research Hospital, Batman, Turkey
E-mail: sinan2438@hotmail.com

Ethics Committee Approval
The study was approved by the Ethics Committee of Bagcilar Training and Research Hospital with the registry number 352 on December 1, 2010. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2024 March 7

Abstract

Background/Aim: This study examines patients diagnosed with vitamin B12 deficiency in our department. Although rare, vitamin B12 deficiency is one of the causes of megaloblastic anemia, which can lead to negative outcomes in patients. We aim to promote earlier diagnosis to protect patients from these negative effects. Therefore, this study will contribute to raising awareness in the literature.
Methods: Retrospectively, we included a total of 127 outpatient children, aged 0–18 years (0–215 months), who were diagnosed and treated for vitamin B12 deficiency at the Bagcilar Training and Research Hospital Child Health and Disease Clinic between October 2014 and February 2015.
Results: Among the patients, 67 (53%) with vitamin B12 deficiency were female, while 60 (47%) were male, indicating a higher occurrence in girls. Vitamin B12 deficiency was most commonly observed in the age groups of 0-2 years and 12-17 years (adolescents). The mean vitamin B12 level was 168.1 (34.1) pg/mL, the mean hemoglobin level was 12 (1.9) g/dL, and the mean MCV (mean corpuscular volume) was 78.4 (8.1) fl. Anemia was observed in 38% of the patients, bicytopenia in 4%, neutropenia in 6%, thrombocytopenia in 9%, pancytopenia in 3%, and macrocytosis in 2%. Non-iron-deficient patients showed no difference in mean hemoglobin and RDW (red cell distribution width) when compared to iron-deficient patients. However, their B12 levels were lower. The prevalence of iron deficiency did not differ between girls and boys. Comparing patients with vitamin B12 levels lower than 150 pg/mL to those with higher levels, there were no significant differences in average Hb, MCV, and RDW.
Conclusion: It should be noted that macrocytic anemia is not exclusive to vitamin B12 deficiency. Vitamin B12 deficiency can manifest as normocytic anemia and should not be overlooked in biochemical assessments. It is recommended to conduct nationwide and regional prevalence studies to evaluate vitamin B12 deficiency as a public health issue and to develop new solutions accordingly.

Keywords: pediatrics, vitamin B12, deficiency

How to cite: Yavuz S, Kaya H, Sert A, Yigit O. Retrospective evaluation of patients with vitamin B12 deficiency in the pediatrics outpatient clinic. J Surg Med. 2024;8(3):51-54.

Introduction

The main source of water-soluble vitamin B12 is animal foods, predominantly found in beef liver and kidney. While humans can fulfill their cobalamin requirements through animal food intake, deficiency symptoms arise when intake is insufficient [1]. Vitamin B12 plays a crucial role in cell development and division by participating in DNA (Deoxyribonucleic Acid) synthesis. Its deficiency particularly affects rapidly growing tissues with high cell turnover [2]. The consequences of deficiency include somatic and motor neuron developmental delays and megaloblastic anemia [3]. Severe deficiency can lead to serious conditions, ranging from the inability to perform basic functions, such as holding the head and sitting up, to coma [4]. Vitamin B12 deficiency represents a significant public health issue, particularly in developing countries. This study aims to retrospectively investigate the frequency, demographic, clinical, and biochemical characteristics of patients with vitamin B12 deficiency. By examining the medical records and computer data of patients treated for vitamin B12 deficiency at the Bagcilar Training and Research Hospital Pediatrics Clinic between October 2014 and February 2015, we seek to compare our findings with existing literature.

Materials and methods

The files of patients aged 0–18 years (0–215 months) who were diagnosed with vitamin B12 deficiency and received follow-up and treatment at the Bagcilar Training and Research Hospital Pediatrics Outpatient Clinic between November 2014 and March 2015 were retrospectively analyzed. Information about the selected patients was obtained by reviewing their medical records and using the hospital automation system records. A total of 127 patients were identified and included in the study. The lower limit for diagnosing vitamin B12 deficiency was set at 200 pg/ml, and patients with values above this threshold were excluded from the research. The study received ethical approval from our hospital's ethics committee, dated 31.12.2010, and numbered 352. The patient follow-up form recorded age, sex, complete blood count, serum iron, total iron-binding capacity, serum ferritin levels, folic acid, and vitamin B12 levels. All patients had vitamin B12 levels below 200 pg/ml, which was considered deficient. The normal range for serum vitamin B12 was defined as 200–800 pg/ml. Iron deficiency was defined as ferritin levels below 20 ng/ml. Hemoglobin (Hb) and hematocrit (Hct) levels below 2 standard deviations from the normal values for age were considered indicative of anemia, while a white blood cell count (WBC) below 4000/mm^3 indicated leukopenia. Neutropenia was defined as a neutrophil count below 1500/mm^3, and a platelet count below 150,000/mm^3 was classified as thrombocytopenia [5]. Bicytopenia was defined as the presence of two impairments in hemoglobin, WBC, or platelet values, while pancytopenia referred to the presence of three impairments. The upper limit for mean corpuscular volume (MCV) in each patient was calculated using the formula [84fl + (age (year) × 0.6)] until it reached the adult value of 96 fl after 6 months. Macrocytosis, defined as an elevated MCV level according to age, was calculated separately for each patient [6]. Macrocytosis was not evaluated in infants younger than 6 months. Vitamin B12, folic acid, ferritin, serum iron, and total iron-binding capacity (TIBC) were measured using the Cobas-Roche (E170, Japan) hormone analyzer with electrochemiluminescence immunoassay (ECLIA) method and Roche brand mass. TIBC was calculated as the sum of total iron and partial iron-binding capacity (PIBC). PIBC were measured using the spectrophotometric method on the Cobas-Roche E170 hormone analyzer with Roche brand mass. Complete blood counts were performed using an automatic blood count device, the Beckman LH750 device, and the Coulter brand kit. Homocysteine levels were measured using the High-performance liquid chromatography (HPLC) fluorescence detector method on an Agilent brand device. The laboratory's normal serum level ranges was as follows: vitamin B12 200–800 pg/ml, folic acid 4.6–18.7 ng/ml, iron 60–158 µg/dl, ferritin 20–275 ng/ml, homocysteine 5–14 µmol/L, and LDH 95–500 U/L.

Statistical analysis

Descriptive statistics were employed to analyze the data, including mean, standard deviation, median, minimum, maximum, frequency, and ratio values. The distribution of variables was assessed using the Kolmogorov-Smirnov test. The Mann-Whitney U test was utilized for analyzing quantitative data, while Spearman correlation analysis was employed for correlation analysis. The analysis was performed using the SPSS 22.0 program.

Results

The patients were categorized by sex, revealing that 67 (53%) were female and 60 (47%) were male (Table 1). There was no significant difference observed in the occurrence of vitamin B12 deficiency between girls and boys (*P*=0.744). Likewise, no significant correlation was found between age and vitamin B12 levels (*P*=0.834) (Table 2). Except for anemia, most of our patients were diagnosed with upper respiratory tract infections, and their follow-up and treatments were conducted through outpatient clinic visits (Table 3).

Table 1: Anemia morphology of patients

		Mean (SD)	Median (Min-Max)
Age, year		7.6 (5.9)	8.0 (1.0-17.0)
		n	**%**
Gender	Female	67	53%
	Male	60	47%
Value by age	Hyperchromic	3	2%
	Hypochromic	41	32%
	Normochromic	83	65%

Table 2: Vitamin B12 characteristics by sex and age

		Vitamin B12 Level			*P*-value
		Mean (SD)	**Median**	**Min-Max**	
Gender	Female	170.4 (26.4)	175	102-200	0.834
	Male	173.4 (23.3)	180	107-200	

Mann-Whitney U test / Spearmen Correlation

The mean vitamin B12 level for the evaluated 127 patients was 168.1 (34.1) pg/ml, with a median value of 175.7. The mean hemoglobin (Hb) level was 12.0 (1.9) g/dl, with a median value of 12.1. The mean MCV was 78.4 (8.1) fl, with a median value of 80.0. The mean RDW was 13.4 (3.5), with a median value of 12.4. The mean folic acid level was 13.5 (5.3) ng/ml, with a median value of 13. No significant correlations were found between vitamin B12 levels and Hb (*P*=0.481) or MCV (*P*=0.448). While macrocytic anemia is typically associated with vitamin B12 deficiency, 65% of our patients had normocytic anemia, 32% had microcytic anemia, and only 2%

had macrocytic anemia. Anemia was observed in 38% of our patients, and there was no significant correlation between vitamin B12 levels and hemoglobin. Thrombocytopenia was detected in 9% of cases, neutropenia in 6%, bicytopenia in 4%, and pancytopenia in 3%. The mean platelet count was 333.0 (102.6) thousand/mm^3, with a median value of 311 ×10^3/mm^3, while the mean leukocyte count was 8.8 (2.7) ×10^3/mm^3, with a median value of 8.5 ×10^3/mm^3. The mean vitamin B12 levels in patients with neutropenia, bicytopenia, thrombocytopenia, and pancytopenia were not significantly lower than those without these conditions (P=0.095). Additionally, the mean vitamin B12 levels in patients with thrombocytopenia and pancytopenia did not significantly differ from those with anemia, neutropenia, and bicytopenia. No significant difference was observed in mean vitamin B12 levels between patients with and without anemia (P=0.073) (Table 4).

Table 3: Diagnoses of the patients with the exception of anemia

Diagnoses	n	%
Acute bronchiolitis	1	1%
Allergic rhinitis	2	2%
Anemia	48	38%
Asthma	4	3%
Enuresis	2	2%
Growth retardation	18	14%
Urinary infection	3	2%
Conjunctivitis	2	2%
Lymphadenitis	3	2%
Myalgia	4	3%
Obesity	4	3%
Oral aphtha	1	1%
Rhinitis	1	1%
Syncope	1	1%
Synovitis	1	1%
Upper respiratory infection	31	24%
Vitamin D deficiency	1	1%

Table 4: Hemogram and other anemia parameters

	Median	Min- Max	Mean (SD)
Vitamin B12	175.7	14.4-200.0	168.1 (34.1)
Ferritin	24.0	1.9-158.0	32.6 (28.5)
TIBC	381.0	44.0-636.0	375.7 (69.9)
Iron	56.5	16.8-167.7	59.5 (32.6)
Folic Acid	13.0	4.6-20.0	13.5(5.3)
Hemoglobin	12.1	6.2-16.6	12.0 (1.9)
Hematocrit	37.0	4.9-51.7	37.0 (6.1)
MCV	80.0	52.0-94.2	78.4 (8.1)
RDW	12.4	1.0-37.7	13.4 (3.5)
WBC	8.5	3.0-20.3	8.8 (2.7)
Platelet	311.0	105.0-729.0	333.0 (102.6)
Vitamin D	17.8	3.0-63.0	22.5 (16.6)

TIBC: Total iron-binding capacity, MCV: Mean corpuscular volume, RDW: Red blood cell distribution width, WBC: White blood cell

Discussion

Vitamin B12 is a water-soluble, red complex coenzyme that contains cobalt ions and cannot be synthesized by humans. It has a molecular weight of 1355.42 Daltons [3]. Structurally, vitamin B12 belongs to the class of compounds known as corrins. The corrin ring refers to the cobalamin tetrapyrrole ring without cobalt and other side chains [7]. Vitamin B12 is composed of three parts:

- The core consists of a cobalt atom surrounded by four reduced pyrrole rings.
- A nucleotide group is attached to both the cobalt atom and one of the pyrrole rings via a phosphate chain. This group differs from the typical nucleotide as it contains 5,6-dimethylbenzimidazole as a ribose-linked basic substance.
- The cobalt atom is further bonded to a small group (CN, OH^-, H_2O, SO3, methyl, 5’-deoxy-adenosyl) through coordination-type bonds [2].

The compound formed by the first two large groups is known as cobalamin (Cbl). Adding one of the molecules from the third group to cobalamin results in the formation of different vitamin B12 derivatives that exhibit enhanced effectiveness [3]. Cobalamin derivatives important for humans include cyanocobalamin (CNCbl), hydroxycobalamin (OHCbl), deoxy-adenosylcobalamin (AdoCbl), methylcobalamin (MeCbl)

Cyanocobalamin and hydroxycobalamin are both stable compounds that can be utilized as drugs. Hydroxycobalamin is eliminated from the body at a slower rate compared to cyanocobalamin. However, its use as a drug is generally not recommended due to the development of antibodies against the complex it forms with transcobalamin, leading to tolerance to its effects. Consequently, cyanocobalamin is more commonly employed as a medicinal treatment. Deoxy-adenosylcobalamin and methylcobalamin, conversely, serve as active coenzymes in tissues [8].

Humans are unable to synthesize vitamin B12 on their own. It is exclusively produced by certain bacteria and mold fungi [9]. While the bacteria in the large bowel do produce vitamin B12, the amount generated is insufficient to meet the body’s requirements, both due to its occurrence in the distal part of the absorption area and the inadequate synthesis [9]. Consequently, individuals need to obtain vitamin B12 precursors from animal-based foods. The highest concentrations of vitamin B12 can be found in beef liver and kidney (40–50 µg/100 g). Plant-based foods do not serve as sources of vitamin B12, although they may

Although humans fulfill their cobalamin requirements by consuming animal-based foods, signs of vitamin B12 deficiency can occur due to insufficient intake. The World Health Organization (WHO) recommends the following dietary intake levels to prevent deficiency: 1 µg for adults, 1.3 µg for lactating mothers, 1.4 µg for pregnant women, and 0.1 µg for infants [11]. In children, the daily requirement starts at 0.4 µg/day during the early months and gradually increases with age, reaching 2.4 µg/day during puberty [12].

The incidence of vitamin B12 deficiency is influenced by factors such as race, environment, gender, age, socioeconomic level, and dietary habits. A study conducted by Allen et al. in Mexico between 1982–1986 revealed a 43% frequency of vitamin B12 deficiency among 219 patients aged 18–36 months [13]. Another study reported by Garcia et al. in Venezuela in 2005 documented an incidence of 11.4% among 5658 cases aged 0–18 years [14].

In our country, there is no prevalence study available that demonstrates the frequency of vitamin B12 deficiency. However, there are a few limited case reports from certain regions. Cetinkaya et al. [15] found a frequency of 0.64% among 3117 children (4–24 months old) hospitalized in Istanbul in 2007. Similarly, Baytan et al. [16] reported an incidence of 0.3% among 3980 cases aged between 3 months and 13 years in Bursa in 2007.

Vitamin B12 deficiency is prevalent among individuals with low socioeconomic status and those under 2 years of age [17]. In a study conducted by Taskesen et al. [18] in Diyarbakir, it was found that 82% of the patients were under the age of 2 years. In our study, we observed that 35% of the patients were under 2 years old, 8% were between 2-5 years old, 16% were between 6–11 years old, and 39.2% were between 12–17 years old. There were no significant differences in the frequency of deficiency between boys and girls. Additionally, no distinction was found in the mean vitamin B12 levels between girls and boys.

The primary hematological manifestation of vitamin B12 deficiency is megaloblastic anemia, characterized by an increased MCV, red cell distribution width (RDW), and hypersegmentation and macrocytosis in neutrophils observed in peripheral smears [3]. In our study, 38% of patients with vitamin B12 deficiency exhibited anemia. Durmus et al. [19] reported that 25% of patients with megaloblastic anemia did not display elevated MCV levels. In the study conducted by Bay et al., MCV values were below 90 fl in one-third of the cases [20]. In contrast to the literature, our study did not identify a significant negative moderate correlation between vitamin B12 levels and MCV. The mean MCV in our study was 78.4 (8.1) fl.

Additionally, the mean MCV of individuals with iron deficiency was not significantly lower than those without iron deficiency. We observed that 14% of patients with vitamin B12 deficiency also had iron deficiency. When comparing children with iron deficiency to those without deficiency in our study, there was no significant difference in the means of RDW; however, the mean RDW was 13.4% (3.5), indicating a slight increase. This suggests an elevation in RDW not only in cases of iron deficiency but also in cases of vitamin B12 deficiency. In contrast, Gupta et al. reported a significantly greater increase in RDW values in megaloblastic anemia compared to aplastic anemia, suggesting its potential use in differential diagnosis [21].

Additional hematological findings associated with vitamin B12 deficiency include leukopenia, neutropenia, bicytopenia, and pancytopenia. In the study conducted by Taskesen et al. [18], neutropenia was observed in 11% of 131 patients with megaloblastic anemia (mean vitamin B12 level of 69 pg/ml), while thrombocytopenia was present in 40% and pancytopenia in 6% of the cases. Cetinkaya et al. [15] reported anemia in 61.6%, thrombocytopenia in 30%, pancytopenia in 5%, and neutropenia in 15% of 20 cases with vitamin B12 deficiency (mean vitamin B12 level of 66.9 pg/ml). In our study, anemia was detected in 38% of our patients, but no significant correlation was found between vitamin B12 levels and hemoglobin. We observed thrombocytopenia in 9%, leukopenia in 6%, bicytopenia in 4%, and pancytopenia in 3% of the cases. The mean platelet count was 333.0 (102.6) thousand/mm^3, with a median of 311 $\times 10^3/mm^3$. The mean leukocyte count was 8.8 (2.7) $\times 10^3/mm^3$, with a median of 8.5 $\times 10^3/mm^3$. In our study, the mean vitamin B12 levels in children with leukopenia, bicytopenia, thrombocytopenia, and pancytopenia were not significantly lower than those without. Furthermore, there was no significant difference in the mean vitamin B12 levels between patients with thrombocytopenia and pancytopenia compared to those with anemia, leukopenia, and bicytopenia.

Limitations

As our study relied on retrospective analysis of patient records, the available information was limited to what had been documented in the files. The records did not consistently provide clear documentation of the improvement in clinical findings for each patient, thereby preventing a comprehensive evaluation of clinical improvement.

Conclusion

This study confirms the high prevalence of vitamin B12 deficiency in children. The concentration of patients within the first 2 years and 12–17 years age groups indicates that these specific age ranges are particularly at risk. Contrary to common knowledge, it was observed that vitamin B12 deficiency could be associated with normocytic anemia in addition to macrocytic anemia. Therefore, the overall assessment should consider the laboratory results. In patients with iron deficiency and inadequate consumption of animal-based foods, vitamin B12 levels should be checked. Furthermore, it is important to recommend animal-based foods to adolescents, considering their increased nutritional needs.

References

1. de Benoist B. Conclusions of a WHO Technical Consultation on folate and vitamin B12 deficiencies. Food and Nutrition Bulletin. 2008;29(2_suppl1):S238-S244.
2. Nathan DG, Oski FA. Hematology of Infancy and Childhood. 1987.
3. Whiteheat V, Rosenblatt D, Cooper B. Megaloblastic Anemia. Ed. Nathan DG, Orkin SH. Nathan and Oski's Hematology of Infancy and Chilhood. In. WB Saunders Co; 2003.
4. Hall CA. Function of vitamin B12 in the central nervous system as revealed by congenital defects. American Journal of Hematology. 1990;34(2):121-7.
5. Lanzkowsky P. Manual of Pediatric Hematology and Oncology. In. Elsevier Academic Press. 2011.
6. Celkan TT. What does a hemogram say to us? Turkish Archives of Pediatrics. 2020;55(2):103.
7. Raux E, Schubert H, Warren M. Biosynthesis of cobalamin (vitamin B12): a bacterial conundrum. Cellular and Molecular Life Sciences CMLS. 2000;57:1880-93.
8. Nohr D, Biesalski HK. Reference Module in Food Science. Elsevier; Amsterdam, The Netherlands: 2016. Vitamin B12.
9. Leal NA. B_{12} Metabolisms In Humans. Dissertation for Doctora Of Philosophy. University of Florida. Florida 2004:1-156.
10. Sela I, Yaskolka Meir A, Brandis A, Krajmalnik-Brown R, Zeibich L, Chang D, et al. Wolffia globosa–mankai plant-based protein contains bioactive vitamin B12 and is well absorbed in humans. Nutrients. 2020;12(10):3067.
11. Organization WH. Requirements of Vitamin A, Iron, Folate, and Vitamin B12: Report of a Joint FAO/WHO Expert Consultation: Food & Agriculture Org. 1988;
12. Thiamin R. Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B_6, Folate, Vitamin B_{12}, Pantothenic Acid, Biotin, and Choline. Washington (DC): National Academies Press (US); 1998.
13. Allen LH, Rosado JL, Casterline JE, Martinez H, Lopez P, Munoz E, et al. Vitamin B-12 deficiency and malabsorption are highly prevalent in rural Mexican communities. The American Journal of Clinical Nutrition. 1995;62(5):1013-9.
14. Garcia-Casal M, Osorio C, Landaeta M, Leets I, Matus P, Fazzino F, et al. High prevalence of folic acid and vitamin B12 deficiencies in infants, children, adolescents and pregnant women in Venezuela. European Journal of Clinical Nutrition. 2005;59(9):1064-70.
15. Cetinkaya F, Yildirmak Y, Kutluk G, Erdem E. Nutritional vitamin B12 deficiency in hospitalized young children. Pediatric Hematology and Oncology. 2007;24(1):15-21.
16. Baytan B, Özdemir O, Erdemir G, Gunes AM. Clinical findings and treatment of vitamin B12 deficiency in childhood. Journal of Uludag University Faculty of Medicine. 2007;33(2):61-4.
17. Roschitz B, Plecko B, Huemer M, Biebl A, Foerster H, Sperl W. Nutritional infantile vitamin B12 deficiency: pathobiochemical considerations in seven patients. Archives of Disease in Childhood-Fetal and Neonatal Edition. 2005;90(3):281-2.
18. Taskesen M, Okur N, Katar S, Okur N, Soker M. Nutritional megaloblastic anemia during childhood: Demographical, clinical and laboratory features of 134 patients from southeastern part of Turkey. e-SPEN, the European e-Journal of Clinical Nutrition and Metabolism. 2009;4(3):152-4.
19. Durmus A, Dilek I, Topcu N, Kocaman C, Cekici S. Should Erythrocytes Always Be Macrocytic in Megaloblastic Anemias. Turkish Journal of Haematology (Supplement). 2002;19(3).
20. Bay A, Oner AF, Nalbantoglu O, Demirtas M, Acikgoz M. Clinical and hematological evaluation of 45 patients with megaloblastic anemia. Van Medical Journal. 2006;13(2):46-8.
21. Gupta P, Saxena R, Karan A, Choudhry V. Red cell indices for distinguishing macrocytosis of aplastic anaemia and megaloblastic anaemia. Indian journal of Pathology & Microbiology. 2003;46(3):375-7.

J Surg Med. 2024;8(3):55-58.
https://doi.org/10.28982/josam.7518

Journal of Surgery and Medicine
e-ISSN: 2602-2079

Research article
https://jsurgmed.com/

HRCT severity score as a predictive biomarker in severity assessment of COVID-19 patients

Dipesh Karki [1], Sundar Adhikari [2]

[1] Consultant Physician, Department of Medicine, Fishtail Hospital and Research Center Private Limited, Pokhara, Kaski, Nepal
[2] Head of Department, Department of Pharmacy, Fishtail Hospital and Research Center Private Limited, Pokhara, Kaski, Nepal

ORCID of the author(s)

DK: https://orcid.org/0000-0002-4789-8765
SA: https://orcid.org/0000-0001-8501-0256

Corresponding Author
Sundar Adhikari
Fishtail Hospital and Research Center Private Limited, Pokhara, Kaski, Nepal
E-mail: adhikari.sndr@gmail.com

Ethics Committee Approval
The study was approved by the Institutional Review Committee, Fishtail Hospital and Research Center Pvt. Ltd., Pokhara, Nepal, with reference no. 077/078/160 on 22 January 2021. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2024 March 15

Abstract

Background/Aim: In 2020, the World Health Organization declared the Coronavirus disease of 2019 (COVID-19) a pandemic due to its widespread nature. The severity of COVID-19 infections leading to patient deaths is influenced by various factors. Therefore, it is crucial to identify and address these contributing causes for effective treatment of COVID-19.

Methods: This study was conducted between 23 January 2021 and 19 June 2021 at a hospital with 100 beds in Western Nepal. Patient demographic data and High-resolution computed tomography severity scores were recorded. Microsoft Excel and Statistical Package for the Social Sciences were used for statistical data analysis. Binomial regression and Chi-square tests were applied, setting the significance level at $P<0.05$ with a confidence interval of 95%.

Results: The study found a significant association between computed tomography (CT) severity, gender, and age with the treatment outcome among COVID-19-infected patients admitted to the hospital. Patients with a CT severity score between 16 and 25 had an eightfold higher mortality rate (OR: -8.802; 95% CI: 3.506–18.491).

Conclusion: The severity and mortality of COVID-19 infections are influenced by factors such as age, gender, and biomarkers indicated by CT severity scores. Identifying additional factors that worsen COVID-19 patient's conditions and increase the risk of mortality is essential.

Keywords: coronavirus, COVID-19, CT severity score, high-resolution computed tomography, Western Nepal

How to cite: Dipesk K, Sundar A. HRCT severity score as a predictive biomarker in severity assessment of COVID-19 patients. J Surg Med. 2024;8(3):55-58.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially discovered in Wuhan, China, in December 2019. The World Health Organization officially named the illness coronavirus disease 2019 (COVID-19) on 11 February 2020 [1]. In March 2020, the World Health Organization declared COVID-19 a pandemic due to its rapid global spread from China to other parts of the world [2]. Therefore, it is of paramount importance to identify more accurate prognostic biomarkers for the disease's prognosis. The potential areas where COVID-19 biomarkers can be instrumental include [3];

1) Early symptom severity and disease suspicion
2) Clear evidence and categorization of disease severity
3) Framing criteria for hospital admission
4) Identifying a cohort at high risk
5) Defining ICU admission standards
6) Therapy rationalization
7) A therapeutic response's evaluation
8) Prediction of outcome
9) Defining the criteria for ICU and/or hospital discharge

High-Resolution Computed Tomography (HRCT) examinations are another method to detect viral infections in the body. They can also assess the severity of pulmonary disease and the presence of sequelae, track the disease's course, and eliminate other possible diagnoses [4]. Numerous studies have reported a correlation between inflammatory lab markers, hospital stay, and oxygen requirements with CT severity scores in COVID-19 patients [5]. However, more research is needed to fully understand the value of chest CT in prognosticating COVID-19 outcomes and its correlation with patient prognosis.

Materials and methods

Study population

This study was conducted from 23 January 2021 to 19 June 2021 at a 100-bed hospital in Western Nepal during the peak of Nepal's second wave of COVID-19. The diagnosis of COVID-19 was confirmed by obtaining nasal and pharyngeal swab specimens from patients, which were tested positive using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for SARS-CoV-2. Prior to conducting the study, consent was obtained from the patients' relatives.

Selection criteria [6-7]

The following patients met the inclusion criteria: (1) hospitalized patients, (2) confirmed COVID-19 cases through nasopharyngeal swab RT-PCR testing, and (3) patients who underwent their first CT scan while hospitalized and later tested positive on RT-PCR. Exclusion criteria included pregnancy, cancer, hematologic malignancies, chronic liver disease, acute coronary syndrome, surgeries or trauma within the last 30 days, and patients without CT imaging.

Ethical approval

The Institutional Review Committee (IRC) of Fishtail Hospital and Research Center Pvt. Ltd., Pokhara, Nepal, approved the study with reference no. 077/078/160.

Data collection

Age and gender information about the respondents were collected, and age was categorized into three groups: 19 to 39 years old, 40 to 59 years old, and 60 years or older [8].

The CT scanner used to calculate the HRCT severity score for COVID-19 patients was the Somatom Spirit (Siemens in Germany Syngo). The data were divided into two groups: COVID-19 patients with CT severity scores of 1 to 15 were categorized as having mild to moderate symptoms, while those with scores of 16 to 25 were classified as having severe symptoms. Additionally, the study noted two outcome categories for treatment: "improved" and "not improved." The "improved" category referred to patients who were either discharged or expressed desire to be discharged independently. On the other hand, patients whose condition was fatal and who were referred to higher centers for more advanced treatment were categorized as "not improved" [9-10].

Statistical analysis

Microsoft Excel and the Statistical Package for the Social Sciences (SPSS) statistical software (version 20.0, IBM) were utilized for all statistical data analyses. To establish the relationship between the dependent and independent variables, Chi-square and binomial regression tests were applied. Statistical values with a significance level of $P<0.05$ at a 95% confidence interval were considered significant.

Results

Sociodemographic characteristics of respondents

A total of 180 respondents participated in the study. Approximately 20% of the 180 participants were aged 19–39, while 30% were in the 40–59 age range. Most respondents (50%) were above 60, and the smallest proportion was in the 19–39 age group (36%). The data regarding gender distribution indicated that most of the respondents were male (54%), as depicted in Figures 1 and 2.

Figure 1: Percentage distribution of gender.

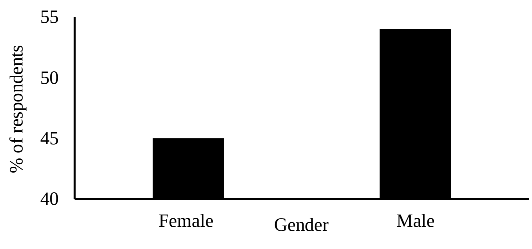
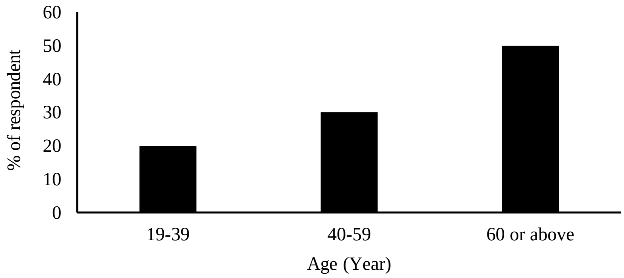


Figure 2: Percentage distribution of patient according to age.



Association of treatment outcome with CT severity score

A notable correlation was observed between the CT severity score and the treatment outcome in COVID-19 patients admitted to the hospital. Patients with a CT severity score of 16-25 were approximately eight times more likely to experience an adverse outcome (OR: 8.802; 95% CI: 3.506–18.491) than patients with a CT severity score of 1–15, as shown in Table 1.

Table 1: Association of treatment outcome with CT Severity Score.

Variables	Treatment Outcome			Chi-square value	*P*-value	OR	95% CI
	DOPR/ Discharged n(f)	Expired n(f)	Total				
CT Severity Score							
1-15	92 (91.1%)	9(8.9%)	101			Ref.	
16-25	43 (54.4%)	36(45.6%)	79	31.771	<0.001*	8.052	3.506-18.491

CI: Confidence Interval, DOPR: Discharge on Patient Request, OR: Odds Ratio, Ref: Reference

Discussion

The screening of effective biomarkers, patient classification, clinical management, and prevention of serious complications are essential in combating the progression of COVID-19, reducing severe and fatal outcomes, and improving treatment strategies [11]. Prominent biomarkers such as D-dimer, Serum ferritin, C-reactive protein (CRP), Interleukin-6, Lactate dehydrogenase (LDH), and HRCT have been identified for this purpose. Additionally, our study found that age, gender, and biomarkers significantly increased the risk of death in patients with COVID-19 [12].

Based on sociodemographic information, males are at a higher risk of COVID-19 than females [13]. They are also more susceptible to experiencing severe acute respiratory distress syndrome (ARDS) or fatal outcomes following SARS-CoV-2 infection. The exact reasons for this gender disparity are not yet fully understood; however, it may be attributed to factors such as smoking habits and higher plasma levels of androgen hormones in men than women. These androgens are believed to play a role in the transcription of Transmembrane serine protease 2 (TMPRSS2), a gene encoding a protease necessary for SARS-CoV-2 cell entry after its spike protein binds to the cell membrane's Angiotensin-converting enzyme 2 (ACE2) [14].

Another study has proposed that the X chromosome and sex hormones, which have been linked to both innate and adaptive immunity, might contribute to the higher susceptibility of males to COVID-19 infection [15].

There was a notable correlation between age groups and COVID-19 patients, with a higher vulnerability observed in the age group above 60. Previous studies have consistently reported that older individuals experience greater COVID-19 morbidity and mortality rates [16]. The aging process is often associated with an increased risk of mortality, which could be attributed to a weakened immune system. As individuals age, their immune competence tends to decline. In our investigation of the relationship between CT severity score and treatment outcomes for COVID-19 patients admitted to the hospital, we found that patients with a CT severity score of 16 to 25 were nearly eight times more likely to pass away than those with a score of 1 to 15. The extent of chest computed tomography involvement is a visible parameter indicating the degree of inflammation [17-19].

Limitations

As this was a single-center study, it is recommended that future research be conducted with a larger sample size across multiple centers. Performing similar studies on a broader scale will provide more robust and generalizable findings. Since this was a single-centered study, similar research should be conducted in the future with a large sample size in several centers.

Conclusion

In conclusion, a positive and significant association was found between oxygen consumption, length of hospital stays, and inflammatory lab markers. Although the prognostic value of chest CT in COVID-19 disease shows promise, further investigation is warranted to establish its correlation with patient outcomes. This study revealed that patients with higher CT severity scores exhibit greater disease severity, leading to an increased mortality risk. Hence, CT severity scores can serve as useful biomarkers for assessing the severity of COVID-19 in patients. Furthermore, additional research is necessary to identify other relevant characteristics and biomarkers that accurately gauge the severity of COVID-19 in patients.

Acknowledgments

The authors would like to acknowledge the Department of Pharmacy, Department of Medicine, Department of Laboratory, Fishtail Hospital and Research Center Pvt. Ltd., Pokhara, Nepal.

References

1. Yang R, Li X, Liu H, Zhen Y, Zhang X, Xiong Q, et al. Chest CT severity score: an imaging tool for assessing severe COVID-19. Radiology: Cardiothoracic Imaging. 2020;2(2):e200047. doi: 10.1148/ryct.2020200047
2. Abdel-Tawab M, Basha MA, Mohamed IA, Ibrahim HM. A simple chest CT score for assessing the severity of pulmonary involvement in COVID-19. Egypt J Radiol Nucl Med. 2021;52(1):1-0. doi: 10.1186/s43055-021-00525-x
3. Biomarkers Definitions Working Group, Atkinson Jr AJ, Colburn WA, DeGruttola VG, DeMets DL, Downing GJ, et al. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharm Therap. 2001;69(3):89-95. doi: 10.1067/mcp.2001.113989
4. Rahman MH, Amir N, Rahman MA, Islam AT, Islam MS, Huda MD, et al. Role of HRCT scan of chest in the evaluation of COVID-19 Pneumonia. TAJ: J Teach Assoc. 2021;34(1):109-14. doi: 10.3329/TAJ.V34I1.54914
5. Saeed GA, Gaba W, Shah A, Al Helali AA, Raidullah E, Al Ali AB, et al. Correlation between chest CT severity scores and the clinical parameters of adult patients with COVID-19 pneumonia. Radiol Res Pract. 2021;2021. doi: 10.1155/2021/6697677
6. Kim JH, Ta CN, Liu C, Sung C, Butler AM, Stewart LA, et al. Towards clinical data-driven eligibility criteria optimization for interventional COVID-19 clinical trials. J Am Med Inform Assoc. 2021;28(1):14-22. doi: 10.1093/jamia/ocaa276
7. Yasin R, Gomaa AA, Ghazy T, Hassanein SA, latif Ibrahem RA, Khalifa MH. Predicting lung fibrosis in post-COVID-19 patients after discharge with follow-up chest CT findings. Egypt J Radiol Nucl Med. 2021;52(1):1-3. doi: 10.1186/s43055-021-00495-0
8. Ye C, Zhang S, Zhang X, Cai H, Gu J, Lian J, et al. Impact of comorbidities on patients with COVID-19: A large retrospective study in Zhejiang, China. J Med Virol. 2020;92(11):2821-9. doi: 10.1002/jmv.26183]
9. Li K, Wu J, Wu F, Guo D, Chen L, Fang Z, et al. The clinical and chest CT features associated with severe and critical COVID-19 pneumonia. Invest Radiol. 2020;55(6):327-31. doi:.10.1097/rli.0000000000000672
10. Karki D, Saksham KC, Gurung R, Adhikari S. Association of HRCT severity score, pre-existing comorbidities, and ABO blood group with treatment outcomes of COVID-19 patients admitted in a hospital of Western Nepal. Asian J Med Sci. 2022;13(4):1-6. doi: 10.3126/ajms.v13i4.42468
11. Karki D, Gurung R, Nepali P, Kaphle HP, Subedi B, Adhikari S. Raised D-dimer among Admitted COVID-19 Patients in a Tertiary Care Centre: A Descriptive Cross-sectional study. JNMA: J Nepal Med Assoc. 2022;60(251):596. doi: 10.31729/jnma.7579
12. Ponti G, Maccaferri M, Cristel R, Tomasi A, Ozben T. Biomarkers associated with Covid-19 disease progression. Crit Rev Clin Lab Sci. 2020;57(6):389-99. doi: 10.1080/10408363.2020.1770685
13. Yazar H, Kayacan Y, Özdin M. Investigation of C-reactive Protein and D-dimer Findings in Patients with COVID-19. Bezmialem Science. 2021;9(Supplement 1):4-8.
14. Wambier CG, Goren A. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is likely to be androgen mediated. J Am Acad Dermatol. 2020;83(1):308-9. doi: 10.1016/j.jaad.2020.04.032
15. Jaillon S, Berthenet K, Garlanda C. Sexual dimorphism in innate immunity. Clin Rev Allergy Immunol. 2019;56(3):308-21. doi: 10.1007/s12016-017-8648-x
16. Davies NG, Klepac P, Liu Y, Prem K, Jit M, Eggo RM. Age-dependent effects in the transmission and control of COVID-19 epidemics. Nat Med. 2020;26(8):1205-11. doi: 10.1038/s41591-020-0962-9

17. Yilmaz A, Sabirli R, Seyit M, Ozen M, Oskay A, Cakmak V, et al. Association between laboratory parameters and CT severity in patients infected with Covid-19: A retrospective, observational study. Am J Emerg Med. 2021;42:110-4. doi: 10.1016/j.ajem.2021.01.040
18. Zhang L, Yan X, Fan Q, Liu H, Liu X, Liu Z, et al. D-dimer levels on admission to predict in-hospital mortality in patients with COVID-19. J Tromb Haemost. 2020;18(6):1324-9. doi: 10.1111/jth.14859
19. Cummings MJ, Baldwin MR, Abrams D, Jacobson SD, Meyer BJ, Balough EM, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. Lancet. 2020;395(10239):1763-70. doi: 10.1016/S0140-6736(20)31189-2

J Surg Med. 2024;8(3):59-64.
https://doi.org/10.28982/josam.7939

JOSAM

Journal of Surgery and Medicine

e-ISSN: 2602-2079

Research article
https://jsurgmed.com/

Vitamin D distribution by month, sex, and season in Turkey, Niğde province: A retrospective cohort study

Ergül Bayram [1], Durmuş Ayan [1,2], Tevfik Balcı [3], Kader Zeybek Aydoğan [4], Doğan Bahadır İnan [5], Umut Karabay [6]

[1] Niğde Ömer Halisdemir University, Research and Training Hospital, Department of Medical Biochemistry, Niğde, Turkey
[2] Niğde Ömer Halisdemir University, Faculty of Medicine, Medical Biochemistry, Niğde, Turkey
[3] Konya City Hospital, Medical Biochemistry, Konya, Turkey
[4] Niğde Ömer Halisdemir University, Faculty of Medicine, Internal Medicine, Niğde, Turkey
[5] Niğde Ömer Halisdemir University, Faculty of Medicine, Department of Pediatric, Niğde, Turkey
[6] Gülhane Research and Training Hospital, Department of Internal Medicine, Istanbul, Turkey

ORCID of the author(s)

EB: https://orcid.org/0000-0003-1708-3036
DA: https://orcid.org/0000-0003-2615-8474
TB: https://orcid.org/0000-0001-6212-0444
KZA: https://orcid.org/0000-0002-9331-9349
DBİ: https://orcid.org/0000-0001-9785-3939
UK: https://orcid.org/0000-0002-9632-360X

Corresponding Author
Durmuş Ayan
Niğde Ömer Halisdemir University Research and Training Hospital, Department of Medical Biochemistry, Niğde, Turkey
E-mail: durmusayan@hotmail.com

Ethics Committee Approval
The study was approved by Non-invasive Clinical Research Ethics Committee of Niğde Ömer Halisdemir University (Date: April 14, 2023, no: 2023/15).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2024 March 19

Abstract

Background/Aim: Epidemiological investigations consistently indicate a widespread deficiency and insufficiency of vitamin D on a global scale. Vitamin D deficiency can lead to various acute and chronic diseases, including pre-eclampsia, autoimmune disorders, cardiovascular diseases, certain cancers, type 2 diabetes, and neurological disorders. However, the relationship between vitamin D status and its implications for global and public health has not been comprehensively explored. Notably, the differing clinical decision thresholds for diagnosing vitamin D deficiency and insufficiency established by various associations can create diagnostic confusion. Therefore, our study aimed to assess the distribution of vitamin D levels in Niğde province, considering variations by month, gender, and season, with respect to the clinical decision thresholds defined by different associations.

Methods: The study sample comprised 57,731 cases (71% women and 19% men) admitted to our hospital between January 2021 and December 2022. We retrospectively evaluated 25-hydroxyvitamin D (25(OH)D) levels based on months, seasons, age, and gender. Additionally, we examined 25(OH)D levels separately using the clinical decision thresholds set by the Vitamin D Council, the Endocrine Society, and the Food and Nutrition Board. Patients with chronic renal insufficiency, hepatic insufficiency, and gastrointestinal malabsorption were excluded from the study, encompassing patients of all age groups. Furthermore, we categorized patients into different age decades and analyzed their vitamin D levels. We compared the same months in 2021 and 2022, monitoring changes in vitamin D levels throughout the year. Vitamin D levels were measured using the electrochemiluminescence assay (ECLIA) on a Roche Cobas E801 instrument.

Results: When comparing the same months in 2021 and 2022, there was no statistically significant decrease or increase in 25(OH)D levels (The P-values for January and December were 0.066, 0.395, 0.907, 0.465, 0.705, 0.541, 0.625, 0.860, 0.695, 0.549, 0.892, and 0.838, respectively). Vitamin D insufficiency was observed in 70.3% of women and 29.7% of men. Participants under one year of age exhibited the highest mean 25(OH)D level (34.9 ng/mL), while participants between 20 and 29 years of age had the lowest mean 25(OH)D level (15.7 ng/mL). The lowest mean 25(OH)D level was recorded in April 2022 (15.6 ng/mL), whereas the highest mean 25(OH)D level was observed in July 2021 (22.7 ng/mL). There was a slight negative correlation between age and 25(OH)D levels ($r=-0.038$, $P<0.001$). The Vitamin D Council classification identified the highest number of patients with vitamin D deficiency (n=50,833; 88%). The Food and Nutrition Board included the lowest number of patients with vitamin D deficiency (n=15,049; 26.1%).

Conclusion: Vitamin D deficiency is prevalent in Niğde province, particularly among women, and remains a significant public health concern. We advocate for the adoption of a unified clinical decision threshold and the expansion of the national vitamin D supplementation program to encompass adolescents and adults.

Keywords: vitamin D, phosphorus, calcium, vitamin D deficiency

How to cite: Bayram E, Ayan D, Balcı T, Aydoğan KZ, İnan DB, Karabay U. Vitamin D distribution by month, sex, and season in Turkey, Niğde province: A retrospective cohort study. J Surg Med. 2024;8(3):59-64.

Introduction

Vitamin D plays a crucial role in maintaining the balance of phosphorus and calcium in the body. It is also a fat-soluble vitamin essential for the health of bones, teeth, and muscles [1]. Vitamin D deficiency is a global public health concern with a high prevalence and adverse effects on both musculoskeletal and nonskeletal health [2]. A deficiency in vitamin D is closely associated with an increased risk of various conditions, including infections, type 1 and type 2 diabetes mellitus, obesity, cardiovascular disease, asthma, breast cancer, ovarian cancer, prostate cancer, colon cancer, and certain neurological diseases [1].

The cholesterol-like precursor molecule (7-dehydrocholesterol) found in skin epidermal cells can undergo transformation into pre-vitamin D, which, upon exposure to UV-B radiation (wavelength 290-315 nm), is isomerized into vitamin D3. Vitamin D3, in its initial form, is biologically inactive and requires enzymatic conversion to become active. Initially, it undergoes a process of 25-hydroxylation in the liver to become 25-hydroxyvitamin D (25(OH)D), which serves as the primary circulating form of vitamin D. Subsequently, in the kidneys, it is further converted through 1-alpha-hydroxylation to become 1,25(OH)2D, also known as calcitriol [3].

The level of 25(OH)D in serum and plasma serves as a marker reflecting the overall vitamin D status [4]. Although various organizations establish different clinical thresholds for assessing 25(OH)D status, many experts consider levels below 20 ng/mL as indicative of vitamin D insufficiency [5]. Interpretation of vitamin D results can vary among experts due to these differing clinical thresholds, making standardization and interpretation challenging [5]. Furthermore, vitamin D levels are influenced by factors such as age, sex, angle of sunlight exposure, subcutaneous synthesis, and the number of sunny days [6].

Vitamin D deficiency poses a significant global and societal concern, but the varying clinical thresholds adopted by different medical associations can lead to confusion when assessing patient outcomes. To address the issues stemming from these disparities, we conducted a retrospective analysis of two years' worth of patient data in Niğde Province. Our evaluation of vitamin D deficiency took into account factors such as age, gender, age deciles, seasons, months, and the diverse clinical thresholds established by various organizations.

Materials and methods

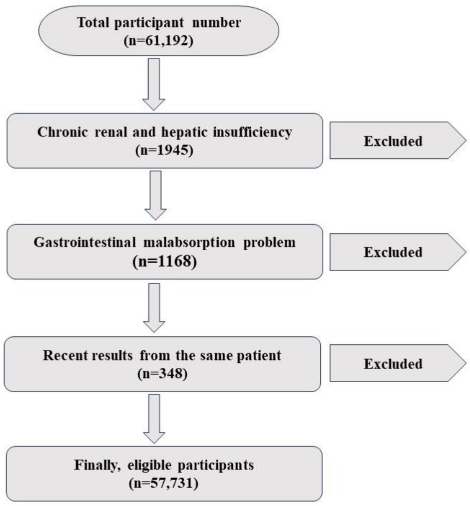
Research design

Our study is a retrospective cohort analysis. The sample consisted of 57,731 cases, with 40,966 (71.0%) being women and 16,765 (29%) being men, who were admitted to our hospital between January 2021 and December 2022 in Niğde, Turkey (latitude 37° 57' 59.99" N). We grouped and evaluated 25(OH)D levels with respect to age, age decades, sex, season, and months. Additionally, we conducted a correlation analysis to examine the relationship between age and 25(OH)D levels.

Vitamin D insufficiency and deficiency were assessed with consideration to different clinical decision points, including those established by the Vitamin D Council (VDC), the Endocrine Society (ES), and the Food and Nutrition Board (FNB). For our assessment, we utilized the clinical decision points defined by the ES, which categorize vitamin D deficiency as 0-20 ng/mL and vitamin D insufficiency as 21–29 ng/mL.

Given the retrospective nature of our cohort study, we were unable to ascertain whether the cases had used vitamin D supplements. We have addressed this limitation in the corresponding section. To maintain the integrity of our study, we excluded cases with chronic renal and hepatic insufficiency, as well as those with gastrointestinal malabsorption. Additionally, patients with recent repeat test results were excluded from the analysis. Diagnosis information for the patients was obtained from the hospital information system (Figure 1).

Figure 1: Flowchart of the study



Patients of all age groups were included in the study. Our research was approved by the Niğde Ömer Halisdemir University Non-Invasive Clinical Research Ethics Committee (Date: April 14, 2023, Approval number: 2023/15).

Laboratory analysis

Blood samples were collected in anticoagulant-free tubes for the measurement of serum 25(OH)D levels. These blood samples were then subjected to centrifugation at 2000g for 10 min at 25°C to obtain serum samples. Subsequently, these serum samples were analyzed using electrochemiluminescence (ECLIA) on a Cobas E801 instrument by Roche Diagnostic.

The measurement range for serum 25(OH)D levels was 3 to 100 ng/mL. Any measurements exceeding 100 ng/mL were diluted and adjusted using a multiplication factor.

Based on the analysis of five-level human serum pools by the manufacturer, which had mean concentrations of 10.5, 21.1, 24.9, 54.9, and 94.3 ng/mL, the coefficient of variation (CV%) for intra-study reproducibility was 7.4%, 4.6%, 3.9%, 3.1%, and 2.8%, respectively. The overall CV% values for reproducibility in the same serum pools were 8.9%, 5.9%, 4.9%, 3.8%, and 3.8%, respectively.

The limit of detection (LOD) was determined to be 3 ng/mL, and the limit of quantitation (LOQ) was determined to be 5 ng/mL using the Clinical and Laboratory Standards Institute (CLSI) EP17 A2 method.

Vitamin D interpretation

To interpret vitamin D levels, we primarily relied on the clinical decision points established by different organizations. According to the ES, levels below 20 ng/mL are classified as vitamin D deficiency, levels between 21 and 29 ng/mL are categorized as vitamin D insufficiency, levels between 30 and 100 ng/mL are considered optimal, and levels above 100 ng/mL are regarded as potentially harmful [7].

In reference to the VDC, levels below 30 ng/mL are defined as vitamin D deficiency, levels between 31 and 39 ng/mL are labeled as vitamin D insufficiency, levels between 40 and 80 ng/mL are designated as optimal, levels between 81 and 149 ng/mL are categorized as vitamin D excess, and levels above 150 ng/mL are considered potentially harmful [5].

Considering the FNB guidelines, levels below 11 ng/mL are recognized as vitamin D deficiency, levels between 12 and 20 ng/mL are categorized as vitamin D insufficiency, levels between 21 and 100 ng/mL are considered optimal, and levels above 100 ng/mL are deemed potentially harmful [8].

Statistical analysis

Statistical analysis was conducted using SPSS for Windows, version 15.0, with a significance level set at 0.05. Descriptive statistics, including mean, median, minimum, maximum, standard error of the mean, and percentages, were employed to summarize the data. To assess normality, the Shapiro-Wilk test was applied, revealing that the data did not follow a normal distribution. Consequently, pairwise comparisons were conducted using the Mann-Whitney U test.

To explore the relationship between age and vitamin D levels, Spearman's correlation coefficient was calculated. Power analysis was performed using G*power 3.1.9.7, with a significance level (α) of 0.05 and a target power of 95%.

Results

Statistical analysis was conducted using SPSS for Windows, version 15.0, with a significance level set at 0.05. Descriptive statistics, including mean, median, minimum, maximum, standard error of the mean, and percentages, were employed to summarize the data. To assess normality, the Shapiro-Wilk test was applied, revealing that the data did not follow a normal distribution. Consequently, pairwise comparisons were conducted using the Mann-Whitney U test.

To explore the relationship between age and vitamin D levels, Spearman's correlation coefficient was calculated. Power analysis was performed using G*power 3.1.9.7, with a significance level (α) of 0.05 and a target power of 95%.

According to the VDC, none of our participants had 25(OH)D levels above 150 ng/mL. However, in accordance with the ES and the FNB guidelines, eight participants exhibited 25(OH)D levels that could potentially have a toxic effect. Across all three organizations, both vitamin D deficiency and insufficiency were more prevalent among female participants than their male counterparts. The classification by the VDC indicated the highest number of participants with vitamin D deficiency (n=50,833, 88%). In contrast, the FNB identified the lowest number of patients with vitamin D deficiency (n=15,049, 26.1%). This discrepancy is due to the fact that the VDC employs a broader range for defining vitamin D deficiency (0-30 ng/mL) compared to the ES and the FNB.

Table 1: Distribution of 25(OH)D levels by month and sex

Months	**n**	**Sex distribution**		**Mean(SEM) 25(OH)D(ng/mL)**	***P*-value**
		Female	Male		
January 2021	2121	66.8%	34.2%	19.5 (0.24)	0.066
January 2022	2229	69.9%	30.1%	17.9 (0.24)	
February 2021	2047	69.9%	30.1%	19.7 (0.25)	0.395
February 2022	2376	70.5%	29.5%	16.0 (0.23)	
March 2021	2410	70.9%	29.1%	19.9 (0.24)	0.907
March 2022	2990	72.3%	27.7%	16.3 (0.24)	
April 2021	1739	71.6%	28.4%	18.0 (0.27)	0.465
April 2022	2792	68.9%	31.1%	15.6 (0.25)	
May 2021	1154	68.9%	31.1%	19.7 (0.34)	0.705
May 2022	2625	71.8%	28.2%	17.7 (0.33)	
June 2021	2311	71.7%	28.3%	20.1 (0.22)	0.541
June 2022	3242	70.6%	29.4%	20.1 (0.22)	
July 2021	1716	70.9%	29.1%	22.7 (0.26)	0.625
July 2022	2115	70.8%	29.2%	22.6 (0.27)	
August 2021	1778	71.4%	28.6%	21.4 (0.24)	0.860
August 2022	3003	69.4%	30.6%	23.1 (0.26)	
September 2021	1829	71.2%	28.7%	21.9 (0.25)	0.695
September 2022	3226	72.4%	27.6%	22.0 (0.24)	
October 2021	1739	73.7%	26.3%	20.5 (0.25)	0.549
October 2022	2824	71.6%	28.4%	21.7 (0.23)	
November 2021	2178	68.7%	31.3%	18.9 (0.22)	0.892
November 2022	3580	71.7%	28.3%	19.9 (0.20)	
December 2021	2318	71.6%	28.4%	17.2 (0.22)	0.838
December 2022	3389	71.9%	28.1%	17.9 (0.21)	

Table 2: Vitamin D Levels according to three organization

Vitamin D Council					
Sex	**Deficient 0-30 ng/mL**	**Insufficient 31-39 ng/mL**	**Sufficient 40-80 ng/mL**	**Excess 81-149 ng/mL**	**Possible harm >150 ng/mL**
Female (n)	36,503	2776	1570	117	-
%	71.80%	62.90%	67.40%	76.50%	-
Male (n)	14,330	1638	761	36	-
%	28.20%	37.10%	32.60%	23.50%	-
Total	50,833	4414	2331	153	
In terms of females (n=40,966)	36,503 (89.10%)	2776 (6.80%)	1570 (3.80%)	117 (0.30%)	-
In terms of males (n=16,765)	14,330 (85.50%)	1638 (9.80%)	761 (4.50%)	36 (0.20%)	-
Endocrine Society					
Gender	Deficient 0-20 ng/mL	Insufficient 21-29 ng/mL	Sufficient 30-100 ng/mL	Possible harm >100 ng/mL	
Female (n)	27,658	8354	4945	4	
%	70.30%	60.90%	63.80%	50.00%	
Male (n)	8598	5366	2802	4	
%	23.70%	39.10%	36.20%	50.00%	
Total	36,256	13.720	7747	8	
In terms of females (n=40,966)	27.658 (67.50%)	8354 (20.40%)	4945 (12.09%)	4 (0.01%)	
In terms of males (n=16,765)	8598 (51.28%)	5366 (32.00%)	2802 (16.70%)	4 (0.02%)	
Food and Nutrition Board					
Gender	Deficient 0-11 ng/mL	Insufficient 12-20 ng/mL	Sufficient 21-100 ng/mL	Possible harm >100 ng/mL	
Female (n)	12,894	14,764	13,299	4	
%	85.70%	69.70%	61.90%	50.00%	
Male (n)	2155	6425	8186	4	
%	14.30%	30.30%	38.10%	50.00%	
Total	15,049	21,189	21,485	8	
In terms of females (n=40.966)	12,894 (31.50%)	14,764 (36.04%)	13,299 (32.46%)	4 (0.01%)	
In terms of males (n=16.765)	2155 (12.85%)	6425 (38.30%)	8186 (48.83%)	4 (0.02%)	

Figure 2 illustrates the distribution of vitamin D levels across different seasons. Outliers falling outside the 2.5–97.5 percentile range were excluded from the analysis. Participants exhibited their highest 25(OH)D levels during the summer of both 2021 and 2022. In contrast, the lowest 25(OH)D levels were observed during the winter of 2022 and the spring of 2022.

A weak negative correlation was observed between age and 25(OH)D levels (r=-0.038, P<0.001) (Figure 3). Table 3 presents the distribution of 25(OH)D levels across age decades. Participants aged under one year exhibited the highest mean 25(OH)D level (34.9 ng/mL), while those aged between 20 and 29 years had the lowest mean 25(OH)D level (15.7 ng/mL).

Figure 2: The Distribution of 25(OH)D levels by season (2.5–97.5 percentile)

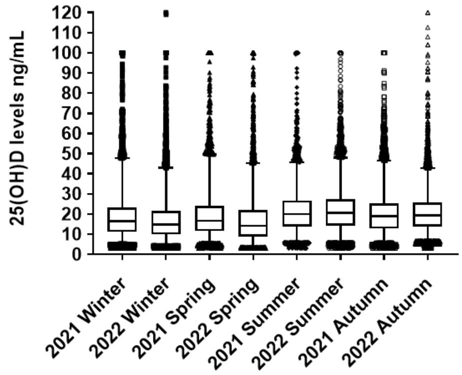


Figure 3: Correlation between age and 25(OH)D levels

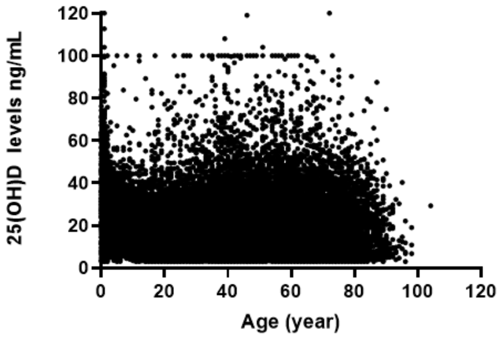


Table 3: 25(OH)D levels in terms of decades

25(OH)D level (ng/mL)	Age groups (years)								
	<1 n=166	1-9 n=9679	10-19 n=7547	20-29 n=7456	30-39 n=7703	40-49 n=8968	50-59 n=7340	60-69 n=5120	≥70 n=3752
Min–Max	3-120	3-120	3-100	3-100	3-108	3-119	3-104	3-100	3-120
Mean	34.9	24.7	16.4	15.7	17.7	18.8	20.1	21.1	20.5
SD	20.3	11.1	8.1	9.1	10.4	10.9	11.3	12.1	12.3
Median	32.1	23.1	15.3	14.0	15.8	17.0	18.4	19.2	18.4
Percent	0.3%	16.8%	13.1%	12.9%	13.3%	15.5%	12.7%	8.9%	6.5%

Min: minimum, Max: Maximum

Discussion

The study investigated the distribution of 25(OH)D levels among residents of Niğde Province, which is located in proximity to both the Mediterranean and Central Anatolian regions. Additionally, the study assessed 25(OH)D levels in relation to the clinical decision points of the VDC, ES, and FNB.

Our results revealed a higher prevalence of vitamin D insufficiency and deficiency among female participants compared to their male counterparts. Furthermore, the findings demonstrated significant variations in vitamin D deficiency with respect to the clinical decision points of the VDC, ES, and FNB. Notably, this study represents the inaugural investigation into the distribution of 25(OH)D levels among residents of Niğde Province.

Vitamin D deficiency and insufficiency are prevalent on a global scale [9], and our findings align with previous studies conducted among both general and local populations [10-13]. However, a discrepancy arises when different clinical decision points are used to assess vitamin D status [14,15]. In our study, we adopted the clinical decision points established by the ES, but we also compared them to those specified by two other organizations. Our results revealed that a significant majority of participants (n=50,833; 88%) were classified as vitamin D deficient according to the VDC criteria, which define vitamin D insufficiency as levels below 30 ng/mL. Meanwhile, according to the ES criteria, more than half of the participants (n=36,256; 62.8%) fell into the vitamin D deficient category, with vitamin D insufficiency defined as levels below 20 ng/mL. Lastly, based on the FNB criteria, over a quarter of the participants (n=15,049; 26.1%) were classified as vitamin D deficient, with vitamin D insufficiency defined as levels below 11 ng/mL. Remarkably, when categorized according to the criteria of these organizations, the number of participants with vitamin D insufficiency or optimal vitamin D levels appeared quite similar. Consequently, this discrepancy in vitamin D deficiency classification may pose diagnostic challenges.

Kader et al. [16] conducted a study in Karapınar, a neighboring settlement to Niğde province, where they reported two significant findings. First, they observed a higher prevalence of vitamin D deficiency and insufficiency among women compared to men. Second, they noted that older adults exhibited a higher incidence of vitamin D deficiency and insufficiency.

In a separate study conducted by Göktaş et al. [11] in the province of Bursa, Turkey, it was revealed that female participants had significantly lower vitamin D levels than their male counterparts. Additionally, they found that local residents had the highest vitamin D levels between March and May but the lowest levels between September and October.

Sezgin et al. [6] focused on vitamin D levels among the population residing in the Marmara region, documenting that three out of four people (75%) had vitamin D insufficiency (<20 ng/mL). Similarly, Hekimsoy et al. [12] conducted a cross-sectional study in the Aegean region and reported that three out of four individuals exhibited vitamin D insufficiency (74.9%) (<20 ng/mL).

In a study carried out by Vurmaz et al. [17] in Afyonkarahisar province, it was found that vitamin D insufficiency was more prevalent among women compared to men.

Finally, Solak et al. [18] conducted a large-scale study in Central Anatolia, reporting two significant findings. First, three out of four individuals had 25(OH)D levels below 20 ng/mL (76.25%). Secondly, women exhibited a lower mean of vitamin D levels.

We found that three out of five participants were vitamin D deficient (62.8%), according to the classifications of three different organizations. Additionally, our findings revealed that vitamin D deficiency was more common among female participants than male participants, a trend consistent with existing literature [6,11,12]. Research indicates that the prevalence of vitamin D insufficiency in Turkey ranges from 58.9% to 66.6%. Furthermore, studies have shown that newborns, pregnant women, and adult women are at an increased risk of vitamin D insufficiency. Alpdemir et al. [19] recommend that experts regularly monitor the 25(OH)D levels of Turkish individuals and encourage the use of vitamin D supplements when necessary.

In a large-scale study, Yeşiltepe-Mutlu et al. [13] assessed the effectiveness of the national vitamin D supplementation program in Turkey. They reported two significant findings. First, vitamin D deficiency was nearly eliminated in children under one year of age. Second, populations aged 11–18 years and 19–30 years had lower 25(OH)D levels than other groups, with levels below 20 ng/mL. Erol et al. [10] emphasized that vitamin D insufficiency is a critical issue among Turkish children and adolescents. They also noted that vitamin D insufficiency persists from late winter through late summer despite vitamin D treatment. Andıran et al. [20] documented the widespread prevalence of vitamin D deficiency in Turkish female adolescents.

Our findings indicate that the national vitamin D program has effectively eradicated vitamin D deficiency in children under one year of age, with a mean 25(OH)D level of 34.9 ng/mL. However, our data reveals that one in four children aged 1–9 years exhibited an average 25(OH)D level of 24.6 ng/mL. Additionally, a notable decline in 25(OH)D levels during adolescence was observed, resulting in vitamin D insufficiency (25(OH)D levels <20 ng/mL). Specifically, our study highlights that individuals aged 20–29 years displayed the lowest 25(OH)D levels.

Turkey is situated between 36–42° north latitude and 26–45° east longitude. At higher latitudes, the solar zenith angle becomes very oblique between November and February, resulting in limited ultraviolet B (UVB) photon penetration to the Earth's surface. UVB radiation is crucial for synthesizing 25(OH)D [21,22]. In Turkey, the window for vitamin D synthesis falls between May and November. It is advisable for people in Turkey to spend time outdoors between 10:00 and 15:00 to optimize their vitamin D synthesis, as this is when the sunlight angle is most conducive [18].

Serum 25(OH)D levels are influenced by both dietary intake and sun exposure. Therefore, research findings suggest that deficiencies become more conspicuous as children grow older [21-23]. Our results affirm that advancing age accentuates vitamin D deficiency in adolescents and adults. Specifically, we observed the two lowest mean 25(OH)D levels in April 2022 (15.6 ng/mL) and February 2022 (16 ng/mL). Conversely, the two highest mean 25(OH)D levels were noted in July 2021 (22.7 ng/mL) and July 2022 (22.6 ng/mL).

Certain changes in 25(OH)D metabolism occur as individuals age, including a reduction in vitamin D receptor levels, renal 1.25(OH)2D synthesis, and cutaneous 25(OH)D production [24]. Çağlayan et al. [25] and Şenyiğit et al. [26] have corroborated these findings, confirming a decline in 25(OH)D levels with increasing age. In our study, we identified a weak negative correlation between age and 25(OH)D levels. Our assessment of the geriatric population revealed a progressive increase in vitamin D insufficiency with advancing age.

Limitations

This study presents four notable limitations. First, we lack data regarding the duration of participants' sunlight exposure, their use of vitamin D supplements, their body mass index, and their choice of attire. Second, comprehensive information on parathyroid hormone, calcium, phosphorus, and magnesium levels was not available for all patients. Third, we did not possess data pertaining to rickets, osteomalacia status, or bone mineral density. Nevertheless, despite these limitations, the substantial dataset employed in this study allows for robust conclusions regarding the relationship between age, sex, and supplementation with 25(OH)D measurements.

Fourth, it's worth noting that the number of female participants significantly exceeded that of male patients, which may have implications for assessing vitamin D insufficiency. Had there been a larger number of male participants, it is plausible that the average 25(OH)D levels might have been higher. Nonetheless, the relatively balanced gender distribution in our study remains an acceptable parameter for evaluating vitamin D insufficiency. Further investigations with a more even distribution of male and female participants are warranted to explore the underlying causes of vitamin D deficiency or insufficiency.

Conclusion

Our findings align with those of studies conducted in various regions of Turkey. Consequently, vitamin D deficiency appears to be a prevalent issue in Niğde province. Notably, the prevalence of vitamin D deficiency is higher among female participants compared to male participants. While the national vitamin D supplementation program appears to be beneficial for infants under one year of age, our data underscores that vitamin D levels decline with increasing age. Consequently, there is a need for the implementation of national supplementation programs targeting other age groups as well. We assert the importance of establishing population-based cutoff values to guide the development of comprehensive national vitamin D supplementation initiatives.

It is worth noting that although Turkey currently employs the clinical decision points of the ES for assessing vitamin D, variations in clinical decision points across different organizations may lead to discrepancies, particularly in diagnosing vitamin D deficiency. Therefore, fostering a consensus among organizations regarding vitamin D deficiency criteria could enhance the effectiveness of treatment strategies. We advocate for further research to corroborate our findings in future studies.

References

1. de La Puente-Yagüe M, Cuadrado-Cenzual MA, Ciudad-Cabañas MJ, Hernández-Cabria M, Collado-Yurrita L. Vitamin D: And its role in breast cancer. Kaohsiung J Med Sci. 2018;34:423-7. doi: 10.1016/j.kjms.2018.03.004.
2. Sosa Henríquez M, Gómez de Tejada Romero MJ. Cholecalciferol or Calcifediol in the Management of Vitamin D Deficiency. Nutrients. 2020;12. doi: 10.3390/nu12061617.
3. Chang SW, Lee HC. Vitamin D and health - The missing vitamin in humans. Pediatr Neonatol. 2019;60:237-44. doi: 10.1016/j.pedneo.2019.04.007.
4. Veugelers PJ, Pham TM, Ekwaru JP. Optimal Vitamin D Supplementation Doses that Minimize the Risk for Both Low and High Serum 25-Hydroxyvitamin D Concentrations in the General Population. Nutrients. 2015;7:10189-208. doi: 10.3390/nu7125527.
5. Sempos CT, Binkley N. 25-Hydroxyvitamin D assay standardisation and vitamin D guidelines paralysis. Public Health Nutr. 2020;23:1153-64. doi: 10.1017/S1368980019005251.
6. Sezgin G, Ozturk G, Turkal R, Caykara B. Vitamin D Levels of Outpatients Admitted to a University Hospital in the Marmara Region of Turkey Over 3 Years. J Med Biochem. 2019;38:181-7. doi: 10.2478/jomb-2018-0027
7. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon MC, Hanley DA, Heaney HP, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1911-30. doi: 10.1210/jc.2011-0385.
8. Ross AC, Taylor CL, Yaktine AL, Del Valle HB. Dietary reference intakes for calcium and vitamin D. National Academies Press (US) Washington (DC). 2011. doi: 10.17226/13050
9. van der Meer IM, Middelkoop BJ, Boeke AJ, Lips P. Prevalence of vitamin D deficiency among Turkish, Moroccan, Indian and sub-Sahara African populations in Europe and their countries of origin: an overview. Osteoporos Int. 2011;22:1009-21. doi: 10.1007/s00198-010-1279-1.
10. Erol M, Yiğit Ö, Küçük SH, Bostan GÖ. Vitamin D Deficiency in Children and Adolescents in Bağcılar, İstanbul. J Clin Res Pediatr Endocrinol. 2015;7:134-9. doi: 10.4274/jcrpe.1888.
11. Göktaş O, Ersoy C, Ercan I, Can FE. Vitamin D status in the adult population of Bursa-Turkey. Eur J Gen Pract. 2020;26(1):156-62. doi: 10.1080/13814788.2020.1846712.
12. Hekimsoy Z, Dinç G, Kafesçiler S, Onur E, Güvenç Y, Pala T, et al. Vitamin D status among adults in the Aegean region of Turkey. BMC public health.2010;10:782. doi: 10.1186/1471-2458-10-782.

13. Yeşiltepe-Mutlu G, Aksu ED, Bereket A, Hatun Ş. Vitamin D Status Across Age Groups in Turkey: Results of 108,742 Samples from a Single Laboratory. J Clin Res Pediatr Endocrinol. 2020;12:248-55. doi: 10.4274/jcrpe.galenos.2019.2019.0097.
14. Kyriakaki A, Fragkoulis E. The vitamin D paradox: high prevalence of deficiency in sunny Athens (Greece). Ann Res Hosp. 2019;3. doi: 10.1159/000514338.
15. Díaz-Rizzolo DA, Kostov B, Gomis R, Sisó-Almirall A. Paradoxical suboptimal vitamin D levels in a Mediterranean area: a population-based study. Sci Rep. 2022;12:19645. doi: 10.1038/s41598-022-23416-1.
16. Kader S, Comaklı H, Tekindal MA. Evaluation of Serum Vitamin D Levels according to Gender and Age at Karapınar City: A Follow-Up Study from Turkey. Dubai Med J. 2019;2:141-5. doi: 10.1159/000503899.
17. Vurmaz A, Köken T. Evaluation of vitamin D levels according to season and age. Med Science. 2020;9:614-8. doi: 10.5455/medscience.2020.05.081.
18. Solak I, Cihan FG, Mercan S, Kethuda T, Eryılmaz MA. Evaluation of 25-Hydroxyvitamin D Levels in Central Anatolia, Turkey. Biomed Res Int. 2018;4076548. doi: 10.1155/2018/4076548.
19. Alpdemir M, Alpdemir MF. Vitamin D deficiency status in Turkey: A meta-analysis. Int J Med Biochem. 2019;2:118-31. doi: 10.14744/ijmb.2019.04127.
20. Andıran N, Çelik N, Akça H, Doğan G. Vitamin D deficiency in children and adolescents. J Clin Res Pediatr Endocrinol. 2012;4:25-9. doi: 10.4274/jcrpe.574.
21. Sahin ON, Serdar M, Serteser M, Unsal I, Ozpinar A. Vitamin D levels and parathyroid hormone variations of children living in a subtropical climate: a data mining study. Ital J Pediatr. 2018;44:40. doi: 10.1186/s13052-018-0479-8.
22. Looker AC, Dawson-Hughes B, Calvo MS, Gunter EW, Sahyoun NR. Serum 25-hydroxyvitamin D status of adolescents and adults in two seasonal subpopulations from NHANES III. Bone. 2002;30:771-7. doi: 10.1016/s8756-3282(02)00692-0.
23. Biçer C, Üstebay S. Relationship between vitamin D receptor gene polymorphisms and vitamin D levels in children. J Surg Med. 2021;5;349-352. doi: 10.28982/josam.911212
24. Gallagher JC. Vitamin D and aging. Endocrinol Metab Clin North Am. 2013;42:319-32. doi: 10.1016/j.ecl.2013.02.004.
25. Çağlayan M, Sonmez C, Senes M, Gonel A, Gulbahar O, Bursa N, et al. 25-hydroxyvitamin D (25-OHD) levels in Turkish geriatric population: A nationwide study. J Med Biochem. 2022;41:450-8. doi: 10.5937/jomb0-36921.
26. Şenyiğit A, Orhanoğlu T, Burak İ, Yaprak B. Vitamin D levels in routine medical examination. J Ist Faculty Med. 2018;81:115-8. doi: 10.26650/IUITFD.391192.

J Surg Med. 2024;8(3):65-68.
https://doi.org/10.28982/josam.7440

JOSAM
Journal of Surgery and Medicine
e-ISSN: 2602-2079

Case report
https://jsurgmed.com/

Does sodium phosphate enema use cause electrolyte disorder?

Songül Tomar Güneysu [1], Okşan Derinöz Güleryüz [1], Nazmi Mutlu Karakaş [2], Özlem Çolak [1]

[1] Gazi University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Emergency, Ankara, Turkey
[2] Gazi University Faculty of Medicine, Department of Pediatrics, Ankara, Turkey

ORCID of the author(s)

STG: https://orcid.org/0000-0003-0573-978X
ODG: https://orcid.org/0000-0001-7348-0656
NMK: https://orcid.org/0000-0003-4286-7086
ÖÇ: https://orcid.org/0000-0001-7939-8506

Corresponding Author
Songul Tomar Guneysu
Division of Pediatric Emergency, Department of Pediatrics, Gazi University Faculty of Medicine, Ankara, Turkey
E-mail: tomarsongul@gmail.com

Informed Consent
The authors stated that the written consent was obtained from the parents of the patient presented with images in the study.

Conflict of Interest
No conflict of interest was declared by the authors.

Financial Disclosure
The authors declared that this study has received no financial support.

Published
2024 March 16

Abstract

Constipation is one of the most common symptoms in childhood. Sodium-phosphate enemas are frequently preferred for the treatment of constipation and bowel cleansing. We present a case of a 5-year-old boy who presented to the Pediatric Emergency Department with complaints of constipation, abdominal pain, abdominal distension and vomiting; had been constipated for about two years and had poor nutrition, and received a full dose of CT enema® twice in the last 12 hours before admission to the hospital. Upon arrival at the Pediatric Emergency Department, the patient was given a pediatric fleet enema because he had dense stools according to radiographic evidence. Poisoning due to Sodium-phosphate enema was considered due to severe hyperphosphatemia and hypocalcemia in the laboratory evaluation. Rapid intravenous hydration and 1 mL/kg calcium gluconate intravenous infusion were started. Electrolytes returned to the normal range at the 14th hour of follow-up without the need for additional treatment. This case is presented to emphasize that due to the widespread use of sodium-phosphate enemas in the treatment of chronic constipation, these enemas can cause phosphate poisoning even when used in healthy patients at therapeutic doses.

Keywords: sodium-phosphate enema, hyperphosphatemia, hypocalcemia, constipation

Introduction

Constipation is a common symptom that occurs in more than 10% of children. In chronic constipation, gastrointestinal, endocrine, neurological, and metabolic system abnormalities are primarily investigated. When no cause is found, the patient is diagnosed with functional constipation [1].

Sodium-phosphate (Na-P) enemas are frequently used in the treatment of chronic constipation and fecaloma in primary care, with hospitalized children, and in emergency departments due to their small volume, effectiveness in relieving constipation, ease of use, and safety [2–3]. Poisoning is rare after rectally administered hypertonic phosphate solutions in healthy children [4]. Phosphate enema poisoning causes electrolyte disturbances, and hyperphosphatemia is the most common [5].

This case is presented to emphasize that due to the widespread use of Na-P enemas in the treatment of chronic constipation, these enemas can cause phosphate poisoning, even when used in healthy patients at therapeutic doses.

How to cite: Güneysu ST, Güleryüz OD, Karakaş NM, Çolak Ö. Does sodium phosphate enema use cause electrolyte disorder? J Surg Med. 2024;8(3):65-68.

Case presentation

A five-year-old male patient was admitted to the pediatric emergency department with complaints of constipation, abdominal pain, abdominal distension, and vomiting. The patient, who did not have stool for about 15 days, also had widespread abdominal pain and vomiting seven times, including what he ate. From his history, it was learned that he had constipation for two years, irregularly used oral laxatives, and had poor nutrition. The family often induces defecation through enema.

He was a child with normal neurological development. It was learned from his family history that he had second-degree parental consanguinity. His mother had 10 pregnancies, three of which died in the intrauterine period, and three died at the age of one due to spinal muscular atrophy (SMA). Two of the other children were healthy, and one had a history of operation due to vesicourethral reflux.

At the initial evaluation, body temperature was 36°C, pulse rate was 96/min, respiratory rate was 24/min, blood pressure was 100/60 mmHg, and oxygen saturation was 96%. On physical examination, the general appearance was good, and there was no sign of dehydration. In his gastrointestinal examination, the abdomen was distended, and there was no tenderness, defense, rebound, or palpable mass. There was a small amount of stool output during the rectal examination. Other system examinations were normal. His body weight was 10^{th} percentile (16 kilograms), and his height was in the 10–25 percentile (105 centimeters).

In the standing direct abdominal X-ray, there was a dense stool appearance and dilated bowel loops (Figure 1). The pediatric surgery department was consulted because of abdominal distention, lack of stool output, and preliminary diagnosis of intestinal pseudo-obstruction, anorectal malformations, and Hirschsprung's disease. A Fleet pediatric enema® was applied to the patient who was recommended to have an enema, and there was copious stool output after 10 minutes. There was an increase in the appearance of dense stool and dilated bowel loops in the standing straight abdominal X-ray taken after the enema was applied, and no distal transition was observed (Figure 2). Abdominal ultrasonography revealed a *"globe vesical, rectum wall thickness of 6 mm"*.

In laboratory examination, blood gas was normal, blood glucose 102 mg/dL, calcium 6.4 mg/dL (8.8-10.8), ionized calcium 0.69, phosphorus 18.9 mg/dL (4–7), and magnesium was in the normal range. The laboratory results and history of the patient were re-evaluated, and it was learned that a full dose of CT enema® was administered twice in the last 12 hours in an external center. The patient was diagnosed with hyperphosphatemia and hypocalcemia due to Na-P enemas based on his history, physical examination, and laboratory results. Half saline intravenous (IV) hydration at 3000 mL/m2/day was started, and 1 mL/kg calcium gluconate IV infusion was given. Phosphorus level at the second hour of hydration was 11.3 mg/dL, at 6 hours 7.2 mg/dL, normal limits at the 14^{th} hour.

Electrocardiogram (ECG) follow-ups were always normal. The patient, who did not need intensive care, was admitted to the pediatrics service and followed up to regulate the etiology and treatment of constipation.

Figure 1: Standing Abdominal X-ray taken in the emergency service

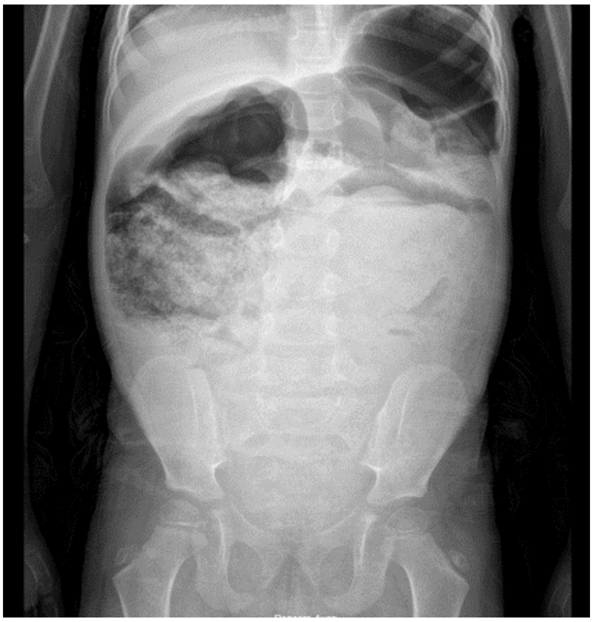


Figure 2: Standing Abdominal X-ray taken following the administration of the enema

In the examinations for the etiology of constipation, there were no atypical cells in the peripheral smear; creatine kinase (CK), lactate dehydrogenase (LDH), uric acid, and bilirubin values were within normal limits. Thyroid function tests and thyroid ultrasonography, vitamin D and parathormone, urinalysis, and metabolic tests were normal.

Abdominal computed tomography for possible abscess, malignancy, and mass exclusion noted the following: *"Rectum, sigmoid colon, more prominent in the transverse colon, diffuse diameter increase in the colon, in the lumen in the distal part of the rectum, with an enlarged appearance secondary to feces and gas content, in the thickest part of the rectum wall on the left lateral A wall thickness increase of 8 mm (secondary to constipation)"*. SMA gene analysis was sent due to sibling history, and it was normal.

No significant disease was found in etiology, and functional constipation was considered. The patient was started regularly on lactulose as a treatment for constipation. In hospital follow-up, it was observed that the patient did not have toilet habits, and with pelvic floor muscle group exercises and toilet training, defecation occurred spontaneously many times. He was discharged without sequelae on the fifth day with oral lactulose treatment. Table 1 summarizes the patient's laboratory follow-up chart.

Table 1: Laboratory follow-up chart

	Reference values	0th hour	5th hour	9th hour	14th hour	Discharge
Sodium (mmol/L)	135-145	145	142	140	137	139
Potassium (mmol/L)	3.5-5.5	3.2	3.1	3.4	3.6	4.1
Phosphorus (mg/dL)	4-7	**18.9**	**11.3**	**7.2**	6	4.2
Calcium (mg/dL)	8.8-10.8	**6.4**	9.3	8.4	8.7	9.5
Ionized calcium (mmol/L)	1.1-1.3	**0.69**			0.91	
pH	7.35-7.45	7.39			7.49	
Magnesium (mg/dL)	1.8-2.6	3.2			2.4	1.9

Verbal informed consent was obtained from the family of the patient participating in the study.

Discussion

The occurrence of hyperphosphatemia due to Na-P enema ingestion, which presents with different results, ranging from complete recovery to severe neurological deficits, has been included in the literature, with many case reports over 45 years. In one study, a case series of children who developed severe hyperphosphatemia after administration of Na-P containing laxatives between 1968 and 2010 was presented, and a systematic review of the literature was made. In that study, 28 publications with a mean age of 2.83 years (8 days–17 years) were examined. When the indications for administration were evaluated, it was reported that 26 cases were due to acute or chronic constipation, and 21 patients were administered rectally as the route of administration. Considering the underlying diseases, four patients had Hirschsprung's disease, four patients had a congenital anorectal malformation, three patients had chronic constipation, one patient had gastroschisis, one patient had Crohn's disease, and nine patients had systemic diseases, such as urological pathology and congenital syndromes. Ten patients were previously reported to be healthy [5]. While our patient was being evaluated with chronic constipation and abdominal distension, electrolyte disturbance was detected, the history was questioned again and it was learned that multiple rectal enemas were performed.

The most common cause of hyperphosphatemia is renal failure. Because the cellular content of phosphorus is higher than that of plasma phosphorus, it can release significant amounts of phosphorus in cell lysis. This explains the etiology and pathophysiology of hyperphosphatemia in tumor lysis syndrome (TLS), rhabdomyolysis and acute hemolysis. Diabetic ketoacidosis, vitamin D poisoning, hypoparathyroidism, hyperthyroidism and excessive cow's milk intake in infants are involved in the etiology of hyperphosphatemia [6]. Our case did not have a history of chronic disease that could cause elevated phosphorus. Renal function tests, CK, LDH, uric acid and bilirubin values were within normal limits. Thyroid function tests and thyroid ultrasonography, vitamin D and parathormone, as well as urine and metabolic tests were normal. There were only three enemas in the last 12 hours, which could explain the etiology.

Constipation is a common problem in childhood. Although its prevalence is 10%, it constitutes 3% of general pediatric consultations and 25% of gastroenterology consultations. One out of every three children with functional constipation experiences an attack of fecaloma. Although there are other options such as oral or enteral osmotic laxatives, osmotic enemas, lubricants and glycerin suppositories for their cleaning, Na-P enemas are commonly used in emergency departments [3]. We also use pediatric fleet enema® or Na-P enemas in our pediatric emergency clinic.

Sodium-phosphate enemas are widely used for constipation because they are hyperosmolar and are considered safe [1]. Hypertonicity causes a large movement of fluid into the intestinal lumen and the formation of a third space that allows evacuation of rectosigmoid fecal contents. Dehydration due to high osmolar effect and hypocalcemia secondary to high phosphorus absorption occur as a result of errors in dosing, administration and elimination of the enema. Phosphorus is often absorbed in the duodenum and jejunum, but it is important to note that colonic absorption may also occur at high concentrations in the rectum. The rapid increase in phosphorus can lead to calcium chelation and precipitation of calcium phosphate salts in soft tissues and kidneys, which causes acute hypocalcemia. Excess phosphorus as inorganic acid and loss of bicarbonate in the intestinal lumen causes metabolic acidosis [3].

Hyperphosphatemia may develop in individuals who receive appropriate doses of Na-P enemas, with an average increase in serum phosphorus level of 1-1.3 mEq/L [7]. Changes in serum phosphorus and calcium levels occur within approximately 40 minutes of ingestion of a phosphate-containing enema [2]. Various factors play a role in the pathophysiology of hyperphosphatemia. Increased intake of sodium and phosphate, possibly due to gastrointestinal pathologies, or decreased elimination due to impaired renal function are two of the mechanisms implicated [5]. Poisoning due to the use of phosphate enemas is especially seen in children younger than 5 years old. Conditions that alter intestinal motility such as constipation, intestinal pseudo-obstruction, paralytic ileus, anorectal malformations, Hirschsprung's disease, myelomeningocele, colostomy, muscle abnormalities including SMA, and kidney failure may increase the risk of toxicity. In rare cases, it can occur in healthy children. In this case, the most common cause is dose error [3,8]. Our patient had chronic constipation as a risk factor, and in addition, adult dose BT enema® and pediatric fleet enema® were administered twice in the last 12 hours. The SMA gene analysis yielded normal results.

Symptoms of phosphate poisoning can range from mild gastrointestinal symptoms to life-threatening fatal arrhythmias. The most common symptoms include abdominal bloating, vomiting, hypernatremic dehydration, QT prolongation and arrhythmias. In severe cases, severe hypocalcemia may lead to neurological symptoms such as irritability, paresthesia, tetany, laryngospasm, altered consciousness, coma, and hyperthermia due to hypothalamic dysfunction. The symptoms manifest within a timeframe ranging from 30 minutes to 4 hours after the administration of the enema [3]. Our patient had intermittent enema intake. Electrolyte disturbances were detected in the examinations performed 30 minutes after the last enema. Our case had no symptoms secondary to hypocalcemia and hyperphosphatemia.

The most common electrolyte imbalance in phosphate poisoning is hyperphosphatemia, which may cause hypertonic dehydration, hypocalcemia, hypokalemia and hypernatremia [4,9]. First of all, if necessary, treatment should focus on emergency airway management and cardiovascular resuscitation. Once hemodynamic stabilization is achieved, the treatment should first focus on restoring fluid status and normalizing electrolytes. Initial fluid therapy is crucial to ensure adequate perfusion and glomerular filtration rate [4-5,9]. In our patient, rapid IV hydration was administered first.

The effectiveness and safety of parenteral calcium administration are still controversial because it causes Ca-P precipitation in the kidney and other tissues, which remains a dilemma for clinicians. in a study, approximately 70% of the cases received IV calcium gluconate therapy to alleviate the symptoms of hypocalcemia [5]. Another publication reported that parenteral calcium replacement should be applied in patients with neuromuscular symptoms and cardiac arrhythmias [10]. Despite having hypocalcemia, our case was lucky because he did not have neurological or cardiovascular symptoms.

Conclusion

Sodium-phosphate enemas are commonly used in chronic constipation. However, their use can lead to life-threatening and even fatal consequences including hyperphosphatemia and secondary hypocalcemia. They should be used with more caution, especially in patients with underlying gastrointestinal or renal abnormalities. Physicians should be aware that phosphate poisoning may occur in healthy patients, even at therapeutic doses, due to rectal administration of a phosphate-containing enema. Neurological and cardiovascular symptoms should be carefully monitored, even in patients who have tolerated phosphate-containing enemas. The first step in treatment is intravenous hydration and diuresis.

References

1. Rubin G, Dale A. Chronic constipation in children. BMJ. 2006;18;333(7577):1051-5. doi: 10.1136/bmj.39007.760174.47.
2. Akyildiz B, Kondolot M, Yikilmaz A, Arslan D, Kurtoğlu S. Ileus and intra-abdominal hypertension due to phosphate-containing enema. Indian J Pediatr. 2016;83(11):1346-8. doi: 10.1007/s12098-016-2166-3.
3. Nunez Sanchez MJ, Leighton Swaneck S, Diaz F. Severe tetany due to phosphate enemas use, case report. Rev Chil Pediatr. 2017;88(3):383-7. doi: 10.4067/S0370-41062017000300011.
4. Biebl A, Grillenberger A, Schmitt K. Enema-induced severe hyperphosphatemia in children. Eur J Pediatr. 2009;168(1):111-2. doi: 10.1007/s00431-008-0705-2.
5. Ladenhauf HN, Stundner O, Spreitzhofer F, Deluggi S. Severe hyperphosphatemia after administration of sodium-phosphate containing laxatives in children: case series and systematic review of literature. Pediatr Surg Int. 2012;28(8):805-14. doi: 10.1007/s00383-012-3124-4.
6. Greenbaum LA. Hyperphosphatemia. In: R.M. Klıegman, J.W.ST. Geme III editors, Nelson Textbook of Pediatrics, 21 edition. pp. 2123-2124.
7. Adamcewicz M, Bearelly D, Porat G, Friedenberg FK. Mechanism of action and toxicities of purgatives used for colonoscopy preparation. Expert Opin Drug Metab Toxicol. 2011;7(1):89-101. doi: 10.1517/17425255.2011.542411.
8. Marraffa JM, Hui A, Stork CM. Severe hyperphosphatemia and hypocalcemia following the rectal administration of a phosphate-containing Fleet pediatric enema. Pediatr Emerg Care. 2004;20(7):453-6. doi: 10.1097/01.pec.0000132217.65600.52.
9. Pawlık W, Drzonek P, Nowak K. Severe Hyperphosphatemıa As The Adverse Effect Of Sodıum-Phosphate Enemas Use: Case Report And Revıew Of The Lıterature. In: The Book Of Articles National Scientific Conference "1st Summer Scientific On-Line School". 2020. pp. 68.
10. Szoke D, Dolci A, Genderini A, Panteghini M. Fatal electrolyte abnormalities following enema administration. Clin Chem. 2012;58(11):1515-8. doi: 10.1373/clinchem.2011.170183.