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Frailty Index is Associated with Vitamin D Insufficiency in Geriatric Surgery Patients: A Prospective Observational Study

Geriatrik Cerrahi Hastalarında Kırılganlık İndeksi D Vitamini Yetersizliği ile İlişkilidir: Prospektif Gözlemsel Çalışma

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ABSTRACT

Objective: In this study, we aimed to investigate the relationship between vitamin D, frailty and postoperative outcomes in geriatric patients undergoing elective surgery.

Methods: In this prospective observational study, a total of 90 elderly patients who had undergone non-cardiac surgery were included. The patients were classified according to the frailty index (FI) score as "Non-frail (FI 0), Pre-frail (FI 1–2) and Frail (FI ≥3)". In addition, patients were divided into two groups according to serum vitamin D concentration: vitamin D insufficiency group (n=41) and vitamin D sufficiency group (n=49). Clinical characteristics and postoperative outcomes of the patients were compared between the groups.

Results: The mean age of the patients was 75.7 ± 7.6 years, the admission rate to Intensive Care Unit (ICU) was 43.3%, and the 30-day mortality rate after surgery was 21.1%. The ICU admission was significantly higher in the "vitamin D insufficiency" group (n=24 versus n=15, p=0.014). In addition, fragility status patients were significantly higher in the "vitamin D insufficiency" group (n=19 versus n=7, p=0.004). Most of the non-frail patients were in the "vitamin D sufficiency" group (n=18 versus n=9).

Conclusion: In our study, we observed higher frailty in vitamin D insufficiency patients. In addition, admission to the postoperative ICU was higher in vitamin D insufficiency and frail patients. Our findings show that frailty and vitamin D insufficiency play an important role in postoperative outcomes.

Keywords: Vitamin D, frailty, geriatrics, intensive care unit

ÖZ

Amaç: Bu çalışmada elektif cerrahi uygulanan geriatrik hastalarda D vitamini, kırılganlık ve postoperatif sonuçlar arasındaki ilişkiyi araştırmayı amaçladık.

Yöntem: Bu prospektif gözlemsel çalışmaya, kalp dışı cerrahi geçirmiş toplam 90 yaşlı hasta dahil edildi. Hastalar kırılganlık indeksi (FI) skoruna göre "Kırılgan olmayan (FI 0), kırılganlık öncesi (FI 1–2) ve kırılgan (FI ≥3)" olarak sınıflandırıldı. Ayrıca hastalar serum D vitamini konsantrasyonuna göre "D vitamini yetersiz grup (n=41) ve D vitamini yeterli grup (n=49)" olmak üzere iki gruba ayrıldı. Hastaların klinik özellikleri ve postoperatif sonuçları gruplar arasında karşılaştırıldı.

Bulgular: Hastaların ortalama yaşı 75,7 ± 7,6 yıl, yoğun bakım ünitesine kabul oranı %43,3 ve ameliyat sonrası 30 günlük mortalite oranı %21,1 idi. "D vitamini yetersizliği" grubunda yoğun bakıma yatış anlamlı olarak daha yüksekti (n=24'e karşı n=15, p=0,014). Ayrıca kırılgan hastalar "D vitamini yetersizliği" grubunda anlamlı olarak daha yüksekti (n=19'a karşı n=7, p=0,004). Kırılgan olmayan hastaların çoğu "D Vitamini yeterli" grubundaydı (n=18'e karşı n=9).

Sonuç: Çalışmamızda D vitamini eksikliği olan hastalarda daha yüksek kırılganlık gözlemledik. Ayrıca D vitamini yetersizliği olan ve kırılgan hastalarda postoperatif yoğun bakıma yatış oranı daha yüksekti. Bulgularımız, postoperatif sonuçlarda kırılganlık ve D vitamini eksikliğinin önemli bir rol oynadığını göstermektedir.

Anahtar sözcükler: D vitamini, kırılganlık, geriatri, yoğun bakım ünitesi

INTRODUCTION

Due to the increase in the world population and the aging of the population, surgical procedures performed on elderly patients have increased. Perioperative management of geriatric surgery patients is becoming increasingly important in today's modern anesthesia practices (1-3). Preoperative determination of the criteria associated with perioperative complications in these patients is very important for both the

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patient and the clinician. These criteria may be useful for individualized decision-making in critically ill patients.

Anatomical and physiological changes due to aging pose a challenge for the anesthetic management of elderly patients. A decrease in physical capacity and an increase in the number of accompanying comorbidities are observed in elderly patients (1,4). Frailty is a state of vulnerability to stress factors due to a decrease in both physiological reserves and physical functions dependent on age. Frailty is present in approximately 10% of people over the age of 65 and 25-50% of people over the age of 85 (3,5). Frailty is likely to be common in geriatric patients undergoing surgery and has been strongly associated with increased perioperative morbidity and mortality in these patients (2-7). The frailty index (FI) is a valuable criterion in the preoperative evaluation of patients undergoing geriatric surgery.

Vitamin D is a systemic hormone with a steroid structure that has important roles in physiology and many tissues and organs (8,9). As vitamin D levels decrease with age, it is well known that vitamin D insufficiency is associated with decreased muscle strength (sarcopenia), increased risk of falls and bone fractures, slower gait speed, and poor physical performance (9,10). Various perioperative complications are also observed more frequently in patients with vitamin D insufficiency. In addition, vitamin D, which is responsible for mineral balance, is strongly associated with frailty (9-11). However, vitamin D insufficiency is a potentially modifiable risk factor for frailty associated with adverse postoperative outcomes in the elderly (8,9). Determining the relationship between preoperative vitamin D levels and frailty and postoperative outcomes in geriatric surgery patients with a known vitamin D insufficiency may improve clinicians' perioperative management strategies.

Although frailty and vitamin D insufficiency have been identified as important determinants of postoperative outcomes, to the best of our knowledge, their roles in surgical elderly patients have not been adequately studied concurrently. Researchers have mostly examined the relationship between vitamin D insufficiency, hip fracture, and osteoporosis in elderly patients undergoing orthopedic surgery (10,12). The present study aimed to investigate the relationship between vitamin D, frailty, and postoperative outcomes in geriatric patients undergoing elective surgery.

MATERIAL and METHODS

Study Design

This prospective observational study was conducted between January and May 2021 at Bozok University Medical Faculty Hospital, a tertiary care center. The study was approved by the Ethics Committee of Bozok University, Turkey (Protocol number: KAEK-189_2020.12.16_11; Date: December 16, 2020), and the Helsinki Declaration guidelines were followed throughout the study. All the participants signed a written informed consent form. This prospective observational study is reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement.

Study Participants

A total of 90 elderly patients who underwent non-cardiac surgery between the specified dates and met the inclusion criteria were included in the study. The study's inclusion criteria were: Age over 65 years, being scheduled for elective non-cardiac surgery, and American Society of Anesthesiologists (ASA) physical status II–IV. The exclusion criteria were surgery requiring local anesthesia or monitored anesthesia care, emergency surgery, and medical records with missing data (Figure 1).

Clinical Data

The patients' demographic data, including age, gender, and ASA physical status were recorded before the operation. Venous blood samples were collected from each patient just before the induction of anesthesia and kept frozen at -80°C until analysis. The data included the need for inotropes and blood transfusions intraoperatively, intensive care unit (ICU) admission, and in-hospital mortality. We applied the frailty score test to all the patients prior to surgery. Based on a self-reported, validated scoring method, we assessed frailty. Frailty is defined as a deterioration with age in five components: Fatigue, resistance, ambulation, illnesses, and weight loss (2,7). The score ranges from 0 to 5 points, with 1 point given to each positive answer. The patients were classified according to the FI score as non-frail (FI 0), pre-frail (FI 1–2), or frail (FI ≥ 3). In addition, the patients were divided into two groups according to serum 25-hydroxyvitamin D concentration: A vitamin D insufficiency group (serum level ≤ 30 ng mL^{-1}) and a vitamin D non-insufficiency group (serum level > 30 ng mL^{-1}). The demographic and clinical characteristics of the patients were compared between the groups.

Sample Collection and Measurement of Serum Levels of Vitamin D, Vitamin D Receptor, and Vitamin D Binding Protein

Just before the induction of anesthesia, venous blood was collected from the patients to measure the serum concentrations of vitamin D, vitamin D receptor (VDR), and vitamin D binding protein (VDBP). The collected blood samples were centrifuged at 3000 rpm for 10 minutes. Then, the supernatant was removed and kept frozen at -80°C. The serum vitamin D, VDR, and VDBP concentrations were measured with

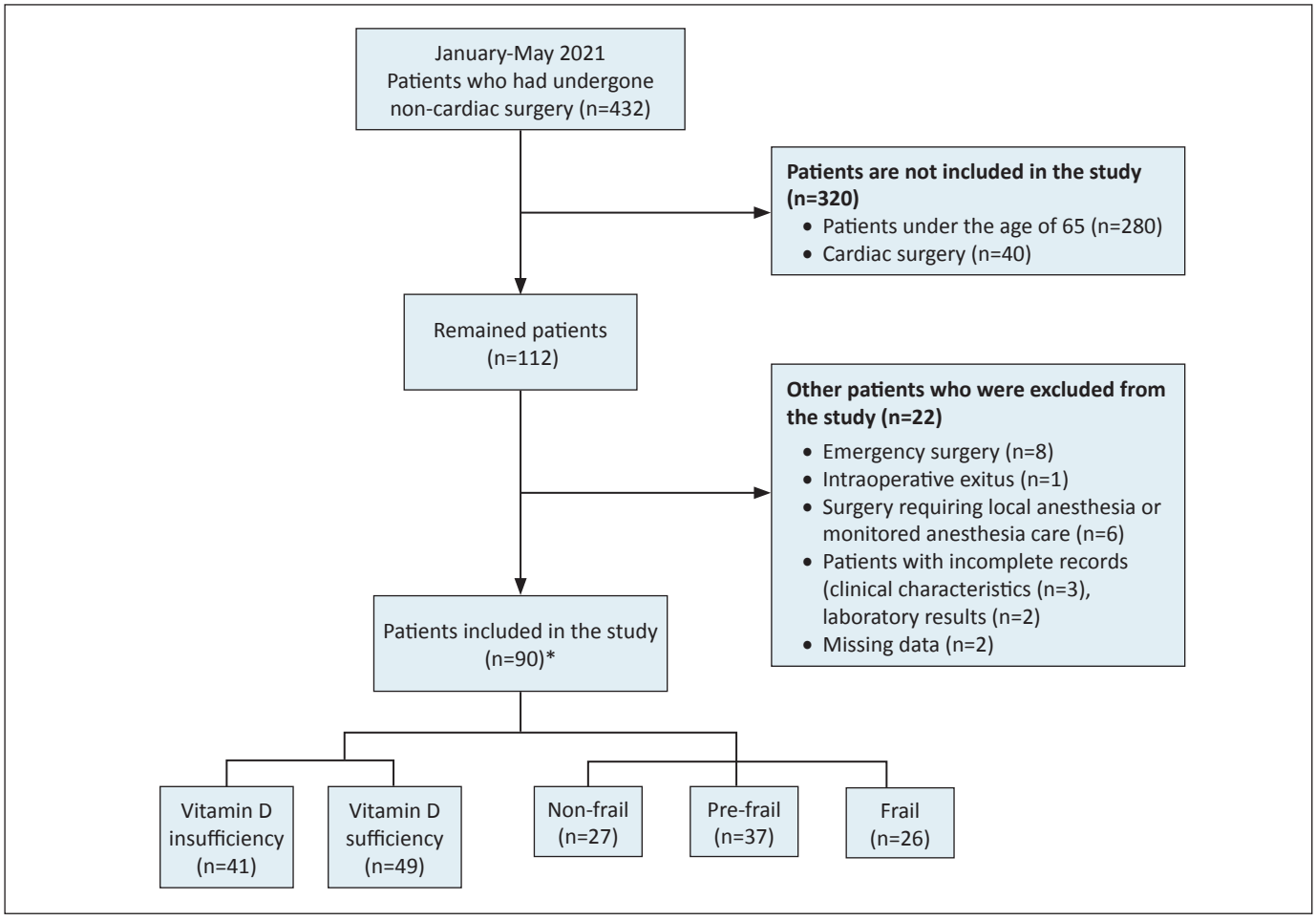

Figure 1. Flow diagram of the study. ***:** All patients were classified both for frailty and vitamin D levels.

an Olympus AU 600 autoanalyzer (Olympus Optical Co., Japan) using commercial ELISA kits (Elabscience Bioengineering Co., Ltd., Wuhan, China). The serum vitamin D and VDBP concentrations were expressed as ng mL^{-1}, while the VDR concentrations were expressed as pg mL^{-1}.

Statistical Analysis

The data were analyzed with IBM SPSS Statistics v. 25 (IBM Corp., Armonk, NY USA). The categorical data are presented as number and frequency, and the continuous data are presented as mean ± standard deviation (SD) and median (interquartile range [IQR]; 25^{th}–75^{th} percentile). The normality of distribution was checked using the Kolmogorov–Smirnov test and histograms. The significance of the differences between the groups in terms of averages were assessed with the chi-square test, the independent samples t-test, and the Mann–Whitney U test. In cross tables, Fisher's exact test was performed if more than 20% of the expected values were smaller than 5 or at least one of the values was smaller than 2. The variables, which were the relationships between the FI score, the serum vitamin D parameters, and age, were examined by a Pearson correlation analysis. All comparative analyses were two-tailed, and a p-value of less than 0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

The baseline characteristics of the subjects are provided in Table I. A total of 90 patients between the ages of 65 to 95 years with a mean age of 75.7±7.6 years that underwent elective surgery and had ASA physical status II-IV were included in the study. Among the patients 52 (57.8%) were female. Postoperatively, 43.3% (n=39) of the patients were accepted to ICU. The mean length of ICU stay was 4.7±7.8 (min=1, max=30) days, and the 30-day mortality rate after surgery was 21.1% (Table I).

Analysis of Clinical Variables in Terms of Serum Vitamin D Levels

The percentages by serum vitamin D levels were 45.6% (< 30 ng mL^{-1}) and 54.4% (≥30 ng mL^{-1}). The mean serum vitamin

D, VDBP and VDR concentrations were 29.63 ± 7.35 ng mL^{-1}, 47.67 ± 6.95 ng mL^{-1} and 41.07 ± 5.40 pg mL^{-1}, respectively (Table I). While the majority of patients (n=49) had vitamin D sufficiency, 41 were vitamin D insufficiency. Demographic and surgical data of the patient groups were similar in terms of serum vitamin D concentrations (Table II). The ICU admission was significantly higher in the "vitamin D insufficiency" group (n=24 versus n=15, p=0.014). In addition, frail patients were significantly higher in the "vitamin D insufficiency" group (n=19 versus n=7, p=0.004). Furthermore, most of the non-frail patients were in the "vitamin D sufficient" group (n=18 versus n=9) (Figure 2).

Table I: Characteristics of Study Subjects

Variables		Total (n=90)
Age (year), mean ± SD		75.7 ± 7.6
Gender, male/female, n (%)		38/52 (42.2/57.8)
ASA, II/III/IV, n (%)		21/51/18 (23.3/56.7/20.0)
Need for inotropics, n (%)		25 (27.8)
Need for blood transfusion, n (%)		24 (26.7)
ICU admission, n (%)		39 (43.3)
In-hospital mortality, n (%)		19 (21.1)
Vitamin D (ng mL^{-1}), median (interquartile range)		31.78 (22.96-35.92)
VDBP (ng mL^{-1}), median (interquartile range)		48.92 (42.67-52.24)
VDR (pg mL^{-1}), median (interquartile range)		41.56 (37.14-45.02)
FI score, n (%)	**0**	27 (30.0)
	1	11 (12.2)
	2	26 (28.9)
	3	19 (21.1)
	4	7 (7.8)
Frailty status, n (%)	**Non-frail (FI 0)**	27 (30.0)
	Pre-frail (FI 1–2)	37 (41.1)
	Frail (FI ≥ 3)	26 (28.9)

ASA: American Society of Anesthesiologists, **VDBP:** Vitamin D binding protein, **VDR:** Vitamin D receptor, **ICU:** Intensive care unit, **FI:** Frailty index.

Table II. Relationship Between Serum Vitamin D Level and Subject Characteristics

Variables		Vitamin D insufficiency Group (n=41)	Vitamin D sufficiency Group (n=49)	p
Age (year), mean ± SD		77.0 ± 7.6	74.7 ± 7.6	0.153[3]
Gender, male/female, n (%)		10/31 (24.4/75.6)	28/21 (57.1/42.9)	0.274[2]
ASA physical status, II/III/IV n (%)		9/24/8 (22.0/58.5/19.5)	12/27/10 (24.5/55.1/20.4)	0.943[2]
Need for inotropics, n (%)		14 (34.1)	11 (22.4)	0.318[1]
Need for blood transfusion, n (%)		14 (34.1)	10 (20.4)	0.219[1]
ICU admission, n (%)		24 (58.5)	15 (30.6)	**0.014[1]**
In-hospital mortality, n (%)		10 (24.4)	9 (18.4)	0.661[1]
Vitamin D (ng mL^{-1}), median (interquartile range)		22.50 (20.06-24.42)	35.73 (33.92-37.42)	**<0.001[4]**
VDBP (ng mL^{-1}), median (interquartile range)		51.27 (48.96-52.26)	45.87 (37.83-49.21)	**<0.001[4]**
VDR (pg mL^{-1}), median (interquartile range)		39.66 (37.88-42.15)	43.48 (35.67-46.90)	0.104[4]
Frailty status	**Non-frail (FI 0)**	9 (22.0)	18 (36.7)	**0.004[2]**
	Pre-frail (FI 1–2)	13 (31.7)	24 (49. 0)	
	Frail (FI ≥ 3)	19 (46.3)	7 (14.3)	

All statistically significant values are reported in bold. [1]Yates's correction for continuity; [2]Pearson's chi-square test; [3]Independant t test; [4]Mann-Whitney U test. **ASA:** American Society of Anesthesiologists, **VDBP:** Vitamin D binding protein, **VDR:** Vitamin D receptor, **ICU:** Intensive care unit, **FI:** Frailty index.

Analysis of Clinical Variables in Terms of Frailty Status

Among the participants, 30.0 % were non-frail (n=27), 41.1% pre-frail (n=37), and 28.9 % frail (n=26). The The median age of frail patients is higher (IQR: 76 to 84, p=0.005). The lowest median serum vitamin D level is in frail patients (IQR: 18.98 to 30.33, p=0.001). Vitamin D insufficiency is also significantly higher in frail patients (n=19, 73.1%, p=0.004) (Table III).

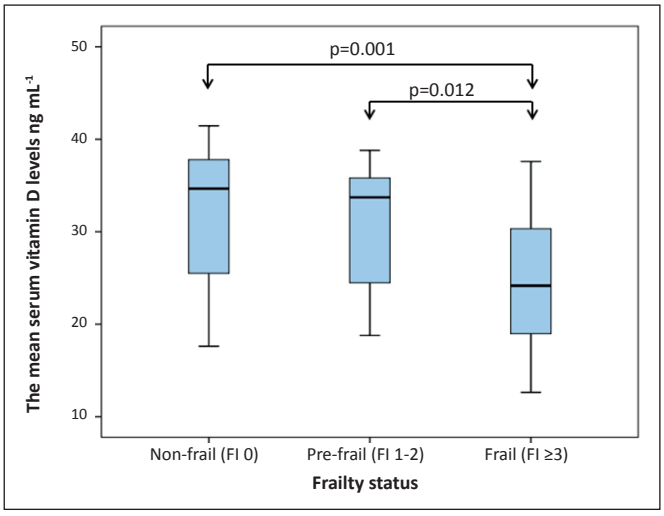

Figure 2. The mean of serum vitamin D levels according to frailty status.

Relationship Between Frailty Index Score, Serum Vitamin D Levels and Age

There was a weak negative correlation between age and vitamin D levels (r=0.233) of the patients, and a moderate negative correlation (r=0.358) with VDR levels (Table IV). In addition, there was a moderate negative correlation between FI score and vitamin D levels (r=0.377) of the patients.

DISCUSSION

Although many clinical studies have shown the relationship between vitamin D levels and frailty, the relationship between vitamin D, frailty and postoperative outcomes in geriatric surgery patients should be adequately investigated in the literature. The purpose of this prospective observational study was to test the hypothesis that serum vitamin D concentrations are associated with frailty and postoperative outcomes in geriatric patients undergoing elective surgery. Several important findings were identified in the present study. Firstly; higher frailty was observed in vitamin D insufficiency patients. Most of the frail patients were vitamin D insufficiency patients. Secondly; it was determined that the rate of admission to the postoperative ICU was higher in vitamin D insufficiency and frail patients.

Table III. Relationship Between Serum Frailty Status and Subject Characteristics

		Frailty Status			
		Non-Frail (FI 0) (n=27)	Pre-Frail (FI 1–2) (n=37)	Frail (FI ≥ 3) (n=26)	p
Gender, n (%)	**Men**	11 (40.7)	18 (48.6)	9 (34.6)	0.531[2]
	Women	16 (59.3)	19 (51.4)	17 (65.4)	
Age (year), mean ± SD		73 (67-78)	72 (68-82)	78.5 (76-84)[x]	**0.005[4]**
ASA, n (%)	**II**	8 (29.6)	7 (18.9)	6 (23.1)	0.070[3]
	III	18 (66.7)	22 (59.5)	11 (42.3)	
	IV	1 (3.7)	8 (21.6)	9 (34.6)	
Need for inotropics, n (%)		4 (14.8)	10 (27.0)	11 (42.3)	0.082[1]
Need for blood transfusion, n (%)		6 (22.2)	15 (40.5)	3 (11.5)	**0.031[1]**
ICU admission, n (%)		10 (37.0)	13 (35.1)	16 (61.5)	0.084[2]
In-hospital mortality, n (%)		3 (11.1)	10 (27.0)	6 (23.1)	0.292[1]
Vitamin D (ng mL^{-1}), median (interquartile range)		34.67 (24.38-37.85)	33.71 (24.49-35.82)	24.17 (18.98-30.33)[y]	**0.001[4]**
VDBP (ng mL^{-1}), median (interquartile range)		47.99 (42.67-52.26)	50.66 (37.83-52.86)	48.59 (44.27-51.27)	0.934[4]
VDR (pg mL^{-1}), median (interquartile range)		42.82 (5.77)	40.91 (5.40)	39.52 (4.63)	0.080[5]
Vitamin D insufficiency		9 (33.3)	13 (35.1)	19 (73.1)	**0.004[2]**
Vitamin D sufficiency		18 (66.7)	24 (64.9)	7 (26.9)	

All statistically significant values are reported in bold. [1]Yates's correction for continuity; [2]Pearson's chi-square test; [3]Fisher exact test; [4]Kruskal Wallis test; [5]One-way analysis of variance. **x for age:** According to pre-frail group (p=0.03), according to non-frail group (p=0.04). **y for Vitamine D:** According to pre-frail group (p=0.001), according to non-frail group (p=0.012). **ASA:** American Society of Anesthesiologists, **VDBP:** Vitamin D binding protein, **VDR:** Vitamin D receptor, **ICU:** Intensive care unit, **FI:** Frailty index.

Table IV. Correlation Analysis Between Frailty Index Score, Serum Vitamin D Parameters, and Age

		Vitamin D	VDBP	VDR
Age	**Pearson Correlation, r**	-0.233*	-0.205	-0.358**
	p	**0.027**	0.052	**0.001**
Frailty index score	**Pearson Correlation, r**	-0.377**	0.006	-0.193
	p	**<0.001**	0.952	0.068

:** Correlation is significant at the 0.05 level (2-tailed). *:** Correlation is significant at the 0.01 level (2-tailed).

Frailty is a multifactorial and complex health problem that develops due to aging as a result of the interaction between genetic, physiological, endocrine and inflammatory risk factors. Age is an important risk factor for frailty. Due to the increasing elderly population, frailty is frequently encountered in geriatric surgery patients (3-7).

Approximately one-third of patients in the current study were fragil. Other studies report a prevalence of frailty between 10% and 60%. (3,5,6,13). In a meta-analysis that included ten recent observational studies, it was reported that the prevalence of frailty in general surgery patients ranged from 10.4% to 37.0% (3). In another meta-analysis, the prevalence of frailty was 39.4% (range 5.9-58.7%) (5). We think that this difference between frailty rates is due to the diversity between the inclusion criteria of patients and frailty assessment scales. The mechanism of frailty is not clearly understood pathophysiologically. Sarcopenia, the decrease in muscle mass as a result of inactivity, malnutrition, endocrine and inflammatory changes, has a strong relationship with frailty (3-7).

In terms of the endocrine system, low concentrations of vitamin D, gonadal hormones and insulin-like growth factor-1 (IGF-1), and high levels of inflammatory mediators are observed in frailty patients. However, vitamin D insufficiency in particular is a potentially modifiable risk factor for frailty that is common among the elderly patients (14). For this reason, we investigated the relationship between vitamin D insufficiency, which is seen frequently in elderly surgical patients, and frailty. We think that awareness of these risk factors in the perioperative period by clinicians can prevent postoperative adverse outcomes. Vitamin D is one of the few important compounds that is both absorbed and produced by the human body. Vitamin D has been associated with many critical processes in the human body, and vitamin D insufficiency is constantly being investigated in the etiology of various diseases (9).

Vitamin D insufficiency is common in Turkey and its prevalence varies between 60% and 75% (15). In the current study, vitamin D insufficiency was observed in approximately half of the elderly patients who would undergo surgery. The prevalence of serum 25(OH)D levels less than 20 ng mL^{-1} was 32% in the US population (16), while concentrations less than 30 ng mL^{-1} were reported in 57.5% of men in a Canadian cohort (8). There is no consensus on the cut-off value of the concentration to define vitamin D status. Different countries have different definitions for vitamin D insufficiency and its optimal values. In our study, 20 ng mL^{-1} value was determined as the cut-off of serum 25(OH)D concentration for vitamin D insufficiency. Differences in this prevalence depend on gender, age, sun exposure, season, or population characteristics such as vitamin D supplementation.

There is a significant relationship between vitamin D insufficiency, sarcopenia, and frailty (9). Since the low vitamin D level observed in elderly patients is associated with muscle weakness, sarcopenia, falls and disability, high frailty is expected in these patients (9,17). As an underlying mechanism, it is known that vitamin D insufficiency causes deterioration in mineral hemostasis, kidney disease, chronic PTH elevation, thus low bone mineral density and muscle weakness (9). In addition, it is known that vitamin D has effects at the molecular level within the muscle cell (18). For all these reasons, a decrease in walking speed, grip strength and stability limits, which define frailty, is observed in elderly people with low vitamin D. There is strong evidence in the literature that demonstrates the relationship between vitamin D status and frailty (9,11,19).

In the current study, nearly half of the vitamin D insufficiency patients were frail. Low vitamin D levels were also observed in the majority of fragil patients. It was found that among Korean older adults aged 70-84 years, those with insufficient vitamin D levels were more likely to be fragile. In the same study, low grip strength, which is among the components of frailty, was significantly associated with low serum vitamin D levels (19). In another study, hypovitaminosis D was reported to be an independent predictor of frailty in men aged 70-88 years. Interestingly, the authors noted that the strong association between vitamin D and mortality was independent of frailty (20). Other studies have also reported high frailty rates in patients with low vitamin D (9,11,19). All these studies provide strong evidence for the important role of vitamin D insufficiency in frailty.

It is known that frailty and vitamin D insufficiency are independent risk factors for postoperative adverse outcomes in

elderly patients (3,5-7,13,21-23). A recent meta-analysis of thirteen observational studies showed that frailty was associated with adverse clinical outcomes such as increased postoperative mortality, longer hospital stay, and reduced discharge home in 58.757 surgical patients admitted to the ICU. In the same study, the authors reported that preoperative assessment of frailty may help to predict higher risks before elective surgery (5). In our study, it was observed that more than half of the fragil patients (61.5%) were admitted to the ICU. However, no difference was observed in hospital mortality in terms of frailty. There was also a negative correlation between vitamin D levels and frailty scores. On the other hand, admission to intensive care was found to be higher in patients with vitamin D insufficiency. Turan et al. also reported that higher vitamin D concentrations were associated with reduced in-hospital mortality/morbidity rates (23). Similarly, another study reported that preoperative hypovitaminosis D (<20 ng mL^{-1}) was associated with poor short-term postoperative outcomes (24).

There are a number of limitations to this study. Firstly, since it is a single-center study and our sample size was relatively small compared to more extensive studies in the literature, it cannot be generalized to all patients undergoing surgery. Secondly, as postoperative adverse clinical outcomes, only ICU admission and in-hospital mortality were examined. Evaluation of the duration of mechanical ventilation and length of stay in the ICU as a negative outcome may be an important focus for future studies. Finally, no adjustments were made for seasonal variation and climate-related factors affecting serum vitamin D levels during the study period. However, blood samples were taken from all patients before induction of anesthesia to determine their current serum vitamin D levels. In future studies, the relationship between seasonal vitamin D levels and frailty can be investigated in patients undergoing surgery. Nevertheless, in the light of the literature, we think that the present study addresses an important issue in the field of surgery and intensive care.

CONCLUSION

In conclusion, in our study, we observed that elderly patients who underwent surgery had high frailty in those with vitamin D insufficiency. In addition, the rate of admission to the ICU as a postoperative adverse outcome was high in patients with vitamin D insufficiency and frailty. Our findings show that frailty and vitamin D insufficiency play an important role in postoperative outcomes. More extensive randomized controlled clinical studies are needed in this area.

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AUTHOR CONTRIBUTIONS

Conception or design of the work: OHM
Data collection: OHM, APC
Data analysis and interpretation: OHM, AYG
Drafting the article: OHM, TH, AYG
Critical revision of the article: OHM, TH
All authors (OHM, TH, APC, AYG) reviewed the results and approved the final version of the manuscript.

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