Original Article
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Does Serum Vitamin D Influence the Prognosis of Critically Ill Patients with Trauma? A Prospective, Observational Study in a Trauma Center

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Background: Vitamin D concentrations are associated with sepsis, pneumonia, and mortality in critically ill patients. However, the role of vitamin D in critically injured patients with trauma remains unknown. This study investigated the effects of vitamin D concentrations on outcomes in critically injured patients with trauma.

Methods: A prospective observational study was conducted by randomly selecting 100 patients among those who visited our trauma center. The serum vitamin D concentration was measured upon arrival at the hospital, and the length of stay in a trauma intensive care unit after admission, duration of mechanical ventilation, number of days spent in the hospital, development of complications, and death were investigated. The association between the surveyed variables and vitamin D concentrations was investigated using regression analysis.

Results: Of the 100 patients, 69 were men and 31 were women with an average age of 51.7 years. The average intensive care unit stay length was 18.4 days, and 6 patients (5.9%) died. Univariate regression analysis showed that the factors affecting patient mortality were age (p = 0.02), volume of blood transfused within 24 hours of arrival (p = 0.009), systolic blood pressure measured upon hospital arrival (p = 0.01), and serum lactate concentration measured upon hospital arrival (p = 0.03). Multivariate regression analysis showed that the factors affecting patient mortality were age (p = 0.01), volume of blood transfusion (p = 0.04), and systolic blood pressure measured upon hospital arrival (p = 0.01).

Conclusions: There were no statistically significant effects of serum vitamin D concentrations in critically ill patients with trauma on death during hospitalization.

Keywords: *Vitamin D, Critically ill, Trauma, Mortality, Intensive care units*

Vitamin D plays a major role in regulating calcium and phosphorus concentration in the blood. However, it is also known to be involved in maintaining the balance of the body and mechanisms of stabilization of nerve cells, glucose metabolism, immune regulation, regulation of inflammation, control of the renin-angiotensin system, cell growth, cell membrane stabilization, angiogenesis, and apoptosis.[1,2] Further, according to recent studies, vitamin D plays an important role in regulating the innate and adaptive immune responses to infectious pathogens, including gram-negative and gram-positive bacteria, fungi, and mycobacteria.[1,2] Vitamin D deficiency is common worldwide, and several studies have reported that vitamin D deficiency is associated with cardiovascular disease, hypertension, congestive heart failure, and diabetes mellitus.[3,4] Vitamin D deficiency has been reported to be closely associated with mortality in noncritically ill patients.[3,5] Vitamin D defi-

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ciency has also been reported to be associated with mortality, prolonged length of stay, the incidence of sepsis, and prolonged duration of mechanical ventilation in critically ill patients.[6-10] A recent "eVIDenCe study" that analyzed the effects of serum vitamin D concentrations in patients who had undergone cardiac surgery reported a high incidence of postoperative infection and organ failure in patients with vitamin D deficiency.[11] Guidelines issued by the European Society for Clinical Nutrition and Metabolism (ESPEN) in 2018 also recommend vitamin D supplementation for critically ill patients.[12] Observational studies conducted on critically ill patients reported that vitamin D deficiency was associated with mortality and the incidence rate of complications in intensive care units (ICUs).[9,13,14] Similar outcomes have been reported in studies conducted on critically ill surgical patients.[15-18] However, no studies have been conducted on patients with trauma. In particular, critically ill patients with trauma experience changes in the systemic immune response due to trauma, unlike general critically ill surgical patients, and may require long-term mechanical ventilation for lung or cardiac injury due to chest trauma. In addition, vitamin D deficiency, which plays a role in modulating the immune and inflammatory systems, is thought to affect the prognosis of patients with various inflammatory responses, such as systemic inflammatory response syndrome or compensatory anti-inflammatory responses to trauma.

This study aimed to examine the prevalence of vitamin D deficiency in critically ill patients with trauma and to investigate the effects of serum vitamin D concentrations measured upon arrival at the hospital from the accident on the prognosis of patients, such as the length of stay in the ICU, duration of mechanical ventilation, development of complications, sepsis, infection, the total number of days spent in the hospital, and mortality.

METHODS

This study was conducted after being approved by the Institutional Review Board of Ajou University Hospital (No. AJIRB-MED-OBS-17-17) and was conducted in accordance with the rules of the Declaration of Helsinki. Written informed consent was obtained from all patients participating in the study.

Study Design

This is a single-center, prospective, observational study conducted on patients with an Injury Severity Score (ISS) ≥ 15 who visited the trauma bay (T-Bay) of our hospital between January 2017 and July 2018.

Definition of Vitamin D Deficiency and Insufficiency

A serum 25-hydroxyvitamin D (25(OH)D) concentration of < 10 ng/mL was considered vitamin D deficiency, a 25(OH) D concentration of ≥ 30 ng/mL was considered sufficient, and a concentration between these two was considered insufficient.

Sample Size Calculation and Participant Selection

In a prior study of 2,399 patients, the prevalence of vitamin D deficiency was 26%, and that of vitamin D insufficiency was 39%. The mortality rate in patients with vitamin D deficiency within 30 days after ICU admission was 1.7 times higher than in the healthy group.[6] A logistic regression of a binary response variable (Y) on a continuous, normally distributed variable (X) with a sample size of 94 observations achieved 80% power at a 0.05 significance level to detect a change in probability (Y = 1) from a value of 0.450 at the mean of X to 0.580 when X was increased to one standard deviation (SD) above the mean. This change corresponded to an odds ratio (OR) of 1.690. Given the dropout probability during the follow-up period, 100 patients were recruited. The inclusion criteria were as follows: adult patients aged ≥ 20 years who visited the trauma center of this hospital, patients with trauma with an ISS ≥ 15, and patients who consented to participate in this study. Exclusion criteria were as follows: (1) patients with cancer that may affect serum vitamin D concentrations, (2) congenital rickets, (3) hyperparathyroidism, (4) active tuberculosis, (5) death on the day of admission, and (6) patients taking vitamin D supplementation during the hospital stay. When patients were admitted to the hospital, their inclusion/exclusion criteria were first evaluated; if they met the requirements, a coin toss was conducted. Patients were included in the study if the coin landed on its front side.

Data Collection

Demographic data, including patient age, sex, past medical history, injury mechanism, time from injury to hospital arrival, physical vitality index upon arrival at the hospital, Glasgow Coma Scale (GCS), volume of blood transfused within 24 hours of trauma, length of ICU stay, duration of mechanical ventilation, total number of hospital stay, Abbreviated Injury Scale, ISS, and complications (pneumonia, acute renal failure, acute cardiac failure, acute respiratory distress syndrome [ARDS], surgical site infection, deep vein thrombosis, and multiple organ failure), were collected. To minimize the effects of blood transfusion or fluid loading, serum vitamin D concentrations were measured in the blood samples collected upon arrival at the T-bay. To examine changes in serum vitamin D concentrations during hospitalization, vitamin D concentrations in patients who were normally discharged from the hospital without particular complications were measured immediately before discharge. Orthopedic fractures were examined at the corresponding sites in accordance with the AO Foundation/Orthopaedic Trauma Association (AO/OTA) classification. All laboratory data from blood tests, X-ray examinations, and medical records, including vital signs, medication and treatment records, progress reports, and operative reports performed during hospitalization, were collected and analyzed.

Duration of Observation and Goal Setting

Patients were observed from when they consented to the observational study upon arrival at the T-bay to the time they were discharged from the hospital, except for patients who died during treatment at the hospital or refused treatment. During this period, the primary outcome measure was death, and the secondary measures were the length of ICU stay, duration of mechanical ventilation, unexpected readmission to the ICU, and development of complications. Readmission to the ICU was defined as a patient's admission to the ICU and discharge from the ICU during the same hospital stay. Infections acquired in the ICU were defined as patients with no prior medical history of infection and who were infected 2 days after ICU readmission.

Serum Vitamin D Concentration

Serum 25(OH)D concentrations were measured using electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). The intra- and inter-assay coefficients of variation (CV) for the 25(OH)D measurements were 2.2% to 6.8% and 3.4% to 13.1%, respectively. The intra- and inter-assay CV of intact parathyroid hormone measurements were 1.1% to 2.0% and 2.8% to 3.4%, respectively.

Statistical Analysis

Statistical analysis was performed using SAS ver. 9.4 (SAS Institute, Cary, NC, USA). For all continuous variables, the

Table 1. Baseline Patient Characteristics

Variable	Survival (n = 94)	Death (n = 6)	Total (n = 100)	*p*-value
Age (yr)	50.5 ± 18.6	70.5 ± 12.2	51.7 ± 18.8	0.01*
Sex (male)	64 (68.1)	5 (83.3)	69 (69.0)	0.66†
Injury mechanism				0.85†
Auto-pedestrian accident	30 (31.9)	3 (50.0)	33 (33.0)	
Motorcycle collision	9 (9.6)	0	9 (9.0)	
Car accident	21 (22.3)	1 (16.7)	22 (22.0)	
Fall down	32 (34.0)	2 (33.3)	34 (34.0)	
Crush	2 (2.1)	0	2 (2.0)	
Body mass index (kg/m^2)	23.4 ± 3.8	21.9 ± 2.9	23.3 ± 3.7	0.32*
Comorbidity (any)	30 (31.9)	4 (66.7)	34 (34.0)	0.10†
Smoking (current)	43 (45.7)	1 (16.7)	44 (44.0)	0.27†
Time from injury to arrival (min)	59.3 ± 32.1	36.7 ± 15.3	48.7 ± 58.6	0.10*
Initial SBP (mmHg)	127.9 ± 27.6	92.7 ± 38.8	125.8 ± 29.4	0.03*
Initial DBP (mmHg)	79.5 ± 20.1	58.0 ± 33.4	78.2 ± 21.5	0.04*
Glasgow Coma Scale	11.9 ± 3.6	11.2 ± 5.0	11.8 ± 3.6	0.51*
Initial lactate (mmol/L)	3.67 ± 2.55	6.50 ± 3.62	3.84 ± 2.69	0.04*
Initial 25(OH)D (ng/mL)	16.0 ± 5.8	13.1 ± 2.8	15.8 ± 5.7	0.19*

Values are presented as mean ± standard deiviation or number (%).
SBP: systolic blood pressure, DBP: diastolic blood pressure, 25(OH)D: 25-hydroxyvitamin D.
Two-sided *p*-values < 0.05 were considered significan: *Student *t*-test. †Chi-square test.

Kolmogorov-Smirnov test was used to test for normality. Normally distributed variables are represented as mean and SD. Non-normally distributed variables are represented by the median and range. Categorical variables are presented as frequencies and percentages. Univariate and multivariate regression analyses were performed for all collected variables to explore associations with the targets and results, such as mortality. ORs were tested at a 95% confidence interval (CI). Two-sided p-values < 0.05 were considered significant.

RESULTS

In total, 2,673 patients were admitted to the trauma center during the study period, of whom 347 (13%) died. One-hundred patients were included in the study, of whom 69 were men and 31 were women. The mean age was 51.7 ± 18.8 years. The personal and injury information of the patients included in the study is presented in Tables 1 and 2 and Fig. 1. Two patients (2%) were vitamin D sufficient, 90 patients (90%) were vitamin D insufficient, and 8 patients (8%) were vitamin D deficient (Fig. 2). There was no statistical difference in seasonal variations in serum vitamin D concentrations (Fig. 3). The average ICU length of stay was 18.4 ± 30.1 days, the average number of days in the hospital was 48.7 ± 58.6 days, and the average duration of mechanical ventilation was 10.7 ± 19.3 days (Table 2). The mean ISS was 22.6 points (range, 9–45 points; SD, 8.9).

Primary Outcome

Six patients (5.9%) died during the study period. Serum vitamin D concentrations at the time of injury had no effect on patient mortality (p = 0.39) (Table 3). Univariate regression analysis showed that factors affecting patient mortality were patients' age (p = 0.02), the volume of blood transfused within 24 hours of arrival (p = 0.009), systolic blood pressure upon arrival at the hospital (p = 0.01), and serum lactate concentration upon arrival at the hospital (p = 0.03). Multivariate regression analysis showed that the factors affecting mortality were age, the volume of blood transfusion, and

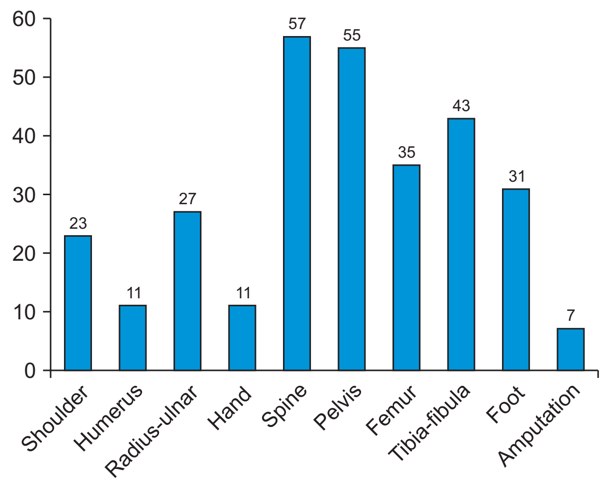

Fig. 1. Distribution of orthopedic injuries.

Table 2. Injury Characteristics

Variable	Survival (n = 94)	Death (n = 6)	Total (n = 100)	p-value
Injured site				
Head	40 (42.6)	3 (50.0)	43 (43.0)	0.52*
Face	28 (29.8)	2 (33.3)	30 (30.0)	0.59*
Chest	66 (70.2)	5 (83.3)	71 (71.0)	0.44*
Abdomen and pelvis	54 (57.4)	3 (50.0)	57 (57.0)	0.52*
Extremities	87 (92.6)	6 (100)	93 (93.0)	0.64*
Packed RBC transfusion for 24 hours	3 (0–44)	14 (2–32)	3 (0–44)	0.01†
Duration of mechanical ventilation (day)	9.4 ± 14.6	30.0 ± 54.1	10.7 ± 19.3	0.13†
In-ICU stay (day)	17.0 ± 24.1	41.3 ± 80.7	18.4 ± 30.1	0.67†
In-hospital stay (day)	49.0 ± 56.9	43.7 ± 88.5	48.7 ± 58.6	0.02*
Complication (any)	17 (18.1)	2 (33.3)	19 (19.0)	0.32†

Values are presented as number (%), median (range), or mean ± standard deiviation.
RBC: red blood cell, ICU: intensive care unit.
Two-sided p-values < 0.05 were considered significant: *Chi-square test. †Student t-test.

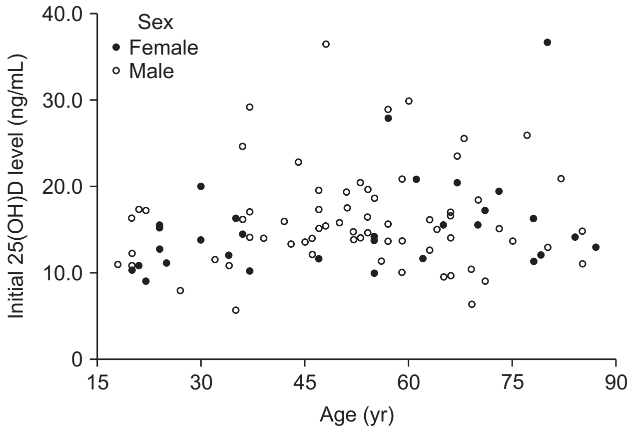

Fig. 2. Distribution of initial 25-hydroxyvitamin D (25(OH)D) concentrations (ng/mL).

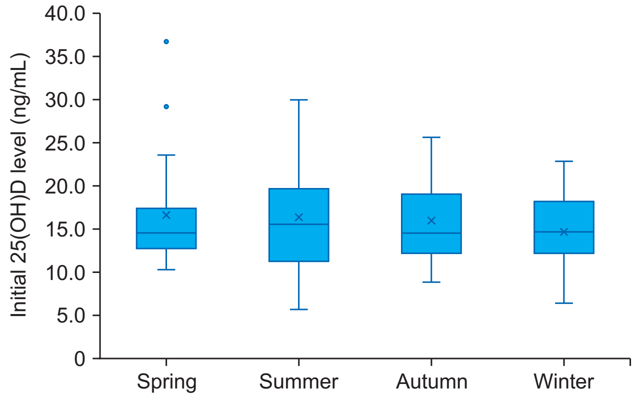

Fig. 3. Seasonal variations in initial 25-hydroxyvitamin D (25(OH)D) concentrations (ng/mL).

systolic blood pressure upon arrival at the hospital.

Secondary Outcomes

Vitamin D concentrations had no impact on the outcomes of critically injured patients. Other factors found to have an impact are summarized in Table 4.

DISCUSSION

Large-scale studies have been conducted on the relationship between vitamin D, mortality rate, and infection in the general population and medically critically ill patients. A meta-analysis conducted by Zittermann et al.[19] on 62,000 patients demonstrated that low vitamin D concentrations in the general population were associated with a higher mortality rate (relative risk, 0.71; 95% CI, 0.50–0.91) and a higher incidence rate of infectious complications. A similar study on ICU patients also reported that adequate vitamin D concentrations contributed to increased survival rates ($p = 0.03$).[20] In the Acute Physiological and Chronic Evaluation (APACHE) II study, in-hospital mortality, 30-day mortality, and 90-day mortality were also significantly increased in ICU patients with vitamin D deficiency and sepsis. Furthermore, patients with 25(OH)D concentrations < 15 ng/mL in ICUs had a higher risk of developing sepsis (OR, 1.51; 95% CI, 1.17–1.94). Except for critically ill patients, the eVIDenCe study conducted only in patients who had undergone elective cardiac surgery reported that vitamin D deficiency increased postoperative ICU stay, in-hospital stay, and the risk of developing postoperative organ dysfunction (OR, 0.95; $p = 0.009$).[11]

Patients with polytrauma frequently exhibit systemic inflammatory and compensatory anti-inflammatory responses, which may lead to organ failure and sepsis. Changes in inflammatory responses in patients with polytrauma can cause complications related to inflammatory responses, such as sepsis, ARDS, and multiple organ failure, which are the main causes of death after trauma.[21,22] We believe that the reported role of vitamin D in the inhibition of proinflammatory cytokines and its possible therapeutic effect in ARDS can affect the mortality rate by reducing the development of possible complications after injury. Therefore, we planned this study to examine the relationship between serum vitamin D concentration upon arrival at the hospital and death after injury. However, unlike the hypothesis of this study, we could not reveal an association between the death of patients with trauma and serum vitamin D concentrations.

For patients with vitamin D deficiency who died in general ICUs, the cause of death is known to be associated with the pleiotropic function of vitamin D. Vitamin D inhibits vascular smooth muscle cell proliferation, protects normal endothelial function, and modulates inflammatory processes. Several studies have shown that vitamin D deficiency causes deterioration in macrophage function, such as the production of chemotaxis, phagocytosis, and proinflammatory cytokines.[1,2] This shows that vitamin D deficiency is associated with in-hospital mortality and mortality rates on days 30, 90, and 365.[1,2,12]

In a previous study by Smith et al.,[22] the factors related to the death of patients with trauma were age, GCS, ISS, and amount of transfusion, while other studies reported that the major factor affecting mortality was serum lactate concentrations. This study also showed that patient age, systolic blood pressure upon arrival at the hospital, serum lactate concentrations, and the initial volume of blood transfusion were associated with patient mortality. As this result is consistent with previous studies, we attempted to

Table 3. Factors Affecting In-Hospital Mortality (Primary Outcome)

Variable	Univariate analysis		Multivariate analysis*	
	Odds ratio (95% CI)	*p*-value	Odds ratio (95% CI)	*p*-value
Sex (male)	2.344 (0.262–20.950)	0.45		
Age (yr)	0.927 (0.858–0.982)	0.02	1.099 (1.019–1.184)	0.01
Smoking	2.300 (0.213–24.795)	0.49		
Comorbidity (any)	4.267 (0.740–24.600)	0.11		
Systolic blood pressure (mmHg)	10.42 (1.012–1.081)	0.01	0.961 (0.925–0.998)	0.04
Glasgow Coma Scale	1.043 (0.825–1.285)	0.70		
Injury Severity Score	0.960 (0.879–1.049)	0.35		
Serum lactate (nmol/L)	0.776 (0.610–0.986)	0.03		
Serum 25(OH)D (ng/mL)	1.099 (0.922–1.405)	0.39		
Packed RBCs transfusion	0.919 (0.861–0.981)	0.01	1.093 (1.005–1.188)	0.04
Complication (any)	2.265 (0.383–13.386)	0.37		

CI: confidence interval, 25(OH)D: 25-hydroxyvitamin D, RBC: red blood cell.
*Hosmer-Lemeshow test (p = 0.790), Nagelkerke R^2 (0.500).

Table 4. Factors Affecting Secondary Outcomes (Multivariate Analysis)

Variable	In-ICU stay (day)*	Ventilation (day)*	Complication†
	β ± SE (*p*-value)	β ± SE (*p*-value)	Odds ratio (95% CI)
Sex (male)			
Age (yr)		0.270 ± 0.099 (0.008)	
Body mass index (kg/m²)			
Smoking			
Comorbidity (any)			5.484 (1.743–17.253)
Systolic blood pressure (mmHg)			
Glasgow Coma Scale			
Injury Severity Score	0.846 ± 0.336 (0.01)	0.551 ± 0.206 (0.009)	1.099 (1.033–1.168)
Serum lactate (nmol/L)	2.652 ± 1.112 (0.02)		
Serum 25(OH)D (ng/mL)			
Packed RBCs transfusion			
Complication (any)			

ICU: intensive care unit, SE: standard error, CI: confidence interval, 25(OH)D: 25-hydroxyvitamin D, RBC: red blood cell.
*Multivariate regression analysis. †Multivariate logistic regression analysis.

investigate the relationship between vitamin D concentrations and mortality by performing multivariate analysis on factors known to be related to the death of patients with trauma, but no statistical significance was found. This is because patients with trauma do not undergo elective surgery, unlike critically ill surgical patients. In addition,

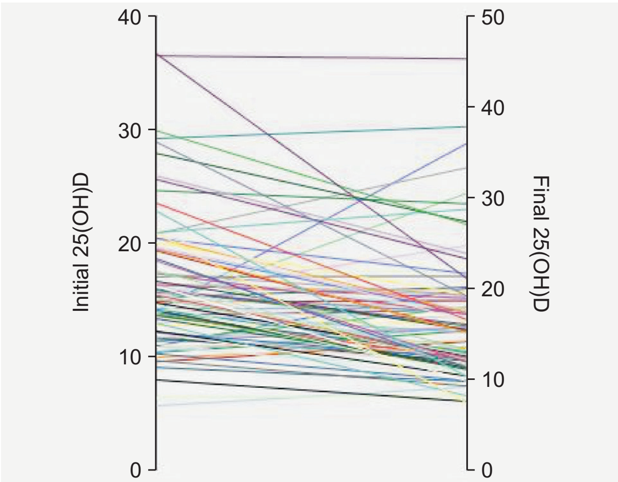

Fig. 4. Changes in 25-hydroxyvitamin D (25(OH)D) concentrations (ng/mL) at admission and discharge.

they had multiple organ injuries or systemic inflammatory responses, which differs from patients who underwent elective surgery in the eVIDenCe study. In this study, the relationship between serum vitamin D concentration and mortality could not be demonstrated due to this difference from the general surgical patients.

Vitamin D can be ingested via food and is synthesized in the skin upon exposure to sunlight.[1,2] However, it is difficult for long-term hospitalized patients, especially critically ill patients, to be exposed to sunlight. The authors of this study assumed that vitamin D concentrations in patients with a longer period of hospitalization would decrease compared with those at the time of admission. To determine the change in serum vitamin D concentrations during hospitalization, vitamin D concentrations in patients who were discharged from the hospital were normally measured immediately before the discharge, except for those who died during hospitalization. The results showed that the serum vitamin D concentration decreased during hospitalization, but the difference was not statistically significant (Fig. 4). Cutaneous synthesis of vitamin D is known to be affected by season, but the patients included in this study did not show any statistical differences in vitamin D concentrations by season (Fig. 3).

This study has several limitations. First, it did not demonstrate an association between long-term mortality (e.g., 3 months, 6 months, and 1 year) and vitamin D concentrations because the analysis was performed only for deaths during hospitalization. In addition, the length of ICU stay and the number of days in the hospital may be affected by various factors, such as the patient's economic status and problems with the hospital room, besides the patient's systemic condition. However, this is a prospective study with strengths in that the single target population only included patients with polytrauma, unlike previous studies. Another strength of this study is the inclusion of patients who were treated using the same protocol at one site. From the viewpoint of previous orthopedics, studies on vitamin D have often been evaluated from the viewpoint of sarcopenia, osteoporotic fracture, grip strength, or bone union. Studies in 617 patients with fractures conducted by Gorter et al.[23,24] showed that 40% were patients with vitamin D deficiency and that vitamin D deficiency was associated with delayed union of bone fracture. We plan to investigate the association between vitamin D deficiency and long-term follow-up outcomes through future research.

Vitamin D deficiency and insufficiency were common in patients with polytrauma (98%). However, there were no statistically significant effects of serum vitamin D concentrations in critically ill patients with trauma on death during hospitalization, duration of mechanical ventilation, ICU length of stay, and the development of complications.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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