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The effect of vitamin K_1 and vitamin K_2 on mortality rate and disease severity in COVID-19 patients: An observational study

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Ethics Committee Approval
This study was approved by the Medical Research Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital on March 12, 2020. Approval number: 027-2020, dated March 12, 2020. All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Informed Consent
The patients' written informed consent was obtained from the patients or their legal representatives in accordance with ICU protocols and ethical rules.

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

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Abstract

Background/Aim: Vitamin K is vital for numerous physiological functions, particularly in coagulation and inflammation. This research investigates the relationship between VK1 and VK2 levels and the severity and mortality of COVID-19

Methods: This prospective study analyzed VK1 and VK2 levels using ELISA in 165 hospitalized COVID-19 patients. Statistical analyses, including logistic regression, were performed to evaluate associations with clinical outcomes, including ICU admission and mortality.

Results: VK2 levels were significantly higher in patients with severe disease ($P<0.01$) and deceased patients ($P<0.05$). Logistic regression identified CT severity and VK1 levels as risk factors for ICU admission and mortality, with odds ratios of 10.65 and 6.43, respectively.

Conclusion Elevated VK2 levels correlated with severe COVID-19 outcomes, suggesting a potential role as a biomarker for disease severity and risk of mortality. These findings underscore the potential clinical utility of VK2 as a biomarker for disease severity and prognosis.

Keywords: COVID-19, vitamin K1, vitamin K2, inflammation, mortality

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Introduction

The COVID-19 pandemic has profoundly disrupted healthcare systems, social dynamics, and global economies on an unprecedented scale [1]. Studies have shown that the severity of COVID-19 in individuals increases during viral clearance, highlighting the crucial role of the host immune response in the disease's pathogenicity [2]. Reports indicate that mortality rates among hospitalized COVID-19 patients range from 4% to 28% [3,4]. Although numerous meta-analyses on COVID-19 have explored disease severity, only a few have specifically examined clinical outcomes related to mortality [5-7].

Several studies have addressed critical clinical questions regarding the progression and outcomes of COVID-19, as well as the risk factors associated with hospitalization and intensive care unit (ICU) admission. Advanced age, male gender, elevated inflammatory markers, and pre-existing comorbidities, such as hypertension and cardiovascular disease, have been identified as key contributors to COVID-19-related hospitalizations [8-11]. Although some meta-analyses have explored the associations between disease severity and mortality with specific comorbidities, laboratory findings, imaging results, and medication use, their assessments of mortality are often constrained by small sample sizes [12-14].

COVID-19 presents with a range of cardiac complications in adults. While some patients exhibit no clinical signs of heart disease, others may show abnormalities on cardiac tests without symptoms, or they may develop symptomatic heart conditions. Cardiac complications associated with COVID-19 include myocardial injury, heart failure, cardiogenic shock, and multisystem inflammatory syndrome [15].

Endothelial dysfunction, characterized by reduced nitric oxide bioavailability, is regarded as an early event in conditions, such as hypertension, diabetes, coronary heart disease, and renal dysfunction—all of which are associated with higher mortality rates in COVID-19 patients [16]. Vitamin K, a vital bioactive compound, plays an essential role in maintaining optimal physiological functions. Its primary isoforms include phylloquinone (K1) and menaquinone (K2). Vitamin K2 (VK2), particularly in its MK-7 form, has been shown to regulate osteoporosis, atherosclerosis, cancer, and inflammation, with minimal risk of adverse effects or overdose [11].

Inflammation and coagulation are closely interconnected processes. Circulating cytokines can exacerbate systemic coagulation by enhancing procoagulant activity while suppressing anticoagulant mechanisms [17]. This interaction may account for the high prevalence of coagulopathy and venous thromboembolism observed in severe COVID-19 cases [18,19]. Vitamin K has demonstrated anti-inflammatory effects through the nuclear factor κB (NFκB) signaling pathway, effectively inhibiting NFκB-mediated inflammatory signal transduction [20].

In this study, we aimed to evaluate the associations between patients' demographic and clinical features, as well as the severity of COVID-19 on CT scans, mortality rates, ICU admissions, and VK1/VK2 levels.

Materials and methods

This study employed a prospective observational design between April and May 2020. SARS-CoV-2 infection was confirmed through polymerase chain reaction (PCR) analysis. Data on patients' comorbidities were retrieved from hospital admission records. Eligible participants included individuals aged 18 years or older who were admitted to the cardiology clinic or intensive care unit (ICU) due to COVID-19-related symptoms. Patients were excluded if their medical records were incomplete or if data on vitamin K1 and K2 levels were unavailable. Additionally, individuals with pre-existing coagulopathies unrelated to COVID-19 were excluded from the study.

Epidemiological, demographic, clinical, and laboratory data, along with treatment and outcome information, were recorded using a standardized data collection form adapted from the WHO/International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) case record form for severe acute respiratory infections [21]. Routine blood tests included complete blood count, coagulation profile, serum biochemical tests (including renal and liver function, creatine kinase, and lactate dehydrogenase), myocardial enzymes, serum ferritin, and procalcitonin. Additionally, CT scans were performed on all included patients.

The levels of VK1 and VK2 were measured using ELISA kits specifically designed for Vitamin K1 (VK1) and Vitamin K2 (VK2) by Abbkine®. The ELISA assays employed a two-site sandwich method to quantify VK1 and VK2 levels in the samples. The detection range was 0.75–12 ng/mL for VK1 and 0.25–4 ng/mL for VK2. The minimum detectable concentrations for VK1 and VK2 were less than 0.05 ng/mL and 0.01 ng/mL, respectively. The severity of COVID-19 on CT scans was assessed semi-quantitatively by scoring lung involvement in each lobe. Scores were assigned based on the percentage of involvement in each lobe, ranging from 0 (no involvement) to 5 (complete involvement). The total lung involvement score, ranging from 0 to 25, was calculated by summing the scores of all five lobes [22].

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Medical Research Ethics Committee of Bakırköy Dr. Sadi Konuk Training and Research Hospital (Approval number: 027-2020, March 12, 2020). Since some participants were ICU patients and in critical condition, informed consent was obtained from the patients themselves whenever possible or from their legal representatives when the patients were unable to provide consent due to their clinical status. All data were anonymized to ensure participant confidentiality and privacy.

Statistical analysis

For statistical analysis, the Number Cruncher Statistical System (NCSS) software (Kaysville, Utah, USA) was used. Descriptive statistical methods, including mean, standard deviation, median, frequency, ratio, minimum, and maximum, were employed to evaluate the study data. The Mann-Whitney U test was used for comparisons between groups of variables that did not follow a normal distribution. Spearman's correlation analysis was performed to assess relationships between variables. Multivariate logistic regression analysis was conducted to identify risk factors associated with ICU admission and mortality. For this analysis, age, gender, computerized tomography (CT) severity,

and VK1 and VK2 levels were included as potential predictors. These variables were selected based on their clinical relevance and previously reported associations with COVID-19 severity and outcomes in the literature. Statistical significance was defined as $P<0.05$.

Results

A total of 165 patients infected with COVID-19 were included in the study, with 50.3% females and 49.7% males. The mean age of the participants was 60.84 (16.64) years. The ICU admission rate was 6.1%, while the mortality rate was 4.2%. Patients were categorized based on disease severity and CT findings. Among them, 65.5% had mild to moderate disease activity, whereas 34.5% exhibited severe disease. Similarly, 84.2% had mild to moderate CT involvement, while 15.8% showed severe pulmonary involvement. The descriptive features and laboratory findings of the patients are summarized in Table 1 and Table 2.

Table 1: Descriptive features of the patients (univariate analysis)

		N[a]	%
Age (year)	Min-Max[b] (Median)	16-94 (61)	
	Mean (SD)[c]	60.84 (16.64)	
Gender	Female	83	50.3
	Male	82	49.7
Disease Severity	Mild and Moderate	108	65.5
	Severe	57	34.5
CT Severity	Mild and Moderate	139	84.2
	Severe	26	15.8
Comorbidities	Diabetes Mellitus	48	29.4
	Hypertension	87	53.4
	Coronary Heart Disease	47	28.8
	Chronic Obstructive Pulmonary Disease	26	16.0
	Malignancy	11	6.7
	Chronic Kidney Failure	8	4.9
	Other	116	71.2
Intensive Care Unit Admission	Absence	155	93.9
	Presence	10	6.1
Length of stay (day)	Min-Max (Median)	3-49 (9)	
	Mean (SD)	11.68 (7.49)	
Mortality	Absence	158	95.8
	Presence	7	4.2

N[a]: Number of patients Min-Max[b]: Minimum- Maximum SD[c]: Standard Deviation

VK1 levels did not show significant differences between the groups ($P>0.05$). However, VK2 levels were significantly higher in patients with severe disease ($P<0.01$) and in those admitted to the ICU ($P<0.01$). Moreover, both VK1 and VK2 levels were elevated in deceased patients ($P<0.05$). These associations are detailed in Table 3.

Logistic regression analysis revealed that CT severity was a significant risk factor for ICU admission, with an odds ratio of 10.65 (95% CI: 2.47–45.99). Similarly, CT severity and VK1 levels were identified as significant risk factors for mortality, with odds ratios of 6.43 (95% CI: 1.03–40.08) and 1.166 (95% CI: 1.003–1.345), respectively. Table 4 provides the logistic regression analysis results.

Additional correlations were identified between VK levels and laboratory parameters, as presented in Table 5 and Table 6. A weak positive correlation was observed between VK1 levels and C-reactive protein (CRP) in patients with mild to moderate CT involvement ($P<0.05$), while a weak negative correlation was found between VK2 levels and albumin levels ($P<0.01$).

Although the other parameters and VK2 level were univariate, they were not statistically significant in multivariate evaluation ($P>0.05$) (Table 7).

Table 2: Patients' laboratory findings

n=165	Min-Max (Median)	Mean (SD)
Hemoglobin	5.3-17.5 (12.1)	11.84 (2.20)
Hematocrit	14.8-51 (37)	36.11 (6.02)
White Blood Cell Count	1.8-26.8 (7.4)	8.70 (4.57)
Lymphocyte	0.4-17.7 (1.4)	1.61 (1.58)
Neutrophil	0.7-73.1 (5.2)	7.22 (8.43)
Platelet Count	29-830 (226)	245.18 (110.10)
Aspartate aminotransferase	9-227 (28)	35.24 (26.05)
Alanine aminotransferase	3-191 (22)	30.95 (30.04)
Urea	5-249 (34)	40.04 (30.68)
Creatinin	0.4-8.5 (0.8)	1.12 (1.13)
Lactate dehydrogenease	118-968 (275)	293.48 (119.66)
Albumin	21.3-46 (35.6)	35.39 (5.46)
Ferritin	5.7-4816 (146.3)	327.16 (564.76)
Triglyceride	31-582 (112)	140.04 (87.56)
Creatin Kinase	10-4088 (80)	169.86 (381.72)
Procalcitonin	0-77.3 (0.1)	1.29 (6.97)
C-Reactive Protein	0.6-358 (48.8)	74.39 (73.67)
Fibrinogen	43-814 (477)	484.28 (119.79)
Prothrombin Time	0-62.4 (13.4)	10.52 (9.07)
Active partial thromboplastin time (a-PTT)	21.7-73.1 (35.4)	36.30 (6.70)
D-dimer	0-7.8 (0.4)	0.91 (1.32)
Troponine	1-836 (6)	25.28 (86.59)
Vitamin K1	2.8-25.2 (13.3)	14.26 (5.82)
Vitamin K2	0.01-8.39 (0.8)	1.07 (1.21)
	N	**%**
Vitamin K1		
Normal	67	40.6
Elevated	98	59.4
Vitamin K2		
Low	20	12.1
Normal	145	87.9

Evaluation of Vitamin K1 and Vitamin K2: According to the variables in the Mann Whitney U test, *$P<0.05$ considered as significant **$P<0.01$considered as significant

Table 3: Evaluation of vitamin K1 and vitamin K2 according to the variables (univariate analysis)

		Vitamin K1		Vitamin K2	
		Mean (SD)	**Min-Max (Median)**	**Mean (SD)**	**Min-max (Median)**
Disease Severity	Mild and Moderate	14.0 (5.3)	13.1 (5.4-25.2)	1.0 (1.4)	0.7 (0-4.2)
	Severe	14.7 (6.7)	13.3 (2.8-25.2)	1.2 (0.7)	1.0 (0-8.4)
	P-value	*0.624*		*0.001***	
Computerized Tomography Severity	Mild and Moderate	14.4 (5.8)	13.3 (2.8-25.2)	1.0 (1.3)	0.7 (0-4.2)
	Severe	13.6 (5.8)	13 (5.1-25.2)	1.3 (0.9)	1.1 (0.2-8.4)
	P-value	*0.455*		*0.005**	
Intensive Care Unit Admission	Absence	14.2 (5.7)	13.2 (2.8-25.2)	1.0 (1.2)	0.8 (0-4.2)
	Presence	15.8 (7.3)	14.9 (5.1-25.2)	1.6 (1.0)	1.4 (0.7-8.4)
	P-value	*0.448*		*0.005***	
Decease	Absence	14.0 (5.7)	13.2 (2.8-25.2)	1.0 (1.2)	0.8 (0-4.2)
	Presence	19.2 (6.1)	16.8 (9.4-25.2)	1.7 (1.3)	1.6 (0-8.4)
	P-value	*0.028**		*0.042**	

*Mann Whitney U test *$P<0.05$ considered as significant;**$P<0.01$considered as significant

Table 4: Logistic regression analysis results for intensive care unit admission

	***P*-value**	**ODDS**	**95% C.I.ODDS**	
			Lower	**Upper**
Age	*0.382*	1.020	0.976	1.066
Gender (Male)	*0.849*	0.867	0.200	3.755
Computerized Tomography Severity	*0.002***	10.650	2.466	45.990
Vitamin K1	*0.461*	1.048	0.925	1.189
Vitamin K2	*0.511*	1.167	0.736	1.853

*Logistic regression analysis results for Intensive care unit admission; **$P<0.01$ considered as significant

Table 5: Correlations between Vitamin K levels and laboratory findings according to disease severity

	Disease Severity							
	Mild and Moderate				Severe			
	Vitamin K1		Vitamin K2		Vitamin K1		Vitamin K2	
	r	*P*	r	*P*	r	*P*	r	*P*
Hemoglobin	0.063	*0.514*	-0.124	*0.201*	-0.151	*0.262*	-0.235	*0.079*
Hematocrit	0.057	*0.559*	-0.094	*0.334*	-0.168	*0.212*	-0.226	*0.091*
White Blood Cell Count	0.012	*0.903*	0.140	*0.149*	0.175	*0.194*	0.027	*0.843*
Lymphocyte	0.228	*0.018**	-0.090	*0.356*	-0.092	*0.494*	-0.093	*0.492*
Neutrophil	0.002	*0.986*	0.109	*0.260*	0.206	*0.125*	0.063	*0.641*
Platelet Count	0.078	*0.421*	0.031	*0.754*	-0.007	*0.959*	0.143	*0.290*
Aspartate aminotransferase	0.012	*0.901*	-0.052	*0.590*	0.097	*0.472*	0.019	*0.888*
Alanine aminotransferase	0.088	*0.367*	-0.135	*0.162*	0.065	*0.631*	0.009	*0.945*
Urea	0.002	*0.986*	-0.038	*0.694*	0.193	*0.150*	-0.137	*0.309*
Creatinin	0.059	*0.545*	0.098	*0.311*	0.002	*0.986*	-0.152	*0.259*
Lactate dehydrogenease	0.032	*0.744*	-0.034	*0.728*	0.042	*0.756*	0.016	*0.907*
Albumin	0.170	*0.078*	-0.162	*0.094*	-0.162	*0.227*	-0.206	*0.124*
Ferritin	0.102	*0.293*	-0.059	*0.547*	0.055	*0.684*	0.086	*0.524*
Triglyceride	0.144	*0.136*	0.014	*0.888*	0.129	*0.340*	0.121	*0.370*
Creatin Kinase	0.189	*0.050**	-0.080	*0.411*	0.068	*0.613*	-0.097	*0.475*
Procalcitonin	0.024	*0.808*	0.058	*0.553*	0.119	*0.378*	0.086	*0.527*
C-Reactive Protein	0.218	*0.023**	0.041	*0.676*	0.141	*0.296*	0.127	*0.347*
Fibrinogen	0.151	*0.118*	0.046	*0.636*	0.029	*0.828*	0.189	*0.160*
Prothrombin Time	0.150	*0.121*	-0.040	*0.678*	-0.006	*0.964*	0.150	*0.265*
Active Partial Thromboplastin Time (a-PTT)	0.168	*0.082*	0.108	*0.265*	-0.017	*0.900*	0.089	*0.513*
D-dimer	0.107	*0.273*	-0.051	*0.599*	0.156	*0.248*	0.129	*0.339*
Troponine	0.013	*0.893*	-0.007	*0.943*	0.277	*0.037**	-0.022	*0.873*

*The Spearman Correlation test was used for analysis. r: Spearman's correlation coefficient; **P*<0.05 considered as significant

Table 6: Correlations between Vitamin K levels and laboratory findings based on lung involvement severity.

	Lung Involvement Severity							
	Mild and Moderate				Severe			
	Vitamin K1		Vitamin K2		Vitamin K1		Vitamin K2	
	r	*P*	r	*P*	r	*P*	r	*P*
Hemoglobin	-0.063	0.462	-0.193	0.023*	-0.189	0.356	-0.138	0.502
Hematocrit	-0.076	0.373	-0.166	0.050*	-0.198	0.333	-0.049	0.814
White Blood Cell Count	0.074	0.385	0.123	0.150	0.033	0.872	0.128	0.533
Lymphocyte	-0.214	0.011*	-0.199	0.019*	-0.104	0.612	0.024	0.906
Neutrophil	0.103	0.229	0.149	0.080	-0.029	0.888	0.012	0.954
Platelet Count	-0.044	0.609	0.104	0.221	-0.059	0.775	-0.153	0.455
Aspartate aminotransferase	0.081	0.344	-0.033	0.698	-0.160	0.435	-0.089	0.664
Alanine aminotransferase	0.029	0.731	-0.087	0.308	-0.178	0.383	-0.241	0.235
Urea	0.028	0.741	-0.031	0.716	0.299	0.138	0.361	0.070
Creatinin	-0.069	0.423	0.069	0.417	0.199	0.329	0.331	0.099
Lactate dehydrogenease	0.034	0.688	0.058	0.500	-0.064	0.756	-0.280	0.167
Albumin	-0.158	0.063	-0.231	0.006**	-0.282	0.163	-0.176	0.389
Ferritin	0.095	0.263	0.050	0.561	0.212	0.299	0.214	0.293
Triglyceride	-0.055	0.517	0.059	0.494	-0.015	0.940	-0.235	0.248
Creatin Kinase	-0.113	0.187	-0.047	0.586	0.051	0.803	0.021	0.921
Procalcitonin	0.055	0.523	0.150	0.078	0.234	0.250	0.294	0.144
C-Reactive Protein	0.174	0.040*	0.147	0.084	0.159	0.439	0.184	0.368
Fibrinogen	0.109	0.200	0.081	0.345	0.144	0.483	0.425	0.031*
Prothrombin time	0.071	0.406	0.011	0.898	0.316	0.116	0.402	0.042*
Active Partial Thromboplastin Time (a-PTT)	0.066	0.443	0.123	0.150	0.228	0.264	0.232	0.254
D-dimer	-0.050	0.557	0.037	0.670	0.306	0.128	0.039	0.850
Troponine	0.094	0.272	0.070	0.412	0.178	0.384	0.040	0.846

* The Spearman Correlation test was used for analysis. r: Spearman's correlation coefficient; **P*<0.05 considered as significant

Table 7 : Logistic regression analysis of age, gender, and CT severity of vitamin K1 and K2 vitamins on mortality (multivariate analysis)

	P-value	ODDS	95% CI ODDS	
			Lower	Upper
Age	*0.316*	1.026	0.976	1.078
Gender (Male)	*0.411*	0.479	0.083	2.761
Computerized Tomography Severity	*0.046**	6.430	1.032	40.082
Vitamin K1	*0.045**	1.166	1.003	1.354
Vitamin K2	*0.935*	1.021	0.622	1.675

Logistic regression analysis of age, gender, and CT severity of vitamin K1 and K2 vitamins on mortality, **P*<0.05 considered as significant

Discussion

The COVID-19 pandemic has significantly affected global health, with severe cases often marked by hyperinflammatory responses, coagulopathy, and multiorgan damage [1,3]. Identifying biomarkers predictive of disease severity and outcomes has been a focus of recent research. Our study highlights the potential role of VK1 and VK2 levels as biomarkers for COVID-19 severity and mortality.

Consistent with previous studies, we observed significantly elevated VK2 levels in patients with severe disease and in those admitted to the ICU. VK2's anti-inflammatory effects, mediated through the inhibition of NFκB signaling, likely play a critical role in mitigating the inflammatory cascade characteristic of severe COVID-19 [20]. This aligns with findings by Dofferhoff et al. [23], who demonstrated that reduced vitamin K status, as measured by dp-ucMGP, was associated with poor outcomes in COVID-19 patients. Our study further expands on this by showing VK2's elevation in deceased patients, suggesting its dual role as a compensatory response and a potential prognostic marker.

In contrast, the association between VK1 levels and mortality observed in our study offers new insights. While VK1 is traditionally linked to coagulation pathways, its role in inflammation and COVID-19 outcomes remains less explored. Elevated VK1 levels in deceased patients may reflect a maladaptive response or an imbalance in vitamin K metabolism during critical illness. This finding partially contrasts with previous studies that predominantly focus on VK2, underscoring the need for further investigation. For instance, Halder et al. [20] and Dofferhoff et al. [23] highlighted VK2's anti-inflammatory and protective roles in severe diseases, whereas VK1's contributions remain underexplored. This finding partially contrasts with previous studies that predominantly focus on VK2, underscoring the need for further investigation.

CT severity emerged as the strongest predictor of ICU admission and mortality, as patients with severe pulmonary involvement were over ten times more likely to require ICU care and over six times more likely to die. This aligns with prior research emphasizing the prognostic value of radiological assessments in COVID-19 management [23]. However, our study uniquely combines imaging findings with biomarker levels, providing a more comprehensive risk stratification approach.

Our analysis also identified correlations between VK levels and laboratory markers, further linking vitamin K status to systemic inflammation and disease severity. For instance, the positive correlation between VK1 levels and CRP in patients with mild to moderate CT involvement aligns with vitamin K's involvement in inflammatory processes. Conversely, the negative correlation between VK2 levels and albumin may reflect hypoalbuminemia-driven VK2 depletion, a hallmark of severe disease.

Limitations

This study, while providing valuable insights into the potential role of VK1 and VK2 levels as biomarkers for COVID-19 severity and mortality, has several limitations. First, certain confounding variables, such as anticoagulant therapy and nutritional status, were not accounted for in our analysis. These factors could significantly influence vitamin K levels and may affect the generalizability of our findings.

Second, the observational nature of the study limits our ability to infer causality. Although associations between VK levels and clinical outcomes were identified, further randomized controlled trials are needed to establish a causal relationship.

Third, the study did not measure specific vitamin K metabolites, such as desphospho-uncarboxylated matrix Gla protein (dp-ucMGP), a more direct marker of vitamin K status.

Future studies incorporating these markers could provide deeper insights into the mechanistic pathways linking vitamin K to COVID-19 severity. In particular, the findings by Dofferhoff et al. [23] highlight the potential of dp-ucMGP as a sensitive indicator of vitamin K deficiency and its prognostic value in COVID-19.

Fourth, while the sample size was adequate for statistical analysis, it may limit the detection of smaller effects or rare associations. Larger, multicenter studies are recommended to validate these findings and enhance their applicability across diverse populations.

Lastly, the study was conducted in a single geographic region during a specific time frame. Variations in healthcare practices, population characteristics, and viral variants might influence the reproducibility of our results in other settings or during different phases of the pandemic. Despite these limitations, this study highlights the significant association between vitamin K levels and COVID-19 outcomes, providing a foundation for further research in this area.

Our study underscores the importance of VK1 and VK2 levels as biomarkers for disease severity and mortality in COVID-19. These findings could guide clinicians in managing patients with severe disease and inform future research into vitamin K's therapeutic potential in mitigating severe outcomes in COVID-19.

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