e-ISSN:2602-2079

Volume 9
Issue 9
2025

JOURNAL of Surgery and Medicine

International Medical Journal

JOSAM

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Vol. 9 No. 9 (2025)

Published: 2025-09-30

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J Surg Med. 2025;9(9):149-153.
https://doi.org/10.28982/josam.8106

JOSAM

Research article
https://jsurgmed.com/

Journal of Surgery and Medicine

e-ISSN: 2602-2079

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.

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

Published
2025 September 4

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

How to cite: Demircioglu DT, Karabulut D, Kasapoglu P, Canbolat Unlu E, Kart Yasar K, Isıksacan N. The effect of vitamin K1 and vitamin K2 on mortality rate and disease severity in covid-19 patients: An observational study. J Surg Med. 2025;9(9):149-153.

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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J Surg Med. 2025;9(9):154-157.
https://doi.org/10.28982/josam.8071

JOSAM

Research article
https://jsurgmed.com/

Journal of Surgery and Medicine

e-ISSN: 2602-2079

Clinical characteristics of female patients with fibromyalgia syndrome

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Ethics Committee Approval
This study was approved by the Clinical Research Ethics Committee of Istanbul Medeniyet University Göztepe Training and Research Hospital, June 30, 2021, decision no: 2021/0357. 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.

Previous Presentation
This study presented as an oral presentation in Turkish Rheumatology Congress With International Attendance 2024, February 9, 2024, Royal Seginus Hotel Lara/Antalya, Turkey

Published
2025 September 1

Abstract

Background/Aim: Fibromyalgia syndrome (FMS) is a chronic condition that places a significant financial and social burden on both patients and society. Delayed diagnosis and the presence of comorbidities exacerbate these challenges. While awareness of FMS is increasing, there is a lack of studies focusing on specific patient demographics and the gaps in healthcare services, particularly in local settings. This study aimed to investigate the clinical characteristics of female FMS patients attending our clinic, with the goal of identifying healthcare-related issues and potential areas for improvement.

Methods: The study included female patients admitted to the Physical Medicine and Rehabilitation outpatient clinic of Göztepe Prof. Dr. Süleyman Yalçın City Hospital between December 1 and December 31, 2023, who were diagnosed with FMS according to the 2013 American College of Rheumatology alternative diagnostic criteria. Demographic characteristics of the patients were recorded, including height, weight, educational status, marital status, occupation, habits, comorbidities, and medications. All patients completed the Fibromyalgia Impact Questionnaire (FIQ) and Beck Depression Inventory (BDI). Ethics committee approval was obtained.

Results: A total of 44 female FMS patients were included in the study. The patients were aged between 26 and 64 years (mean: 46.65 [7.63]). Body mass index (BMI) ranged from 16.65 to 45.72 (mean: 28.8 [6.11]). While 20.5% of the patients had normal BMI, 75% were in the overweight or obese category. The majority of the participants were primary school graduates (50%), married (84.1%), and housewives (59.1%). In total, 34% of the patients were active smokers, and 52.3% had a chronic comorbidity. When asked about the presence of chronic diseases such as chronic obstructive pulmonary disease, diabetes mellitus, coronary artery disease, or hypertension, the most common comorbidities were diabetes mellitus and hypertension, reported by 25% and 18.2% of patients, respectively. Most of the patients (95.5%) were fully independent in activities of daily living and ambulated without assistance. According to the FIQ results, 23.6% of the patients were severely affected by fibromyalgia and 45.5% were moderately affected. According to the BDI results, 22.7% of the patients had severe depression and 36.4% had moderate depression.

Conclusion: This study emphasizes the need for comprehensive care for fibromyalgia patients, particularly addressing comorbidities such as depression and obesity. Our findings also highlight the impact of social factors, including educational limitations, on patient outcomes. By focusing on these areas, we contribute valuable insights to the literature and underscore the importance of a multidisciplinary approach to improve the care and management of fibromyalgia patients.

Keywords: comorbidities, demographic characteristics, depression, fibromyalgia syndrome (FMS), fibromyalgia impact questionnaire (FIQ)

How to cite: Yumuşakhuylu Y, Yağcı HÇ, Zengin M, Erhan B. Clinical characteristics of female patients with fibromyalgia syndrome. J Surg Med. 2025;9(9):154-157.

Introduction

Fibromyalgia syndrome (FMS) is a rheumatic disease of unknown etiology characterized by widespread pain and specific tender points in various parts of the body [1,2]. In addition to pain, it is associated with various somatic and psychological symptoms, including fatigue, morning stiffness, depression, and sleep problems [2]. With an annual prevalence of 2–4%, this disease usually affects women aged 40–55 years [1,3]. Studies show that neuroendocrine, autonomic, and immunological systems play a role in FMS and that genetic predisposition combined with environmental, physiological, and psychological factors contribute to the development of the disease [1,2,4]. At its core is a somatosensory disorder leading to hypersensitivity to pain (allodynia and hyperalgesia) [5].

FMS has long been recognized as a psychological condition, with mood disorders and sleep problems often accompanying pain [6]. Psychological factors are particularly recognized as an element of chronic pain and can interact with each other to increase pain [7]. Previous research shows that mood disorders such as depression and anxiety are more common in patients with FMS compared to the general population [8]. Quality of life is a concept related to how individuals perceive and evaluate their own lives, and it varies depending on cultural and value systems [9]. There are many studies showing that quality of life is negatively affected in patients with FMS [10]. Pain, fatigue, sleep disorders, and psychiatric symptoms may negatively affect quality of life. The treatment goal for the disease is to reduce pain and improve quality of life [11].

FMS patients use a variety of methods and medications to alleviate their symptoms, and they have frequent healthcare visits, both of which increase the financial burden of the disease [12]. The economic burden of chronic diseases on society is also important [13]. Previous studies have reported that delayed diagnosis of patients, performing a wide variety of tests, conducting multiple doctor visits, and medical and non-medical treatments after diagnosis create a financial burden [14]. In addition, the loss of workforce of FMS patients due to the disease is also important for society [15]. It is important to diagnose the disease early on and to treat patients with related problems [16]. Moreover, it is very important to know disease-specific demographic data for diagnosis and treatment [17].

The aim of this study was to investigate the clinical characteristics of patients with FMS admitted to our clinic and to identify problems in health services and other areas that can be solved.

Materials and methods

Between December 1 and December 31, 2023, patients admitted to the Physical Medicine and Rehabilitation outpatient clinic of Göztepe Prof. Dr. Süleyman Yalçın City Hospital were included in the study. The sample included female patients aged 18–65 years who were diagnosed with FMS according to the 2013 American College of Rheumatology (ACR) alternative diagnostic criteria. Participants with neurological disorders or cognitive impairments that would hinder their ability to respond to questions were excluded from the study.

Demographic characteristics of the patients including height, weight, educational status, marital status, occupation, smoking and alcohol habits, comorbidities, and medications were recorded. In addition to answering demographic questions, all participating patients completed the Fibromyalgia Impact Questionnaire (FIQ) and Beck Depression Inventory (BDI) [18].

The following criteria were employed to establish a diagnosis of fibromyalgia:

1. Symptoms and pain locations had been persistent for at least the last 3 months
2. Pain location score ≥17
3. Symptom Impact Questionnaire (SIQR) symptom score ≥21

Pain Location Score: A pain location score was calculated based on the number of areas with persistent pain over the past week. This score ranged from 0 to 28, encompassing areas such as shoulders, arms, wrists, hands, hips, thighs, knees, ankles, feet, jaws, chest, back, and neck.

Symptom Impact Questionnaire (SIQR): Participants completed a 10-item SIQR assessing the intensity of various symptoms experienced in the past week. Each symptom (pain, energy, stiffness, sleep, depression, memory problems, anxiety, tenderness to touch, balance problems, and sensitivity to environmental stimuli) was rated on a scale from 0 (no symptoms) to 10 (severe symptoms). The SIQR score was computed as the sum of individual symptom scores, yielding a total score between 0 and 100, which was then divided by 2 for analysis [19].

The presence of other pain disorders or related symptoms did not rule out a diagnosis of fibromyalgia.

Patients' body mass index (BMI) was calculated as body weight divided by the square of height (kg/m²). BMI values were divided into intervals and named as follows: 18.5 and below was classified as underweight, 18.5 to 24.9 as normal, 25 to 29.9 as overweight, 30 to 34.9 as class I obesity, 35 to 39.9 as class II obesity, and 40 and over as class III obesity. Patients were classified as normal, overweight, or obese according to these criteria.

Depression Evaluation

The presence and severity of depression were assessed using the BDI. This scale consists of 21 items, each one consisting of four sentences. These sentences are ranked from neutral (0 points) to the most severe (3 points). In our study, patients were asked to choose the most appropriate sentence in the scale, which was organized as a questionnaire. A total score of 0–16 was considered minimal depression, 16–28 moderate depression, and 29–63 severe depression.

Functional Assessment and Quality of Life

In our study, the FIQ was used to assess quality of life and functional status in patients with FMS [18]. This scale measures 10 characteristics, including physical function, feeling well, inability to go to work, difficulty at work, pain, fatigue, morning fatigue, stiffness, anxiety, and depression. With the exception of well-being, lower scores indicate improvement or being less affected by the disease. The FIQ is completed by the patients themselves. The maximum score is 100. In this study, a score of 0–50 was considered mildly affected, 50–70 moderately affected, and above 70 severely affected.

Statistical analysis

For data analysis, SPSS 25 was used to summarize the demographic and clinical characteristics of the participants.

Univariate analysis was conducted. For categorical data, frequency and percentages were calculated. For numerical data, descriptive statistics such as mean, median, mode, standard deviation, and minimum and maximum values were used to better understand the distribution.

Ethical Considerations

All participants received detailed information about FMS and the purpose of the study. They were informed about the data collection process, potential risks and benefits, and how their data would be used in the research. Participants were assured that their names and identities would remain confidential throughout the study. Informed consent was obtained in writing from all patients, ensuring they understood their rights to withdraw from the study at any time without any consequences. The research was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Istanbul Medeniyet University Göztepe Training and Research Hospital (decision no: 2021/0357).

Results

A total of 44 female FMS patients were included in the study. Our patients were between 26 and 64 years old (mean: 46.65 [7.63]). BMI ranged from 16.65 to 45.72 (mean: 28.82 [6.11]). While 20.5% of the patients had normal BMI, 75% were in the overweight or obese category (Table 1). The majority of the participants were primary school graduates (50%), married (84.1%), and housewives (59.1%) (Table 2 and 3). A total of 34% of the patients were active smokers, and 52.3% had a chronic comorbidity. When asked about the presence of chronic diseases such as chronic obstructive pulmonary disease, diabetes mellitus, coronary artery disease, and hypertension, the most common comorbidities were diabetes mellitus and hypertension, reported by 25% and 18.2% of patients, respectively. Most of the patients (95.5%) were fully independent in activities of daily living and ambulated without assistance. According to the FIQ results, 23.6% of the patients were severely affected and 45.5% were moderately affected (Table 4). According to the BDI results, 22.7% of the patients had severe depression and 36.4% had moderate depression (Table 5).

Table 1: Statistics

		Age	Height	Weight	BMI	FIQ	Depression
n	Accurate	44	44	44	44	44	44
	Lost	0	0	0	0	0	0
Mean		46.65	159.47	73.27	28.82	52.00	20.50
Median		45.50	159.50	73.50	27.97	54	18
Mod		41.00a	158a	62a	31.60	25a	15
Standard Deviation		7.63	5.76	15.78	6.115	18.19	10.21
Minimum		26	147	45	16.65	22	4
Maximum		64	170	120	45.72	93	45

a In case of multiple modes, the mode with the smallest value is taken.

Table 2: Occupation

	Frequency (n)	Percent(%)
Civil Servant	6	13.6
Worker	6	13.6
Housewife	26	59.1
Retired	3	6.8
Other	3	6.8
Total	44	100

Table 3: Education Status

	Frequency (n)	Percent (%)
Illiterate	2	4.5
Primary school/secondary school	22	50.0
High school	10	22.7
University	10	22.7
Total	44	100

Table 4: FMS Impact

	Frequency (n)	Percent (%)
Slightly Affected	18	40.9
Affected	20	45.5
Severely Affected	6	23.6
Total	44	100

Table 5: Depression

	Frequency (n)	Percent (%)
Mild	18	40.9
Moderate	16	36.4
Severe	10	22.7
Total	44	100

Discussion

Özcan et al. [11] analyzed demographic data from 100 female patients diagnosed with FMS based on the 1990 ACR criteria. In their study, 88% were married, 53% were primary school graduates, and 26% exhibited severe FIQ scores, with 47% showing moderate to severe depression. The mean BMI was reported as 27.6 (4.7), but without classification into normal, overweight, or obese categories. Our study, conducted over a decade later, included a similar demographic profile, with a mean age of 46.65 (7.63) years, compared to 42.2 (9.4) years in Özcan et al.'s study. Educational attainment was comparable, with 50% primary school graduates in our cohort versus 53% in theirs. Marital status also showed slight differences, with 84.1% of our patients being married versus 88% in the previous study.

Interestingly, despite the passage of over 10 years and potential variations in socioeconomic factors, the demographic characteristics of patients have remained largely unchanged. The prevalence of depression across both studies underscores the necessity of a multidisciplinary treatment approach, particularly for managing mental health issues alongside fibromyalgia.

In a pilot study conducted in Turkey by Dernek [20] between 2017 and 2018, 254 FMS patients were evaluated, revealing that 49.6% were housewives. In our study, 59.1% of patients were housewives, indicating a consistent trend in patient demographics across different studies.

Wolfe et al. [21] assessed the prevalence of fibromyalgia in the general population, linking low educational attainment and economic status with increased incidence. In their findings, 53% of the patients were married, aligning with our results. However, the higher divorce rates noted in their study compared to the general population warrant further investigation. Our study did not include a control group, limiting the ability to statistically assess the relationship between fibromyalgia and these demographic factors.

Cacace et al. [22] examined FIQ scores among FMS patients and found significant differences when compared to healthy controls, establishing a cut-off value of 66.85. In our study, we utilized a slightly higher cut-off of 70, which could reflect differing patient populations or study methodologies.

A study conducted by Aparicio et al. [23] in Spain included 127 women with FMS. The majority of participants were married (73%), with an average age of 51.3 (7.3) years. Notably, 8% of the sample did not complete their education, while 42% completed primary school, 21% completed secondary school, and 29% graduated from university. Additionally, 60% of participants were housewives. They reported a mean FIQ total score of 66.8 (14.0) and a mean BMI of 28.4 (5.6). A HADS-depression score ≥8 was associated with severe fibromyalgia (OR=4.95; 95% CI:

2.02–12.10). Despite being conducted in a different country, the findings align with ours, highlighting the prevalence of low educational levels and the high percentage of housewives among FMS patients, reinforcing the need for comprehensive management of both physical and psychological aspects of the condition.

Limitations

Our study has several limitations. The small sample size limited our ability to demonstrate statistically significant relationships between various factors. Additionally, while correlating demographic data with the disease, it is crucial to consider the demographics of a healthy control group from the same population; the absence of such a control group restricts our findings.

Moreover, the selection of patients solely from an outpatient clinic introduces potential selection bias. Although we anticipated a greater bias related to socioeconomic status and educational level due to ease of communication, our findings indicated that 50% of participants were primary school graduates. This suggests that our sample may still reflect a broader demographic, thereby mitigating some selection bias.

Overall, addressing these limitations in future research will be essential for enhancing the robustness of findings related to fibromyalgia.

Conclusion

In conclusion, this study suggests that patients with fibromyalgia require comprehensive care that goes beyond pain management to address comorbid conditions, particularly depression and weight management issues. A multidisciplinary approach, involving psychiatrists and dietitians, can enhance treatment effectiveness and improve patient outcomes.

Importantly, our findings provide valuable insights into the social aspects of fibromyalgia, highlighting the significant prevalence of depression and educational limitations among patients. This study adds to the literature by suggesting that these social factors may play a critical role in the management of fibromyalgia. Given that a significant portion of our participants were married and had only primary education, future research should explore the social challenges that may accompany fibromyalgia. It is imperative for healthcare professionals to recognize the complexity of fibromyalgia and adopt a holistic, multidisciplinary management strategy to optimize patient care.

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J Surg Med. 2025;9(9):158-161.
https://doi.org/10.28982/josam.8374

JOSAM

Research article
https://jsurgmed.com/

Journal of Surgery and Medicine

e-ISSN: 2602-2079

Time-stratified comparison of quality of life following laparoscopic vs abdominal hysterectomy

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Ethics Committee Approval
The study was approved by the Ethics Committee of the University of Health Sciences, Etlik Zübeyde Hanım Health Training and Research Hospital (Approval Number: 2018/30, dated June 27, 2018).
Written informed consent was obtained from all participants before inclusion in the study. No identifying personal information of participants was included in the manuscript.
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
2025 September 16

Abstract

Background/Aim: Hysterectomy is a widely used surgical procedure for benign gynecologic conditions. Although total abdominal hysterectomy (TAH) has traditionally been the standard, total laparoscopic hysterectomy (TLH) is increasingly preferred due to its minimally invasive nature. Despite extensive research on perioperative outcomes, longitudinal data on quality of life (QoL) and urinary function remain limited.

Methods: A retrospective cohort study was conducted including 252 perimenopausal women who underwent either TLH (n=134) or TAH (n=118) at a tertiary hospital in Türkiye between 2014 and 2021. QoL was assessed using validated Turkish versions of the SF-36 and UDI-6 questionnaires at three postoperative intervals: early (≤3 months), mid-term (4–12 months), and long-term (>12 months). Additional parameters included hospital stay duration and postoperative complications.

Results: TLH patients reported significantly better QoL outcomes in the early and mid-term periods, particularly in physical functioning, bodily pain, and social functioning ($P<0.05$). Early urinary distress scores also favored the TLH group. However, these differences had diminished at the long-term follow-up. TLH was also associated with shorter hospital stays and fewer febrile episodes.

Conclusion: TLH offers superior short-term improvements in QoL and urinary outcomes compared to TAH. These advantages tend to decrease over time, resulting in similar long-term recovery. Time-stratified assessment provides a more nuanced understanding of postoperative recovery and may aid in personalized surgical planning.

Keywords: abdominal hysterectomy, laparoscopic hysterectomy, quality of life

How to cite: Kurtay S, Altınbaş ŞK, Tapısız ÖL. Time-stratified comparison of quality of life following laparoscopic vs abdominal hysterectomy. J Surg Med. 2025;9(9):158-161.

Introduction

Globally, hysterectomy ranks among the most commonly performed gynecologic operations, indicated for a wide spectrum of benign and malignant pathologies [1]. Over the years, several surgical techniques have been developed. These include the traditional total abdominal hysterectomy (TAH), the total vaginal hysterectomy (TVH), and the minimally invasive total laparoscopic hysterectomy (TLH) [2,3]. TLH has gained substantial acceptance owing to its benefits, including minimized intraoperative hemorrhage, enhanced postoperative comfort, reduced hospitalization duration, and accelerated convalescence [4].

Despite these benefits, TAH continues to be widely practiced in many settings. Factors, such as surgeon expertise, patient comorbidities, and institutional resources contribute to the continued use of this approach [2,5]. However, emerging data have challenged the equivalence of TAH and TLH, particularly concerning long-term quality of life metrics.

In contemporary hysterectomy research, patient-centered endpoints like QoL have become increasingly significant, shifting focus away from solely surgical outcomes [6]. Validated assessment tools, such as the Short Form-36 (SF-36) and the Urogenital Distress Inventory-6 (UDI-6), are frequently employed to evaluate domains including physical function, emotional health, and urinary symptoms [7]. Although numerous studies have compared TLH and TAH, few have assessed postoperative quality of life using a stratified temporal framework [8]. Such an approach may provide deeper insight into the progression of patient recovery.

The present study aims to evaluate postoperative QoL outcomes of TLH and TAH in perimenopausal women, using SF-36 and UDI-6 scores across different postoperative intervals. To our knowledge, this represents one of the few retrospective analyses to adopt a time-stratified design in a large cohort.

Materials and methods

This retrospective observational study was conducted on perimenopausal women aged 40–55 years who underwent either total abdominal hysterectomy or total laparoscopic hysterectomy for non-malignant gynecologic conditions, such as symptomatic fibroids, abnormal uterine bleeding, or adenomyosis. The surgeries were performed at a tertiary care center in Türkiye between January 2014 and December 2017. Participants were excluded if they had a history of gynecological malignancy, prior pelvic radiotherapy, severe pelvic organ prolapse, or had undergone vaginal or robotic hysterectomy. Only patients with complete quality of life (QoL) data and at least 12 months of postoperative follow-up were included in the final analysis.

Clinical and surgical data were retrospectively obtained from institutional patient records. These included demographic information, intraoperative variables (such as surgery duration, estimated blood loss, and any complications), as well as postoperative follow-up documentation. Quality of life (QoL) was assessed using the Turkish-validated, patient-reported outcome tools: SF-36 (Short Form-36) and UDI-6 (Urogenital Distress Inventory-6). Patients completed these questionnaires at three specific time points after surgery: the early period (within 3 months), mid-term (4 to 12 months), and long-term (beyond 12 months).

The SF-36 questionnaire, a comprehensively validated tool for measuring health-related quality of life, evaluates eight distinct domains encompassing both physical and mental well-being. Similarly, the UDI-6 instrument targets the severity of urinary complaints and how they influence daily functioning. Turkish versions of both tools, verified for psychometric reliability and validity, have been frequently employed in urogynaecological research [9].

Given the retrospective nature of the study and inclusion of all eligible individuals within the designated timeframe, an a priori sample size calculation was not performed. Nonetheless, the final cohort was considered adequate to capture clinically meaningful distinctions in quality of life between individuals who underwent TAH and those who had TLH.

Ethics approval

The study protocol was reviewed and approved by the Institutional Review Board of the University of Health Sciences, Etlik Zübeyde Hanım Training and Research Hospital (Approval No. 2018/30, dated June 27, 2018). All study procedures conformed to the ethical standards set forth in the Declaration of Helsinki. Informed written consent was obtained from all participants prior to their inclusion in the study.

Statistical analysis

All statistical analyses were performed using SPSS software (version 22.0; IBM Corp., Armonk, NY). To assess the distribution of continuous variables, the Kolmogorov–Smirnov test was applied. If data followed a normal distribution, intergroup comparisons were conducted using the independent samples t-test. For non-normally distributed variables, the Mann–Whitney U test was employed. Categorical variables were evaluated with either the chi-square test or Fisher's exact test, based on their appropriateness. A two-sided *P*-value less than 0.05 was considered statistically significant.

Results

The final sample consisted of 252 women who met the inclusion criteria, with 118 undergoing total abdominal hysterectomy and 134 undergoing total laparoscopic hysterectomy. Demographic and baseline clinical characteristics—including age, BMI, obstetric history, and comorbidities—did not differ significantly between the TAH and TLH groups (Table 1). Compared to the TAH group, the TLH group had a shorter duration of hospitalization (2.1 (0.5) vs. 3.6 (0.9) days; $P<0.001$) and less intraoperative blood loss ($P=0.012$). However, the mean operative time was significantly longer in the TLH group, with a mean of 89.6 (18.4) minutes versus 74.1 (16.7) minutes in the TAH group ($P<0.001$).

Early adverse events, i.e., febrile episodes, urinary retention, wound infections, and transfusion requirements, were more frequently observed among patients in the TAH group. Among these complications, only febrile morbidity reached statistical significance, occurring in 13.5% of TAH cases versus 5.2% of TLH cases ($P=0.014$). Bladder injuries occurred in three patients (2.5%) following TLH and in two patients (1.7%) after TAH, with no significant intergroup difference ($P=0.64$).

Table 1: Baseline demographic and clinical characteristics of women treated with TLH or TAH.

Parameter	TLH (n=107)	TAH (n=179)	*P*-value	Cohen's d
Age (years) [a]	46.3 (4.1) [37 - 58]	47.1 (3.9) [25 - 56]	0.081	-0.201
BMI (kg/m²) [a]	32 (3)	32 (3)	0.558	-0.100
Gravida, median (IQR) [c]	3 (2–4)	3 (2–4)	0.351	—
Parity, median (IQR) [c]	2 (2–3)	2 (2–3)	0.907	—
Living child, median (IQR) [c]	2 (2–3)	2 (2–3)	0.938	—
Smoking	**TLH (n=107)**	**TAH (n=179)**		
No, n (%)	86 (80.4%)	142 (79.3%)	0.832 [b]	—
Yes, n (%)	21 (19.6%)	37 (20.7%)	0.832 [b]	—
Comorbidity	**TLH (n=107)**	**TAH (n=179)**		
None	67 (62.6%)	116 (64.8%)	0.999	—
Hypertension	8 (7.5%)	25 (14%)	0.780	—
Diabetes mellitus	9 (8.4%)	9 (5%)	0.999	—
Other	20 (18.7%)	24 (13.4%)	0.999	—
HT + DM	3 (2.8%)	5 (2.8%)	0.999	—
Medication use	**TLH (n=107)**	**TAH (n=179)**		
No	80 (74.8%)	132 (73.7%)	0.848 [b]	—
Yes	27 (25.2%)	47 (26.3%)	0.848 [b]	—
History of abdominal surgery median (IQR) [c]	0 (0–1)	0 (0–1)	0.829	—
Other surgical history	**TLH (n=107)**	**TAH (n=179)**		
No	85 (79.4%)	153 (85.5%)	0.186 [b]	—
Yes	22 (20.6%)	26 (14.5%)	0.186 [b]	—

BMI: Body Mass Index, HT: Hypertension, DM: Diabetes Mellitus, TLH: Total Laparoscopic Hysterectomy, TAH: Total Abdominal Hysterectomy. a: Values were mean (standard deviation), Student's t-test was used. b: Chi-square test, c: Values were reported as median (1st and 3rd quartile values) and the Mann-Whitney U test was used.

Table 2: Postoperative SF-36 subscale outcomes at different follow-up intervals in TLH and TAH groups.

	Early			Mid-term			Late-term		
Parameter	**TLH (n=36)**	**TAH (n=54)**	***P*-value [a]**	**TLH (n=35)**	**TAH (n=59)**	***P*-value [a]**	**TLH (n=35)**	**TAH (n=66)**	***P*-value [a]**
Physical functioning	83.9 (10.2)	78.5 (9.9)	0.018	81.4 (14.2)	77.7 (16.9)	0.285	83.5 (10.6)	79.8 (16.8)	0.584
Social functioning	86.7 (18.2)	75.9 (9.2)	<0.001	81.2 (23)	60.3 (21.6)	<0.001	84.3 (9.5)	68 (27.1)	0.006
Physical role functioning	82.6 (27.9)	75.5 (36.8)	0.602	73.6 (34.3)	76.3 (36.4)	0.383	76.4 (24.6)	74.2 (35.9)	0.560
Emotional role functioning	50.5 (28)	52 (20)	0.989	49.2 (32.7)	50.4 (27.1)	0.775	49.6 (26.9)	49 (24.8)	0.901
Mental health	78.4 (18.7)	79.3 (12.2)	0.494	75.4 (20.2)	75.3 (22)	0.694	77 (21.2)	76.4 (22.3)	0.901
Energy/Viability	69.9 (18.8)	67.7 (13.2)	0.234	63.9 (19.9)	63.6 (23.7)	0.697	65.6 (20)	63.7 (25)	0.924
Pain	80.5 (27.4)	68.2 (31.1)	0.027	76.1 (24.4)	74.6 (30.7)	0.772	77.4 (26)	75.7 (33.5)	0.690
General health perception	69.3 (21)	65.5 (20.3)	0.386	65.7 (21)	64.1 (25.4)	0.941	68.7 (24.4)	68 (26)	0.983

SF-36: Short Form-36, TLH: Total Laparoscopic Hysterectomy, TAH: Total Abdominal Hysterectomy, a: Student's t-test. Values were shown as mean (standard deviation).

Both surgical groups demonstrated marked improvement in quality of life, as assessed via SF-36, when compared to preoperative baseline scores. Notably, patients in the TLH cohort consistently achieved superior scores across multiple domains of the SF-36, especially within the first three months post-surgery. Table 2 details the distribution of SF-36 subscale scores at early, intermediate, and late follow-up intervals. Within the first three months, TLH patients showed significantly better results in physical functioning, social functioning, and bodily pain. While these advantages continued through the intermediate recovery period (4–12 months), they largely waned by the one-year follow-up, with social functioning being the sole domain retaining a significant intergroup difference.

Comparable patterns emerged in the analysis of urinary distress symptoms. UDI-6 scores improved significantly in both groups, but greater early improvements in urgency and leakage symptoms were noted among TLH patients ($P<0.05$). At the 12-month postoperative follow-up, UDI-6 subdomain scores did not differ significantly between the TLH and TAH cohorts. Summary statistics for UDI-6 outcomes at the 12-month follow-up are presented in Table 3.

Stratified analysis by postoperative period revealed that TLH consistently yielded more favorable quality-of-life metrics during early recovery, as measured by both SF-36 and UDI-6 instruments. In contrast, mid- and long-term differences between TLH and TAH were modest and failed to reach statistical significance.

Table 3: UDI-6 scores at 12-month follow-up in TLH and TAH groups.

Parameter	TLH (n=35)	TAH (n=66)	*P*-value [a]
UDI-6 Urge	1 (1.5)	0.7 (1.3)	0.362
UDI-6 Stress	1.1 (1.6)	0.9 (1.3)	0.943
UDI-6 Obstruction	1 (1.5)	0.8 (1.1)	0.932
Total	16.8 (22.9)	13.5 (17.1)	0.923

UDI-6: Urinary Distress Inventory-6, TLH: Total Laparoscopic Hysterectomy, TAH: Total Abdominal Hysterectomy, a: Student's t-test. Values were presented as mean (standard deviation).

Discussion

This study evaluated postoperative outcomes—including quality of life, surgical features, and complication rates—in perimenopausal women who underwent either total laparoscopic or total abdominal hysterectomy for non-malignant gynecological conditions. One of the main findings was that patients in the TLH group exhibited more noticeable short-term improvements, particularly in physical performance, pain, urinary symptoms, and aspects of daily and social well-being, compared to those who had TAH. Despite these early benefits, the advantages diminished over time, with differences between the two approaches becoming less prominent by the end of the first year. This suggests that the positive impact of TLH is most pronounced during the initial recovery period.

Previous research on pelvic surgery outcomes also supports the benefits of less invasive methods. For instance, studies conducted by Bartels [10] as well as by Ghanbari [11], indicated that laparoscopic hysterectomy may offer improved postoperative quality of life, especially during the early and mid-recovery phases. The improved physical function and reduced pain levels noted in TLH patients may stem from reduced surgical trauma and quicker postoperative mobilization inherent to laparoscopic techniques. Moreover, the lower incidence of postoperative febrile events and shorter hospitalization duration support the safety and operational efficiency of the TLH approach.

Although the short-term QoL improvements were clear, the differences between TLH and TAH largely disappeared within one year, a trend also reported by Nieboer [5]. The short-term benefits observed in urinary distress scores are also consistent with earlier research suggesting that laparoscopy may mitigate postoperative bladder discomfort and functional disturbances.

Nonetheless, the convergence of UDI-6 outcomes over time implies that both procedures ultimately result in similar long-term recovery of urinary function. Similar recovery trends were also evident in the findings of Skorupska [12] and Oplawski [13], both of whom observed parallel gains in urinary and sexual health outcomes after minimally invasive hysterectomy procedures.

Strengths and limitations

One notable strength of the present research lies in its utilization of a time-segmented framework for assessing quality of life outcomes across various postoperative phases. This methodological choice is further supported by the findings of Taheri et al. [14], who validated the clinical robustness of SF-36 and UDI-6 in hysterectomy populations. In contrast to studies limited to a single follow-up point, this design enables a more nuanced understanding of recovery trajectories and patient-reported experiences.

Certain weaknesses inherent to this investigation must also be noted. Given the retrospective design, there is a risk of selection bias and possible data loss from incomplete medical records. Secondly, reliance on patient-reported outcome measures may have introduced recall bias or subjective variation in response accuracy. Thirdly, the lack of random allocation and potential confounding due to institutional practices limit the causal interpretations of observed associations. Lastly, while the sample was sufficiently powered for group comparisons, the absence of a priori power estimation represents a methodological limitation.

Upcoming studies would benefit from adopting a prospective, randomized design incorporating extended follow-up durations and cost-effectiveness assessments. Such studies would provide stronger evidence to confirm these findings and support more informed surgical decision-making.

Conclusion

In summary, TLH demonstrated superior short-term benefits in postoperative quality of life and recovery when compared to TAH in perimenopausal women undergoing benign hysterectomy. Although these improvements tend to taper in the long term, their early impact remains clinically meaningful. Surgical decision-making should be individualized, taking into account patient preferences, surgical expertise, and institutional capabilities. Incorporating a time-segmented assessment of quality of life offers a more holistic view of postoperative recovery and can enhance the interpretation of treatment efficacy.

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J Surg Med. 2025;9(9):162-165.
https://doi.org/10.28982/josam.8115

JOSAM

Review
https://jsurgmed.com/

Journal of Surgery and Medicine

e-ISSN: 2602-2079

Type 2 diabetes mellitus and vitamin metabolism

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Abstract

Type 2 Diabetes Mellitus (T2DM) is a disease characterized by chronic hyperglycemia and oxidative damage, leading to harm in tissues and organs. Studies have shown a relationship between increased oxidative stress, decreased insulin sensitivity, and the effectiveness of antioxidant therapy in managing T2DM. Early diagnosis, lifestyle changes, drug therapy, and vitamin supplements are essential in managing T2DM. Antioxidant vitamins, in particular, are crucial for reducing oxidative stress caused by T2DM and minimizing related complications.

Keywords: type 2 diabetes mellitus, antioxidant vitamins, insulin sensitivity, oxidative stress, glycemic control

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Ethics Committee Approval
Ethical approval was not required for this 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
2025 September 3

How to cite: Sert T, Arslan Ş. Type 2 diabetes mellitus and vitamin metabolism. J Surg Med. 2025;9(9):162-165.

Introduction

According to the World Health Organization (WHO), Diabetes Mellitus (DM) is a chronic metabolic disease characterized by high blood sugar levels, which can lead to significant damage to the heart, blood vessels, kidneys, eyes, and nerves over time. The latest etiological classification by WHO identifies four clinical types of DM: Type 1 Diabetes Mellitus (T1DM), Type 2 Diabetes Mellitus (T2DM), DM due to other causes (e.g., infections, genetic disorders), and Gestational Diabetes Mellitus (GDM) [1].

T2DM results from the body's resistance to insulin or insufficient insulin production, often associated with lifestyle factors such as sedentary behavior, dietary habits, and obesity. Conversely, T1DM occurs due to the immune system's destruction of insulin-producing pancreatic cells [2].

The prevalence of T2DM is rising globally, posing significant health and economic challenges. Early intervention through lifestyle changes and pharmacological strategies can prevent complications. Vitamins with antioxidant properties have become increasingly important in mitigating oxidative damage in T2DM.

Antioxidants have been shown to reduce oxidative stress and prevent complications. A systematic review found that vitamins—especially vitamins C, D, and E—improve plasma oxidative stress markers and positively affect overall metabolic parameters [3].

Additionally, another meta-analysis evaluating the effects of vitamins highlighted their role in improving oxidative stress markers in T2DM. However, further studies are needed to assess their long-term benefits [4].

Prevention and Treatment

Environmental, genetic, and metabolic risk factors contribute to the development of T2DM. A family history of T2DM, obesity, advanced age, and a sedentary lifestyle are significant risk factors for the condition. Insulin resistance increases the likelihood of impaired glucose tolerance and the risk of developing T2DM. Preventing and delaying T2DM requires modifying environmental risk factors, such as increasing physical activity and reducing obesity. Awareness of T2DM risk factors is essential for early diagnosis and treatment, and screening high-risk populations can help reduce both macrovascular and microvascular complications [5].

In addition to lifestyle changes, certain oral antidiabetic drugs have been shown to delay and prevent hyperglycemia. Metformin, the most commonly used oral antidiabetic drug, belongs to the biguanide group. It enhances insulin sensitivity in peripheral tissues, reduces glucose variability, and suppresses hepatic glucose production [6].

Thiazolidinediones (TZDs) are insulin-sensitizing agents that improve pancreatic beta-cell function by increasing glucose uptake and insulin sensitivity in adipose tissues and skeletal muscles. Alpha-glucosidase inhibitors work by inhibiting the alpha-glucosidase enzyme, reducing carbohydrate absorption in the small intestine, and lowering postprandial glucose levels [7].

Diabetes and Vitamins

Vitamin A

Studies have shown a relationship between increased oxidative stress and decreased insulin sensitivity, demonstrating the efficacy of antioxidant therapy in T2DM management. Vitamin A, among all vitamins, has the strongest antioxidant capacity. Beyond its antioxidant properties, vitamin A exhibits pleiotropic effects on cell regulation, endocrine development, and pancreatic functions. Some studies have shown that serum vitamin A concentrations are lower in diabetic patients compared to healthy subjects [8].

Yamada et al. [9] investigated the relationship between serum antioxidant vitamin concentrations and T2DM. The study found that diabetic patients had significantly lower β-carotene and vitamin C concentrations compared to the control group, which were associated with diabetes. Evidence also suggests that daily vitamin A intake improves pancreatic β-cell function and may prevent or delay the progression from prediabetes to T2DM.

Another study by Manolescu et al. [10] reported that retinoic acid (RA) treatment reduced body weight, basal serum glucose, serum retinol, and RBP4 levels, increased insulin sensitivity, and lowered the retinol-to-RBP4 ratio. RA was suggested to be an effective antidiabetic agent for T2DM treatment.

Meerza et al. [11] conducted a study on mice, showing that vitamin A has both antioxidant and antihyperglycemic potential, supporting its use as a dietary supplement for T2DM patients.

Vitamin D

Various studies in different populations have highlighted the association of plasma vitamin D levels with cardiovascular diseases and diabetes. Vitamin D deficiency has been linked to the onset of coronary artery disease and the development of T2DM [12].

One study examined the effects of vitamin D supplementation on metabolic and oxidative stress markers in T2DM patients. Daily oral supplementation over 3–6 months improved HbA1c levels, and higher doses over three months significantly reduced advanced oxidation protein product levels [13]. Other studies reported that vitamin D supplementation improved HbA1c levels in overweight or obese T2DM patients with vitamin D deficiency [14] and that vitamin D3 supplementation improved glycemic control and reduced the dosage requirements of oral antidiabetic drugs [15].

Long-term studies of metformin's effects on vitamin D levels found no impact on serum 25[OH]D after 16 months of treatment [16]. Another study confirmed that vitamin D supplementation significantly reduced glycosylated hemoglobin levels in T2DM patients with vitamin D deficiency [17].

Vitamin E

Vitamin E is a potent antioxidant that reduces oxidative stress and inflammation, which play critical roles in the pathogenesis of diabetic complications. Its two main components, tocotrienols and tocopherols, exhibit anti-glycemic, anti-inflammatory, anticholesterolemic, cardioprotective, and neuroprotective properties. Tocopherols have been shown to have stronger antioxidant capabilities compared to tocotrienols [18].

Pramanik et al. [19] demonstrated that T2DM patients regularly taking riboflavin, niacin, pyridoxal phosphate, thiamine, α-tocopherol, and ascorbic acid along with oral antidiabetic drugs had reduced markers of lipid peroxidation, increased serum levels of intracellular antioxidants, and slower progression of diabetic retinopathy. A study on tocotrienol-rich vitamin E showed improved nerve conduction parameters in T2DM patients, highlighting its potential for addressing diabetic peripheral neuropathy [20].

Vitamin K

Vitamin K-dependent proteins play a significant role in the pathological calcification of bones and the vascular system. Despite optimal treatment, cardiovascular risk remains high in T2DM patients, who are also more prone to fractures and arterial calcifications [21].

Vitamin K1, naturally found in green leafy vegetables, suppresses arterial calcification through the carboxylation of matrix GLA protein. Observational studies have linked vitamin K deficiency with increased arterial calcification burden and cardiovascular events. Three months of combined K1/D vitamin supplementation in T2DM patients prevented the development of new calcified lesions in coronary arteries and the aorta [22]. Another study evaluated the clinical effects of vitamin K4 supplementation in T2DM patients and found improvements in triglyceride levels, insulin resistance, and the dosage of oral antidiabetic drugs [23].

Vitamin C

In vitro and in vivo studies emphasize the beneficial effects of vitamin C on the cellular functions of the immune system. Vitamin C supports neutrophil migration, oxidative bursts, phagocytosis, and microbial killing in infected tissues. In T2DM patients with poor glycemic control, 1,000 mg/day of vitamin C was shown to enhance oxidative bursts and PMN phagocytosis [24]. Another study explored the combined effects of metformin with acetylsalicylic acid and ascorbic acid on cardiovascular risks associated with diabetes, reporting significant improvements in glucose metabolism, lipid profile, and reductions in long-term diabetes complications [25].

Vitamin B12

Diabetic neuropathy (DN) is one of the most common microvascular complications of diabetes and is often underdiagnosed in clinical practice. DN in DM patients is thought to result from metabolic events such as hyperglycemia, accumulation of advanced glycation end products, and oxidative stress. Vitamin B12 levels are frequently low in DM patients receiving metformin therapy.

Supplementing with 1 mg of oral methylcobalamin for 12 months increased plasma B12 levels and improved sudomotor functions, neurophysiological parameters, pain scores, and quality of life in DN patients [26]. In a study examining the relationship between long-term metformin use and vitamin B12 deficiency in patients with T2DM, prolonged use of metformin was biochemically associated with B12 deficiency and anemia. The study emphasized the necessity of periodically monitoring B12 levels in patients receiving metformin therapy [27]. In another study, the relationship between metformin dosage and vitamin B12 deficiency in T2DM patients was investigated. The findings indicated that a 1 mg increase in daily metformin dosage resulted in a slight decrease in vitamin B12 levels, but no association was found between the duration of metformin use and B12 deficiency [28].

Discussion

T2DM represents a complex interplay of genetic, lifestyle, and metabolic factors, leading to chronic oxidative stress and organ damage. The findings highlight the therapeutic value of vitamin supplementation in T2DM management. Antioxidant vitamins not only reduce oxidative damage but also support glycemic control and decrease the incidence of complications. Despite promising results, further randomized controlled trials are needed to determine the optimal doses and long-term effects of vitamin therapies across diverse populations.

Conclusion

This study has reviewed the literature on T2DM and vitamin metabolism, compiling the findings to contribute to the body of knowledge on the subject.

In conclusion, T2DM causes irreversible damage to tissues and organs through oxidative stress, while antidiabetic agents can lead to deficiencies in certain vitamins. Early diagnosis, lifestyle modifications, and medication are crucial for the management and treatment of T2DM, and vitamins play a significant role in managing the condition and preventing complications. Each vitamin contributes through distinct biochemical mechanisms to the prevention of major and minor complications caused or exacerbated by diabetes.

In particular, antioxidant vitamins are emphasized as essential in reducing oxidative stress caused by T2DM and minimizing related complications. Studies have demonstrated that the appropriate use of vitamin supplements can enhance the quality of life for individuals with T2DM and serve as a valuable strategy in slowing disease progression. Research in this area continues to pave the way for the development of new strategies to manage T2DM more effectively.

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J Surg Med. 2025;9(9):166-168.
https://doi.org/10.28982/josam.8084

JOSAM

Journal of Surgery and Medicine

e-ISSN: 2602-2079

Case report
https://jsurgmed.com/

A rare manifestation of Ewing sarcoma: Primary intracranial Ewing sarcoma

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Abstract

Primary intracranial Ewing sarcoma (ES) is an extremely rare condition, frequently presenting as supratentorial and intraparenchymal. This case report presents a 22-year-old male diagnosed with primary intracranial ES exhibiting dura, muscle, and bone invasion. The patient initially presented with swelling in the preauricular region and was operated on with a preliminary diagnosis of meningioma, but pathology confirmed primary intracranial ES. This case highlights the rarity of primary intracranial ES and provides significant contributions to the diagnostic process.

Keywords: Ewing sarcoma, primary intracranial Ewing sarcoma, dura invasion, muscle invasion, bone invasion

Introduction

Ewing sarcoma (ES) is a highly aggressive small round cell tumor that typically originates from bone and soft tissue, predominantly affecting children and adolescents [1]. The most common sites are the pelvis and extremities, with about 30% of cases involving soft tissues [2]. Primary intracranial ES is exceedingly rare, often presenting as supratentorial and intraparenchymal [3,4]. Clinically and radiologically, primary intracranial ES can mimic various other tumor types. This report describes a case initially operated on with a provisional diagnosis of meningioma, but later confirmed as primary intracranial ES through pathology. The purpose of this article is to present this rare case of primary intracranial ES, as reports in the literature are limited.

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Informed Consent
The authors stated that the written consent was obtained from 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
2025 September 14

Case presentation

A 22-year-old male with no known chronic illnesses presented to the otolaryngology clinic with swelling in the preauricular region following blunt head trauma two months prior. The patient was referred to our neurosurgery clinic after a brain computed tomography (CT) scan and magnetic resonance imaging (MRI). The patient's history revealed that the headache started post-trauma and the swelling in the preauricular region appeared a week later. A physical examination showed a firm, immobile swelling of approximately 4x4 cm in the left temporal muscles. The neurological examination was normal.

The brain CT and MRI revealed a parenchymal lesion and vasogenic edema, with mass involvement in the dura, temporal muscle, and bone (Figure 1, 2a, 2b). Considering these findings, meningioma was preliminarily diagnosed, and a Simpson grade 1 surgical excision was planned. The patient underwent gross total excision of the lesion, the invaded dura, bone, and temporal muscle. The dura was repaired with synthetic dura, and the bone defect was covered with a titanium mesh. Postoperative examination was consistent with the preoperative state, with no early or late surgical complications. The patient was discharged after the removal of sutures in the first postoperative week.

Pathology results indicated "surgical specimen CD99 diffuse positive, CD56 focal positive, synaptophysin focal positive; PAX5, CD20, CD45, TTF1, chromogranin negative". Diagnosis was Ewing sarcoma, central nervous system (CNS) Grade 4 [5]. A positron emission tomography (PET) was performed to investigate additional foci, with no other foci detected. The patient was diagnosed with primary central nervous system Ewing sarcoma based on the current pathology results.

The patient received focal radiotherapy from radiation oncology, and chemotherapy planning was done by medical oncology.

Figure 1: Brain CT shows a hyperdense nodular lesion in the left temporal pole with minimal surrounding edema.

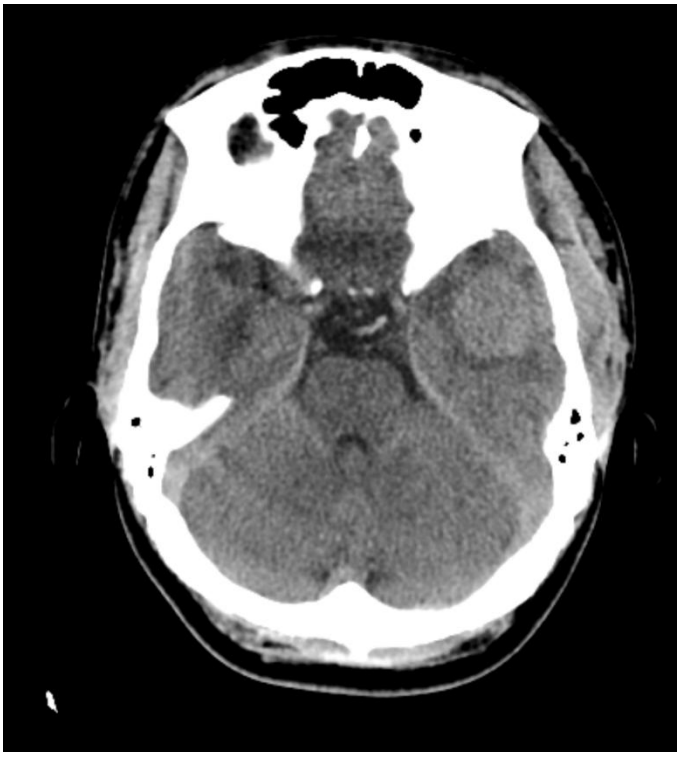


Figure 2a: MRI with contrast shows a parenchymal lesion with homogenous contrast enhancement and vasogenic edema, with mass involvement in the dura, temporal muscle, and bone.

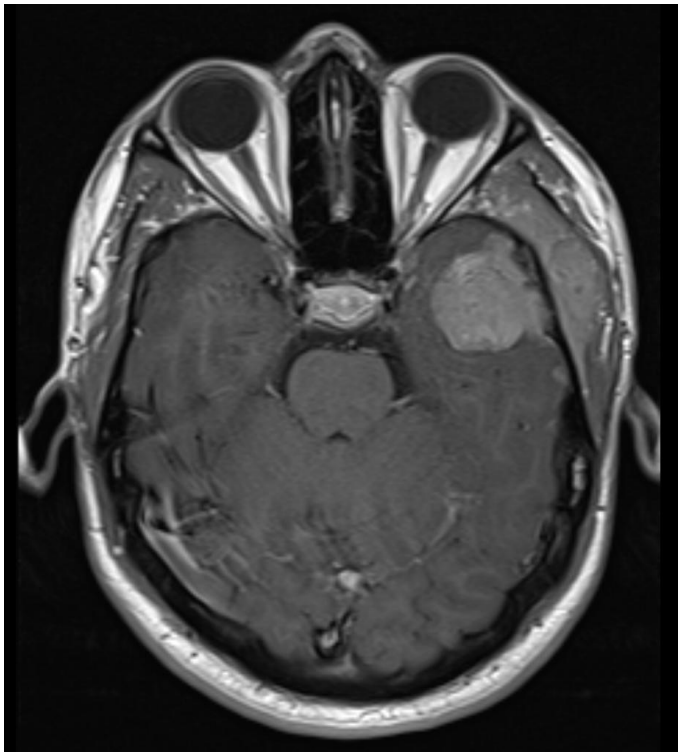
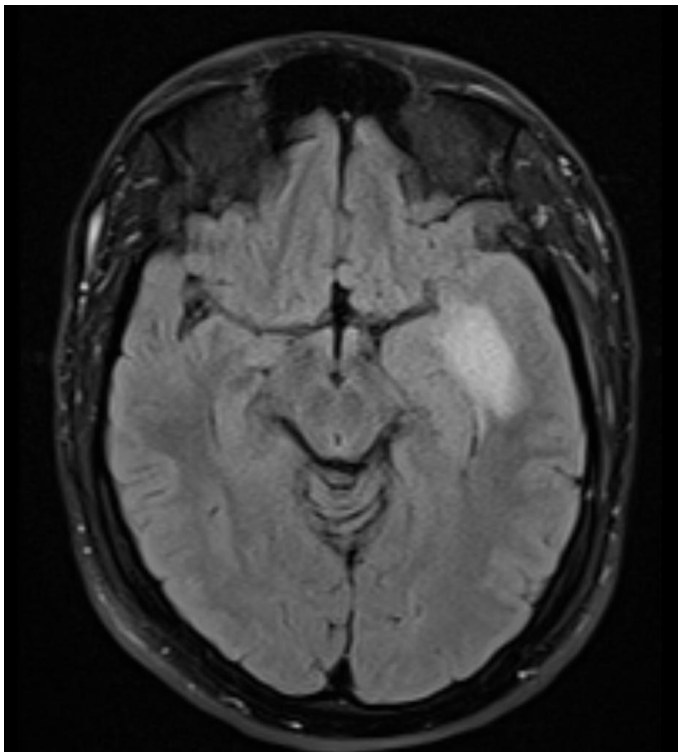


Figure 2b: MRI shows a vasogenic edema, with mass involvement in the dura, temporal muscle, and bone.



Discussion

ES is a malignant bone tumor characterized by round nuclei and primitive small cells [1]. High failure rates (>80%) in patients treated solely with local therapy before the advent of systemic chemotherapy suggest that most patients with ES have micrometastases at diagnosis [3]. Distant organ metastasis mainly occurs hematogenously, commonly affecting the lungs (38%), bones (31%), and bone marrow (11%), with the spine being a frequent site for bone metastasis [3,4,6]. CNS metastases of ES are rare, usually resulting from the growth of the sarcoma into the extradural space and meninges. The incidence of isolated central

nervous system ES ranges from 1.1% to 4.3% [3]. In a study by Paulus et al., only one out of 2500 patients operated on for intracranial mass was reported as ES [7].

Primary intracranial ES, constituting 0.03% of all intracranial tumors, is exceedingly rare [8]. It typically arises in bone or surrounding soft tissues, predominantly in supratentorial locations [9]. While ES mainly affects children and adolescents, it can also be seen in the second decade of life and is more common in males [10]. Our patient, consistent with the literature, was a male in his second decade.

All reported cases of primary intracranial ES in the literature originate from the dura, with the majority (70%) located in the cerebral hemispheres and two cases (20%) in the posterior fossa [11]. Kim et al. [11] reported on a rare case that originated from brain parenchyma in a 50-year-old patient with no known history of ES who presented with headaches unresponsive to analgesics. In our case, the absence of a clear boundary between the dura and tumor surface during surgery and the tumor's adherence to brain parenchyma suggested a parenchymal origin.

The most common clinical features of primary intracranial ES are seizures, headaches, vomiting, and other signs of increased intracranial pressure (ICP) [12]. However, reported cases also include symptoms such as hemiplegia, hearing loss, lethargy, fatigue, and ataxia, with an average symptom duration of 5.9 months [8]. Our patient presented with a headache, and the symptom duration was two months, shorter than reported in the literature. The trauma history and subsequent diagnosis were unique features of our case, although the lack of acute phase radiological imaging post-trauma precluded determining the trauma's role in tumor development.

Radiological findings in reported primary intracranial ES cases typically show mixed iso-hypointense signals on T1-weighted MRI and iso-hyperintense signals on T2-weighted MRI [8]. In Cherif et al.'s [9] study of 48 primary intracranial ES cases, contrast-enhanced MRIs showed heterogeneous enhancement in approximately 40% of cases, dense enhancement in 52.5%, and moderate enhancement in 7.5%. Our findings were consistent, showing iso-hypointense signals on T1-weighted MRI, iso-hyperintense signals on T2-weighted MRI, and dense contrast enhancement on contrast-enhanced MRI.

ES is a highly aggressive tumor with focal necrosis, composed primarily of small, round, or oval undifferentiated cells with hyperchromatic nuclei, increased mitotic activity, and slightly basophilic cytoplasm [8]. Tumor cells are also notably fibrotic, highly mitotic, and separated into cell groups by collagen bands. CD99 expression is a highly reliable and sensitive diagnostic biomarker for primary intracranial ES, detected in nearly all reported cases [9]. However, it is not specific to ES, as it can also be found in other small, blue round cell tumors, such as lymphoblastic lymphomas, ependymomas, and rhabdomyosarcomas [8,9]. In our case, CD99 was diffusely positive, CD56 and synaptophysin were focally positive, and PAX5, CD20, CD45, TTF1, and chromogranin were negative, consistent with other cases in the literature.

Primary intracranial ES is predominantly described as a dura-based tumor [11]. Radiological diagnosis is challenging, as it can be confused with other extra-axial tumors, such as meningiomas, hemangiopericytomas, solitary fibrous tumors, and leiomyomas [6]. Primary intracranial ES often mimics meningioma radiologically, showing dura, bone, and muscle invasion and appearing as a well-defined, homogeneously enhancing solid mass [9]. Similar to other cases, our patient was initially diagnosed with meningioma and underwent Simpson grade 1 surgical excision.

The aggressive behavior of locally situated ES and its early onset reduces survival and necessitates combined therapy. Although there is no standard treatment approach for these malignancies, gross total surgical excision remains the cornerstone of treatment [9,10]. In addition to surgery, chemotherapy and radiotherapy are also treatment options [3]. Standard chemotherapeutic agents include vincristine, etoposide, doxorubicin, and ifosfamide [9,10]. Our patient received focal radiotherapy following gross total surgical excision, and chemotherapy planning was done during follow-up by medical oncology.

Conclusion

This report presents a rare primary intracranial ES case diagnosed post-trauma, highlighting its rarity and potential for misdiagnosis with other tumor types. Primary intracranial ES should be considered in the differential diagnosis of various tumors, particularly in patients in their second decade of life. Intraoperative and histopathological findings are critical for confirming the diagnosis. A PET scan should always follow postoperative pathological diagnosis to assess metastasis.

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J Surg Med. 2025;9(9):169-171.
https://doi.org/10.28982/josam.8126

JOSAM

Journal of Surgery and Medicine

e-ISSN: 2602-2079

Case report
https://jsurgmed.com/

A rare agent of empyema: *Gemella morbillorum*

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Abstract

Gemella morbillorum is a pathogen that rarely causes pleural infections. This case report presents an 80-year-old male patient diagnosed with empyema, in whom *Gemella morbillorum* was identified in the pleural fluid culture. This case highlights the importance of considering rare pathogens in pleural infections and how pleural fluid cultures can aid in accurate diagnosis and treatment.

Keywords: empyema, *Gemella morbillorum*, thoracentesis

Introduction

Gemella morbillorum is a rare pathogen associated with pleural infections such as empyema. While it is typically found in the human flora, including the oral cavity and gastrointestinal tract, it is infrequently isolated and has been linked to infections in immunocompromised patients, such as soft tissue abscesses, meningitis, and endocarditis [1]. This case highlights the clinical importance of considering rare pathogens like *Gemella morbillorum* in pleural infections.

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Informed Consent
The authors stated that the written consent was obtained from 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.

Previous Presentation
This case report was presented as an e-poster on 30 April 2024 at the Turkish Thoracic Society's 27th Annual National Congress in Kyrenia, North Cyprus.

Published
2025 September 10

How to cite: Özpınar SB, Mutlu P. A rare agent of empyema: Gemella morbillorum. J Surg Med. 2025;9(9):169-171.

Case presentation

An 80-year-old male patient with known COPD presented to the emergency department with fever, cough, and sputum for 10 days. Accompanying marked pleuritic chest pain and dyspnea were present. The patient provided informed consent for the case report, in accordance with ethical guidelines. There was no known history of tuberculosis, concomitant disease, or continuously taken medication. Physical examination found a body temperature of 36.8 °C, a pulse rate of 102/min, blood pressure of 124/76 mmHg, and oxygen saturation of 93% in room air. On auscultation, decreased respiratory sounds were heard on the left, and percussion was dull. Systemic examination revealed no additional pathological findings. Laboratory findings included WBC of 20810/mm³ (lymphocyte 9.3%, PNL 81.5%) and a C-reactive protein value of 242 (normal: 0–5).

In the chest radiograph of the patient, homogenous density increase was present in all zones in the left lung (Figure 1). Four days prior, non-contrast thorax computed tomography performed at an external center showed bronchiectatic areas and pneumonic consolidations in the left lower lobe. The left lower lobe bronchus was observed to be totally occluded, with air images and pleural fluid with high density present in the parenchyma in the left lower lobe (Figure 2). Due to the symptoms and laboratory findings, the patient was admitted to the chest diseases service for further examination, with a prediagnosis of empyema.

Levofloxacin 1x750 mg and metronidazole 3x500 mg were started intravenously (IV). Fiberoptic bronchoscopy was performed after obtaining consent from the patient. On bronchoscopy, the left lower lobe bronchial mouth was found to be narrowed all around in the left bronchial system. Mucosa was fragile and diffuse purulent secretions were present. Biopsy and lavage samples were obtained from the left lower lobe bronchus and sent to microbiology and pathology. The biopsy specimen was reported as “Reactive bronchial epithelium, no evidence of malignancy”.

Thoracentesis was performed, and the pleural fluid sample revealed an LDH level of 2505 U/L, glucose of <2 mg/dL, and pH of 6.6. Tube thoracostomy via thoracic surgery was planned, in which 1300 cc pus-like fluid was drained. Pleural fluid samples were sent to microbiology, biochemistry, and pathology. The pathology result was reported as “Benign cytology.” The pleural fluid samples were cultured in aerobic and anaerobic cultures. The mycobacteria culture was negative. Gemella morbillorum was grown in aerobic and anaerobic cultures. The patient was referred to the infectious diseases department, and the culture result was taken to indicate a causative agent. Antibiotherapy was thus changed to ceftriaxone 1x2 gr IV and metronidazole 3x500 mg IV.

During follow-up, yellow crusty lesions were observed, especially in the areas where the nasal cannula was in contact with the patient, and the patient was referred to the dermatology department. HSV infection was considered, and valacyclovir 2x1 g tablets were added to the treatment.

After 21 days of IV antibiotherapy was completed, pleural fluid decreased radiologically, the patient’s general condition improved, and infection parameters decreased. It was arranged for oral antibiotherapy to be taken at home, and the patient was referred to the outpatient clinic. Oral antibiotics for home use were prescribed, and the patient was discharged for outpatient follow-up.

Figure 1: Homogenous density increase in all zones in the left lung

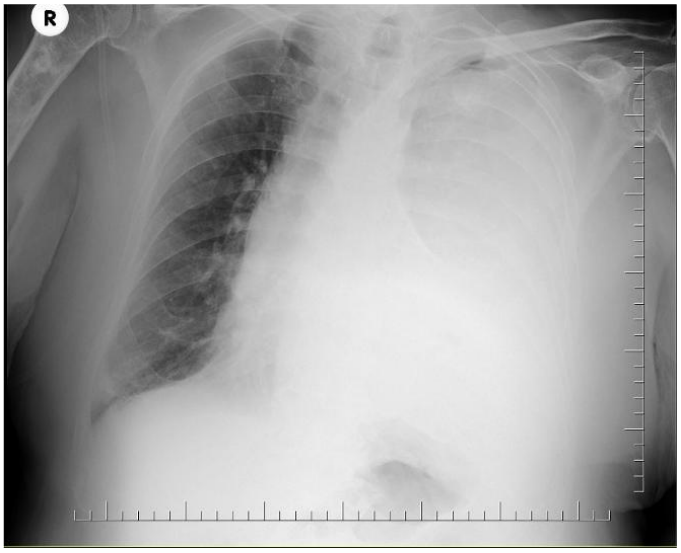
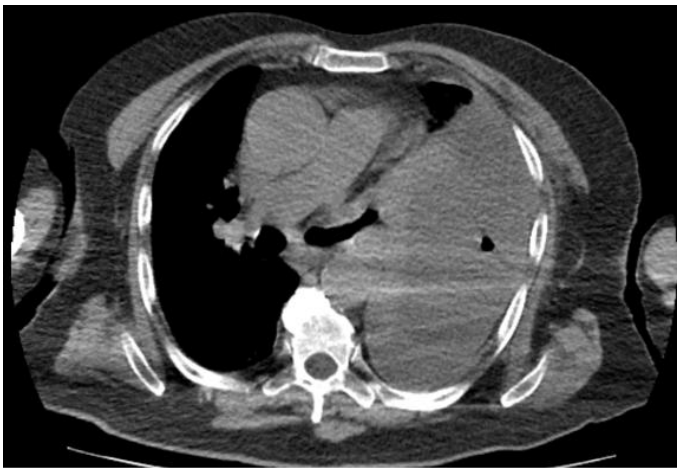


Figure 2: Total occlusion of the left lower lobe bronchus and dense pleural fluid in the left hemithorax on thorax CT



Discussion

Most Gemella infections reported to date include cases of endocarditis [2]. Lung abscess and/or thoracic empyema with Gemella morbillorum are rare. Pulmonary infections associated with Gemella morbillorum are usually associated with conditions that facilitate aspiration, such as laryngectomy. Other cases suggest bacteremia following poor oral care or previous dental surgery [3].

In our case, the patient had no history of dental surgery or laryngectomy but had poor oral hygiene.

Empyema is defined as the collection of pus in the pleural space and occurs as a result of complicated parapneumonic effusions. In patients with empyema, hospitalization is prolonged and mortality is increased [4]. Empyema is more common in the elderly and in men, but it can occur at any age. The risk of empyema increases in the presence of underlying chronic diseases such as COPD, bronchiectasis, malignancy, and diabetes mellitus [5]. In our case, the patient had COPD and bronchiectasis, which may have been contributing factors to the development of empyema.

Conclusion

In conclusion, although Gemella morbillorum is a bacterium found in the oral flora, it can cause serious infections in the presence of predisposing factors. Although rare, it may play a role in the etiology of empyema and lung abscess. It is important to cultivate aerobic and anaerobic cultures and antibiograms of samples taken from pleural fluid. However, the absence of long-term follow-up and further pathogen studies limits the generalizability of these findings.

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