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Research Article

Has acute diverticulitis ceased to be a disease of the elderly?

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ABSTRACT

Objective: This study aimed to determine whether acute diverticulitis can still be regarded solely as a disease of the elderly and to compare colonic localization, disease severity, and inflammatory indices between patients younger than 50 years and patients aged 50 years and older.

Materials and Methods: This retrospective cross-sectional study included 132 patients older than 18 years who were diagnosed with acute diverticulitis confirmed by contrast-enhanced abdominal computed tomography (CT) at Istanbul Haseki Training and Research Hospital between January 2017 and December 2021. Patients were divided into two groups: those younger than 50 years (n=64) and those aged 50 years and older (n=68). Diverticulitis localization was classified as distal (rectosigmoid/sigmoid/descending colon) or proximal (cecum/ascending colon/hepatic flexure). Disease severity was assessed according to the Hinchey classification, and Hinchey stage 1B or higher was defined as complicated diverticulitis. Demographic characteristics, comorbidities, laboratory parameters, and hemogram-derived inflammatory indices including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), lymphocyte-to-monocyte ratio (LMR), and C-reactive protein (CRP)-to-albumin ratio were analyzed. Groups were compared using the Chi-square test, Fisher's exact test, and Mann–Whitney U test.

Results: The overall mean age was 49.8±14.7 years. Male sex predominated among patients younger than 50 years (64.1%), whereas female sex predominated among patients aged 50 years and older (67.6%). Distal colonic involvement was similar in both groups (81.2% vs 82.4%; p=1.0). Overall, 82.6% of patients had Hinchey 1A disease. Although complicated diverticulitis appeared more frequent in younger patients, the difference was not statistically significant (20.3% vs 14.7%; p=0.536). Hypertension, cardiac disease, and previous abdominal surgery were significantly more common in patients aged 50 years and older. CRP levels and NLR showed a tendency to be higher in the older group, whereas the CRP-to-albumin ratio was significantly higher (1.14 [0.44–2.67] vs 1.78 [1.13–3.19]; p=0.045). PLR, SII, LMR, and length of hospital stay were similar between groups. Most patients were managed conservatively, consistent with the predominance of uncomplicated disease in the cohort.

Conclusion: Colonic localization of acute diverticulitis was similar in younger and older patients. Although complicated diverticulitis appeared numerically more frequent in younger patients, systemic inflammatory burden, particularly the CRP-to-albumin ratio, was more pronounced in patients aged 50 years and older. The comparable number of younger and older patients in the same center suggests that acute diverticulitis should no longer be regarded solely as a disease of the elderly. Larger prospective studies are needed to confirm these findings and to further clarify age-related differences in treatment and outcomes.

Keywords: acute diverticulitis, Hinchey classification, inflammatory indices, colonic diverticular disease

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Introduction

Colonic diverticular disease is a common condition that increases in frequency with age, particularly in Western populations, and may lead to substantial lifelong morbidity (1). Diverticula are most commonly located in the sigmoid colon. The pathogenesis is thought to involve age-related weakening of the colonic wall together with factors such as a low-fiber diet, chronic constipation, increased intraluminal pressure, obesity, sedentary lifestyle, smoking, and familial predisposition (2,3). Right-sided colonic diverticula are less common in Western societies; however, they may present at a younger age and are often considered a distinct clinical phenotype in which structural or genetic predisposition may play a more prominent role (4,5).

Acute diverticulitis is an inflammatory condition of diverticula with a clinical spectrum ranging from mild localized inflammation to perforation and generalized peritonitis (6-8). Contrast-enhanced CT is the principal diagnostic tool for assessing disease severity and guiding management, and the Hinchey classification remains one of the most commonly used staging systems. As the Hinchey stage increases, the risk of complications and the need for surgical intervention also increase (9).

In recent years, hemogram-derived inflammatory indices and acute phase reactants have emerged as practical biomarkers in predicting the severity of acute diverticulitis (10,11). NLR, PLR, SII, LMR, and the CRP-to-albumin ratio are easily calculated parameters reflecting systemic inflammatory burden. Several studies have shown that increased NLR, PLR, SII, and CRP-to-albumin ratio may be associated with higher Hinchey stages, complicated disease, and a greater need for intervention (12,13).

Current guidelines, including those of the European Society of Coloproctology and the World Society of Emergency Surgery, recommend classification of acute diverticulitis into uncomplicated and complicated forms based on CT findings, with treatment strategies tailored according to disease stage, including observation, antibiotic therapy, percutaneous drainage, and/or surgery (14,15).

This study was designed to investigate whether acute diverticulitis can still be considered solely a disease of the elderly. The primary aim was to compare colonic localization and disease severity between patients younger than 50 years and patients aged 50 years and older. Secondary aims were to compare comorbidity burden, baseline laboratory findings, inflammatory indices, treatment patterns, and length of hospital stay between age groups.

Materials and Methods

This retrospective cross-sectional study was conducted by reviewing the records of patients presenting to the emergency department or general surgery outpatient clinic of Istanbul Haseki Training and Research Hospital between January 2017 and December 2021 with a diagnosis of acute diverticulitis. Only patients older than 18 years with acute diverticulitis confirmed by contrast-enhanced abdominal CT and staged according to the Hinchey classification were included.

Based on CT reports, disease localization was categorized as distal colon (rectosigmoid, sigmoid, or descending colon) or proximal colon (cecum, ascending colon, or hepatic flexure). Patients with missing clinical or laboratory data and those without imaging-confirmed diagnosis were excluded from the study.

Demographic characteristics, baseline laboratory values, comorbidities, previous abdominal surgery history, and hospitalization records were obtained from the hospital information system. Laboratory parameters included white blood cell count, CRP, albumin, neutrophil count, lymphocyte count, monocyte count, and platelet count. Inflammatory indices were calculated as follows: NLR (neutrophil/lymphocyte), PLR (platelet/lymphocyte), SII

(neutrophil × platelet / lymphocyte), LMR (lymphocyte/monocyte), and CRP-to-albumin ratio.

Patients were divided into two groups according to age: patients younger than 50 years and patients aged 50 years and older. Disease severity was categorized according to the Hinchey classification, and Hinchey stage 1B or higher was considered complicated diverticulitis.

Available treatment-related data were also reviewed. Conservative management, hospitalization, and invasive interventions, when documented, were noted in order to better characterize the clinical course of the disease in both age groups.

Categorical variables were expressed as number and percentage, whereas continuous variables were presented as mean ± standard deviation or median [interquartile range], according to data distribution. Categorical variables were compared using the Chi-square test or Fisher's exact test, and continuous variables were compared using the Mann–Whitney U test. A p value below 0.05 was considered statistically significant. Ethical approval for the study was obtained from the local ethics committee.

Results

A total of 132 patients diagnosed with acute diverticulitis were included in the study (Table 1). Among them, 64 patients were younger than 50 years and 68 were aged 50 years and older. The overall mean age was 49.8±14.7 years. Mean age was 38.7±8.4 years in the younger group and 60.3±8.5 years in the older group.

Sex distribution differed significantly between the two groups. Male patients predominated among those younger than 50 years (41/64, 64.1%), whereas female patients predominated among those aged 50 years and older (46/68, 67.6%).

Comorbidity analysis is summarized in Table 1. Hypertension was significantly more frequent in patients aged 50 years and older (42.6% vs 6.2%, p<0.001). Similarly, cardiac disease, including coronary artery disease, arrhythmia, and heart failure, was significantly more common in the older group (14.7% vs 3.1%, p=0.044). Diabetes mellitus was numerically more frequent in older patients, although the difference did not reach statistical significance (17.6% vs 6.2%, p=0.082). A history of previous abdominal surgery was also significantly more common in the older group (25.0% vs 9.4%, p=0.034).

Evaluation of CT-based disease localization showed that distal colonic involvement was similar in both age groups. Among patients younger than 50 years, 52 cases (81.2%) had distal and 12 cases (18.8%) had proximal disease. Among patients aged 50 years and older, 56 cases (82.4%) had distal and 12 cases (17.6%) had proximal disease (p=1.0).

When disease severity was assessed according to the Hinchey classification, most patients had Hinchey 1A disease (109/132, 82.6%). In patients younger than 50 years, Hinchey stages were distributed as follows: stage 1A in 51 patients (79.7%), stage 1B in 9 patients (14.1%), and stage 2 in 4 patients (6.2%). No patient in this group had stage 3 disease. In patients aged 50 years and older, 58 patients (85.3%) had stage 1A, 4 patients (5.9%) had stage 1B, 2 patients (2.9%) had stage 2, and 4 patients (5.9%) had stage 3 disease. Although complicated diverticulitis was numerically more frequent among younger patients, the difference was not statistically significant (20.3% vs 14.7%, p=0.536).

In laboratory analysis, CRP levels tended to be higher in patients aged 50 years and older (59.7 [19.8–119.3] vs 80.2 [48.1–148.5] mg/L; p=0.056). Albumin levels were significantly lower in older patients (43.0 [40.3–46.0] vs 41.0 [39.0–43.0] g/L; p=0.010). NLR also tended to be higher in the older group (3.84 [2.66–5.17] vs 4.28 [3.29–6.19]; p=0.068). No statistically significant differences were found between the two age groups in terms of PLR, SII, or

Table 1. Comparison of demographic characteristics and systemic inflammatory indices according to age group

Variable	Patients younger than 50 years (n=64)	Patients aged 50 years and older (n=68)	p value
Age, years (mean±SD)	38.7±8.4	60.2±8.5	<0.001
Male sex, n (%)	41 (64.1)	22 (32.4)	<0.001
Diabetes mellitus, n (%)	4 (6.2)	12 (17.6)	0.082
Hypertension, n (%)	4 (6.2)	29 (42.6)	<0.001
Cardiac disease*, n (%)	2 (3.1)	10 (14.7)	0.044
Pulmonary disease**, n (%)	2 (3.1)	5 (7.4)	0.442
Renal failure, n (%)	0 (0.0)	2 (2.9)	0.497
Extra-colonic malignancy, n (%)	0 (0.0)	2 (2.9)	0.497
Previous abdominal surgery, n (%)	6 (9.4)	17 (25.0)	0.034
Distal colonic localization, n (%)	52 (81.2)	56 (82.4)	1.000
Proximal colonic localization, n (%)	12 (18.8)	12 (17.6)	1.000
Hinchey 1A, n (%)	51 (79.7)	58 (85.3)	0.536
Hinchey 1B or higher, n (%)	13 (20.3)	10 (14.7)	0.536
WBC (/μL), median [IQR]	12.96 [11.11–16.01]	12.70 [10.20–14.71]	0.244
CRP (mg/L), median [IQR]	59.65 [19.82–119.25]	80.20 [48.10–148.50]	0.056
Albumin (g/dL), median [IQR]	43.00 [40.25–46.00]	41.00 [39.00–43.00]	0.010
NLR, median [IQR]	3.84 [2.66–5.17]	4.28 [3.29–6.19]	0.068
PLR, median [IQR]	109.60 [90.14–157.04]	127.96 [101.52–171.86]	0.165
SII, median [IQR]	1028.30 [712.44–1518.64]	1100.94 [796.16–1715.06]	0.366
LMR, median [IQR]	2.56 [1.91–3.30]	2.62 [2.03–3.49]	0.682
CRP-to-albumin ratio, median [IQR]	1.14 [0.44–2.67]	1.78 [1.13–3.19]	0.045
Length of hospital stay, days (mean±SD)	4.2±2.1	4.8±3.2	0.158

SD, standard deviation; WBC, white blood cell count; CRP, C-reactive protein; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune-inflammation index; LMR, lymphocyte-to-monocyte ratio; IQR, interquartile range.

* Cardiac diseases included coronary artery disease, arrhythmia, and heart failure.

** Pulmonary diseases included asthma, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, and emphysema.

LMR. However, the CRP-to-albumin ratio was significantly higher in patients aged 50 years and older (1.14 [0.44–2.67] vs 1.78 [1.13–3.19]; p=0.045). Length of hospital stay was similar between the groups, with a mean duration of 4.2±2.1 days in younger patients and 4.8±3.2 days in older patients (p=0.158).

Regarding management, most patients were treated conservatively, which was in line with the high proportion of Hinchey 1A disease in the cohort. A limited number of patients with complicated diverticulitis required more advanced management according to disease severity. Because of the retrospective nature of the study, detailed standardized treatment and short-term complication data were not uniformly available for all patients. Nevertheless, the available records suggested that the majority of patients were managed without emergency surgery.

Discussion

This cross-sectional study compared the clinical characteristics of acute diverticulitis between patients younger than 50 years and patients aged 50 years and older. The main findings were that disease localization was similar between

age groups, the proportion of complicated diverticulitis was numerically higher in younger patients without reaching statistical significance, and systemic inflammatory burden, particularly the CRP-to-albumin ratio, was more pronounced in older patients.

The similar distribution of proximal and distal disease in both age groups suggests that colonic localization may not differ substantially according to age in this cohort. Although previous studies have suggested that right-sided diverticular disease may be more common in younger patients and may reflect a distinct clinicopathological phenotype, our findings did not demonstrate a significant age-related difference in localization (16). At the same time, the presence of comparable numbers of younger and older patients in a single-center contemporary cohort supports the view that acute diverticulitis is no longer confined predominantly to older populations.

Although the rate of complicated diverticulitis was somewhat higher in patients younger than 50 years, this difference was not statistically significant (17). Still, a more detailed view of Hinchey staging suggests a potentially relevant clinical distinction: younger patients more often had stage 1B–2 disease, whereas stage 3 disease was observed only in patients aged 50 years and older. This may indicate that while localized complicated disease can be encountered in younger individuals, older patients may be more vulnerable to advanced inflammatory presentations such as diffuse purulent peritonitis, possibly due to a greater comorbidity burden and altered physiological reserve.

The laboratory findings also support age-related differences in inflammatory response (17). CRP values and NLR were higher in the older group, and the CRP-to-albumin ratio was significantly elevated in these patients. This is clinically meaningful because the CRP-to-albumin ratio integrates both acute inflammation and nutritional or physiological reserve, and it may therefore better reflect the overall systemic burden of disease, especially in older patients. Previous studies have suggested that hemogram-derived inflammatory indices may help identify patients at greater risk of complicated diverticulitis or more severe disease (18). In the present study, however, PLR, SII, and LMR did not differ significantly between age groups (11). This may be explained by the predominance of uncomplicated cases and the relatively limited sample size.

The addition of treatment-related observations further supports the clinical interpretation of the data. Most patients were managed conservatively, which is expected in a cohort in which the majority of cases were classified as Hinchey 1A. More invasive treatment strategies were required only in a limited subgroup of patients with more severe disease. Although detailed treatment pathways and complication profiles were not uniformly available for all patients, the overall pattern suggests that disease stage remained the main determinant of management rather than age alone. Future studies incorporating standardized treatment modalities, intervention rates, postoperative outcomes, and short-term complications may help clarify whether younger and older patients differ not only in inflammatory burden but also in therapeutic needs and clinical course.

This study has several limitations. First, its retrospective design restricted the availability of certain clinical details, including standardized treatment protocols, short-term complications, recurrence, and long-term follow-up outcomes. Second, the study was conducted at a single center, which may limit generalizability. Third, the number of complicated cases was relatively low, which may have reduced the power to detect significant differences in severe disease patterns between age groups. Nevertheless, the study has important strengths, including CT-confirmed diagnosis in all patients, consistent Hinchey staging, and systematic calculation of inflammatory indices.

Overall, the findings suggest that acute diverticulitis should no longer be considered

solely a disease of older individuals. At the same time, age appears to influence the inflammatory profile of the disease, with older patients showing signs of greater systemic inflammatory burden. These findings may have implications for risk stratification and patient monitoring in daily clinical practice.

Conclusion

In this cohort of patients with acute diverticulitis, colonic localization was similar between patients younger than 50 years and those aged 50 years and older. Although complicated diverticulitis was numerically more frequent in younger patients, the difference was not statistically significant. In contrast, the significantly higher CRP-to-albumin ratio in older patients suggests a greater systemic inflammatory burden in this age group. The comparable number of younger and older patients in the same center indicates that acute diverticulitis should no longer be regarded solely as a disease of the elderly. Larger prospective studies are needed to better define age-related differences in disease severity, management strategies, and outcomes.

Ethical approval

The study was approved by the İstanbul Haseki Training and Research Hospital Ethics Committee (date: 23.06.2021, number: 58-2021).

Author contribution

Study conception and design: NA, BCT, AH; Data collection: NA, AH, BCT, SCO; Analysis and interpretation of results: NA, SCO, OHT; Draft manuscript preparation: NA, BCT, OHT. All authors reviewed the results and approved the final version of the article.

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The authors declare that there is no conflict of interest.

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Research Article

Effects of sodium valproate on anxiety and depression in WAG/Rij rats with absence epilepsy

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ABSTRACT

Objective: Anxiety and depression are common comorbidities in patients with epilepsy. Sodium valproate is a long-established antiepileptic drug used for seizure control. The present study aimed to evaluate the effects of sodium valproate on anxiety-related behavior in genetically determined absence epileptic WAG/Rij rats using the open field test.

Materials and Methods: Twenty-eight WAG/Rij rats were randomly divided into four groups (n = 7/group): control, sodium valproate (VPA) 50 mg/kg, VPA 100 mg/kg, and VPA 200 mg/kg. Valproate was administered intraperitoneally once daily for 21 days. The control group received saline (0.5 ml/kg, i.p.). At the end of the treatment period, anxiety-related behavior was assessed using the open field test for 5 minutes under video recording. Horizontal locomotor activity, vertical activity (rearing), and grooming behavior were analyzed.

Results: Compared with the control group, low-dose VPA (50 mg/kg) significantly increased horizontal locomotor activity. Higher doses of VPA did not produce significant changes in locomotion. Grooming behavior increased in the VPA 100 and 200 mg/kg groups, while rearing behavior did not differ between groups.

Conclusion: Chronic VPA at 50 mg/kg increased horizontal activity in the open field, a pattern consistent with an anxiolytic-like profile in this assay. VPA at 100–200 mg/kg increased grooming, indicating a dose-dependent modulation of self-directed behavior; however, because grooming can reflect multiple behavioral states (e.g., stress-coping/displacement, arousal changes, or stereotypy), this finding should not be interpreted as a specific depression-related effect without additional behavioral and ethological analyses.

Keywords: sodium valproate, anxiety-like behavior, depression, absence epilepsy, WAG/Rij rats

Introduction

Epilepsy is a chronic neurological disorder frequently accompanied by psychiatric comorbidities, particularly anxiety and depression (1). Approximately one-third of patients with epilepsy experience clinically significant mood disorders, which are associated with poorer quality of life and reduced treatment response (2). However, standard antiseizure medications often fail to address these psychiatric symptoms (3) adequately.

The Wistar Albino Glaxo/Rijswijk (WAG/Rij) rat is a well-established genetic model of absence epilepsy that also exhibits depression-like behaviors, including reduced exploration and anhedonia (4,5). Suppression of spike–wave discharges has been shown to alleviate these behavioral comorbidities (6).

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Sodium valproate (valproic acid, VPA) is a broad-spectrum antiepileptic drug widely used for generalized epilepsies, including absence seizures, and also functions as a mood stabilizer. Its mechanisms involve enhancing GABAergic neurotransmission and modulating neuronal excitability (7). Preclinical studies demonstrate dose-dependent anxiolytic and antidepressant-like effects of VPA, with higher doses producing sedative actions comparable to benzodiazepines (7,8).

To the best of our knowledge, the effects of sodium valproate on anxiety-like behavior have not been previously investigated in WAG/Rij rats. At the same time, only one study has reported antidepressant-like outcomes following chronic treatment in this model. Accordingly, the present study provides the first integrated assessment of sodium valproate's effects on both anxiety- and depression-related behaviors in the WAG/Rij model of absence epilepsy.

In the present study, we aimed to evaluate the effects of chronic valproate treatment on anxiety- and depression-related behaviors in WAG/Rij rats, a model of absence epilepsy. We hypothesized that valproate treatment would modulate these behaviors in a dose-dependent manner – specifically, that a low dose of VPA might reduce anxiety-like behavior (manifested as increased exploratory activity in the open field). In contrast, higher doses might have sedative effects and potentially lessen depression-like signs (for example, by normalizing grooming or other stress behaviors). By comparing the open field metrics across control and VPA-treated groups, our goal was to determine whether chronic valproate can alleviate the anxiety and depression tendencies associated with genetic absence epilepsy in WAG/Rij rats.

Materials and Methods

Animals and experimental design

In the present study, 6-month-old WAG/Rij rats (250 ± 24) with genetic absence epilepsy were used. All animals were allowed to acclimatize to the laboratory environment for one week before the experiments. During this period, food and water were provided ad libitum. All experimental procedures were performed between 09:00 and 12:00 each day to maintain circadian rhythm consistency. Rats were housed in standard cages under controlled environmental conditions (22–25 °C, 12-h light/12-h dark cycle). Body weights were recorded at the beginning and at the end of the study. All procedures were approved by the Tokat Gaziosmanpasa University Animal Ethics Committee (Approval No: 51879863-15).

Experimental groups

Animals were randomly assigned to four groups as follows:

WAG/Rij Control group: saline (0.5 ml/kg, i.p.)

WAG/Rij + Sodium valproate: 50 mg/kg, i.p.

WAG/Rij + Sodium valproate: 100 mg/kg, i.p.

WAG/Rij + Sodium valproate: 200 mg/kg, i.p.

Drug

The VPA dose range (50, 100, and 200 mg/kg, i.p.) was selected to span low-to-high doses that have been evaluated in genetic absence epilepsy models and that cover reported anti-absence efficacy ranges in WAG/Rij rats. In a dose–response study in WAG/Rij rats, VPA doses up to 280 mg/kg (i.p.) were examined, and the ED50 for reducing spike–wave discharges was approximately 121 mg/kg. Therefore, 50 mg/kg was chosen as a low dose below the reported ED50, 100 mg/kg as an intermediate dose near the ED50, and 200 mg/kg as a higher dose within the effective range used in rodent studies.

Surgical procedure

All WAG/Rij rats with spontaneous absence epilepsy were subjected to electrocorticographic (ECoG) evaluation. Animals were fasted for 24 hours before surgery. Anesthesia was induced using ketamine (90 mg/kg) and xylazine (10 mg/kg). Following adequate anesthesia, the scalp was incised longitudinally (~3 cm), and the periosteum covering the skull was carefully removed. The bregma was identified as the reference point (Figure 1).

Using a microdrill with a 1-mm drill bit, three small burr holes were created in the skull. Tripolar electrodes were then implanted epidurally to allow ECoG recordings from the right frontal cortex, right occipital cortex, and left occipital cortex. Electrodes were positioned to contact the dura mater gently. Postoperative analgesia was provided by xylazine (10 mg/kg), administered immediately after surgery and subsequently at 8-hour intervals.

ECoG recording

Animals were allowed to recover for one week. Following recovery, a 3-hour baseline ECoG recording was obtained from each experimental group (Figure 1). After completion of baseline recordings, dexketoprofen or saline was administered to the respective groups, and ECoG activity was continuously recorded for an additional 3 hours. All recordings were performed using the MP150 Biopac System.

Electrocorticographic data were analyzed to determine the total number of spike-and-wave discharges (SWDs), SWD duration, number of spikes per burst, and mean amplitude values. Upon completion of ECoG recordings, animals underwent the open field test (Figure 1).

Open field test

The open field test was used to evaluate the baseline emotional state of the animals and to detect behavioral changes following experimental interventions. This test is widely employed to assess anxiety-related behavior, locomotor activity, and sedation.

All experimental groups received either saline (0.5 ml) or sodium valproate at the designated doses for 21 consecutive days. On day 21, rats were subjected to the open field test for a duration of 5 minutes. The open field test was conducted in a square arena (100 × 100 cm) divided into 64 equal squares. The arena walls were 25 cm high and constructed of white opaque material. Testing was performed in a quiet experimental room under constant

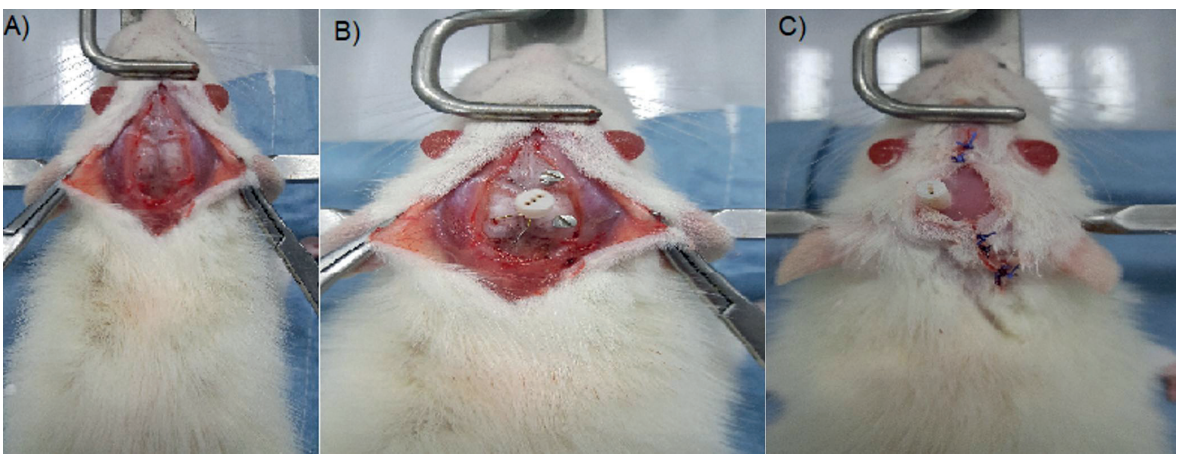

Figure 1. Surgical implantation of tripolar electrodes in anesthetized WAG/Rij rats.

(A) Exposure of the skull following scalp incision and creation of burr holes using a microdrill.

(B) Placement of the tripolar electrode onto the skull with contact to the dura mater.

(C) Fixation of the electrode to the skull using dental acrylic, followed by closure of the surgical incision with sutures.

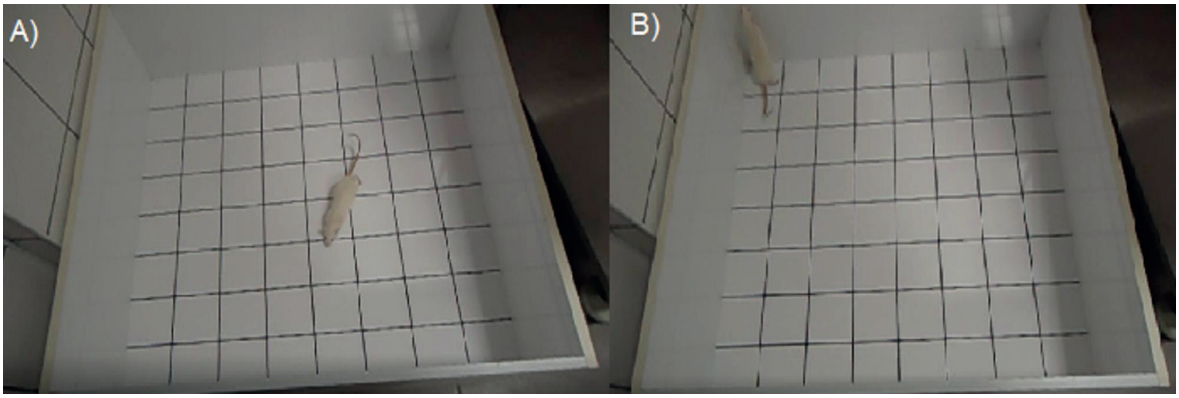

Figure 2. Open Field test.
A) Rat movements in the horizontal plane (transition from one square to another)
B) Rat movements in the vertical plane (rearing on the hind limbs)

illumination (150 lux measured at floor level in the center of the arena) and minimal external noise. Each rat was placed in the center of the arena and recorded for 5 min. After each trial, the arena was cleaned with 70% ethanol and allowed to dry to minimize olfactory cues (Figure 2).

Each animal was individually placed in the center of the arena, and behavior was recorded using a video camera for 5 minutes. During the test period, horizontal locomotor activity (number of squares crossed), vertical activity (rearing behavior), and grooming behavior were recorded and analyzed. Following data acquisition, the results were subjected to appropriate statistical analysis. Each rat was placed in the center of the arena and recorded for 5 min. After each trial, the arena was cleaned with [e.g., 70% ethanol] and allowed to dry to minimize olfactory cues.

Statistical analyses

Data are presented as mean ± SEM. Group differences were evaluated using one-way ANOVA, followed by Tukey's post hoc test for multiple comparisons. Exact p-values are reported for omnibus and post hoc tests where applicable. Effect sizes were reported as [η^2 or partial η^2] for ANOVA and Cohen's d for key pairwise comparisons. Statistical significance was set at $p < 0.05$. Analyses were performed using GraphPad Prism (version 7.0).

Results

ECOG recording

A dose-dependent decrease in both the number and duration of spike-and-wave discharges (SWDs) was observed (Figure 3).

Open field test

All behavioral data were analyzed using one-way ANOVA followed by Tukey's multiple comparisons test, with each group consisting of n = 7 animals.

Horizontal locomotor activity (number of squares crossed)

A one-way ANOVA revealed a statistically significant difference among groups ($F(3,24) = 11.99$, $p < 0.0001$, $R^2 = 0.5999$), indicating a strong treatment effect. Post hoc Tukey analysis showed that the VPA 50 mg/kg group exhibited a significant increase compared with the control group (mean difference = 27.86, 95% CI: 11.28–44.43, adjusted $p = 0.0006$), whereas no significant differences were observed between control and VPA 100 mg/kg ($p = 0.6966$) or VPA 200 mg/kg ($p = 0.7648$). Furthermore, locomotor activity in the VPA 50 mg/kg group

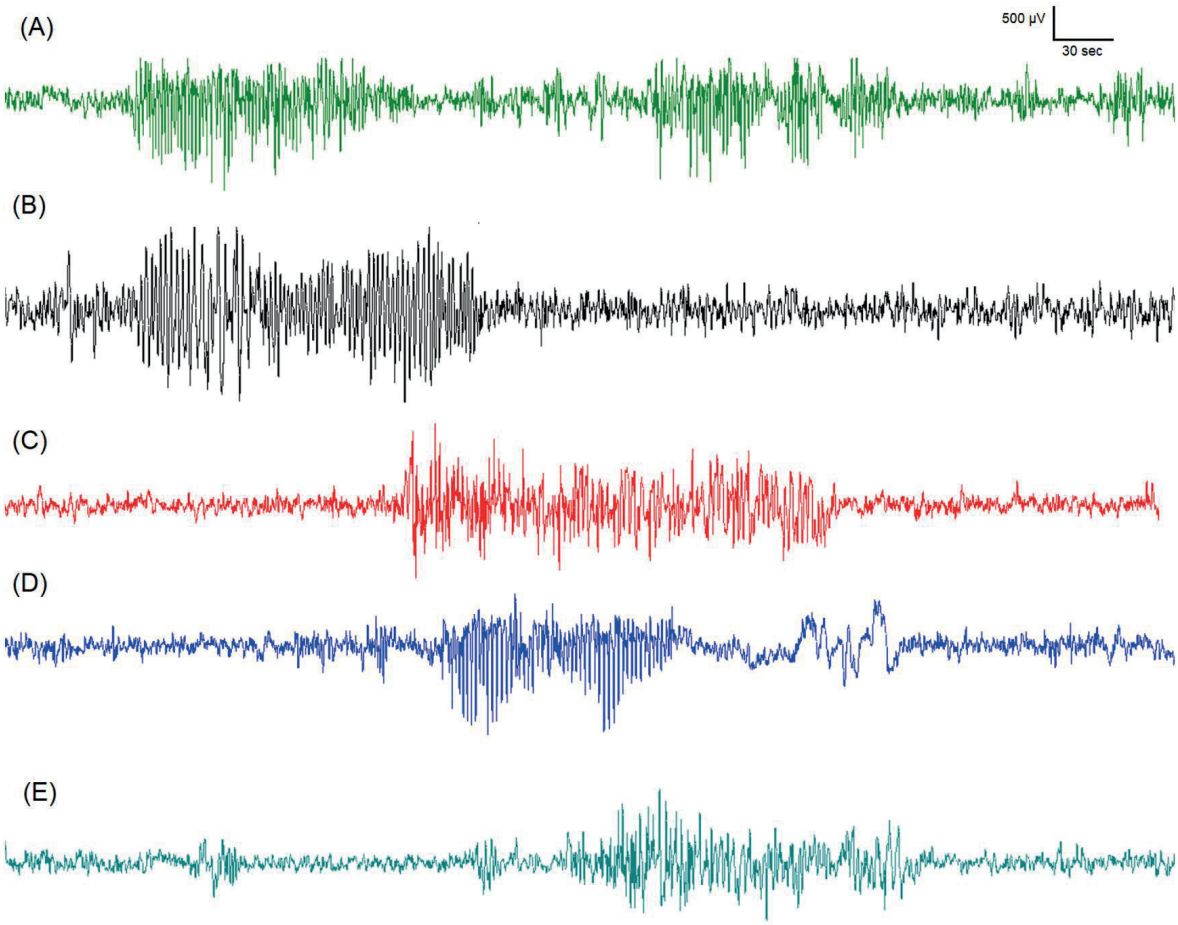

Figure 3. (A) Control group demonstrating baseline EEG activity. (B) VPA 50 mg/kg group showing increased frequency and amplitude of spike-and-wave discharges. (C) VPA 100 mg/kg group exhibiting moderate epileptiform activity. (D) VPA 200 mg/kg group showing reduced and more irregular discharges compared with lower doses. (E) [if applicable: treatment/other group] displaying attenuated epileptiform activity. Scale bars: 500 µV (vertical) and 30 s (horizontal).

was significantly higher than in both the VPA 100 mg/kg (mean difference = 21.29, p = 0.0084) and VPA 200 mg/kg groups (mean difference = 33.71, p < 0.0001), while no difference was detected between the VPA 100 mg/kg and VPA 200 mg/kg groups (p = 0.1920). The effect size was large ($\eta^2 \approx 0.60$) (Figure 4).

Grooming behavior

One-way ANOVA demonstrated a significant overall group effect ($F(3,24) = 18.45$, $p < 0.0001$, $R^2 = 0.6976$), indicating a very strong treatment effect. Post hoc analysis revealed that grooming activity was significantly increased in the VPA 100 mg/kg group (mean difference = -6.38, 95% CI: -11.18 to -1.58, p = 0.0062) and the VPA 200 mg/kg group (mean difference = -8.64, 95% CI: -13.44 to -3.84, p = 0.0002) compared with the control group, whereas no significant difference was observed between the control and VPA 50 mg/kg groups (p = 0.4501). In dose-dependent comparisons, grooming activity in the VPA 50 mg/kg group was significantly lower than that in both the VPA 100 mg/kg (p = 0.0001) and VPA 200 mg/kg groups (p < 0.0001), while no significant difference was found between the VPA 100 mg/kg and VPA 200 mg/kg groups (p = 0.5718). The effect size was very large ($\eta^2 \approx 0.70$) (Figure 5).

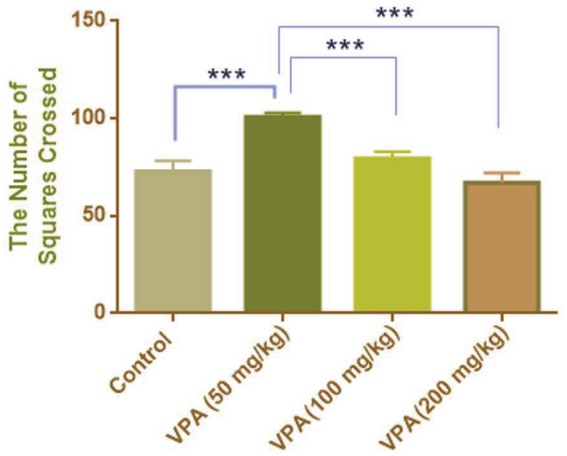

Figure 4. Horizontal locomotor activity of all experimental groups in the open field test. Horizontal movement was significantly increased in the low-dose sodium valproate group (VPA, 50 mg/kg) compared with the control group ($p < 0.05$). No significant differences were observed in the VPA 100 mg/kg or VPA 200 mg/kg groups relative to controls ($p > 0.05$). In addition, horizontal locomotor activity in the VPA 50 mg/kg group was significantly higher than that in the VPA 100 mg/kg and VPA 200 mg/kg groups ($p < 0.05$).

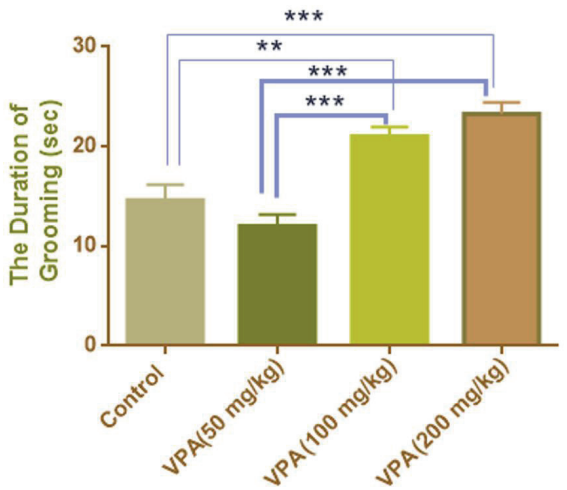

Figure 5. Grooming activity duration of all experimental groups in the open field test. Grooming behavior was significantly increased in the VPA 100 mg/kg and VPA 200 mg/kg groups compared with the control group ($p < 0.05$). No significant difference in grooming activity was observed in the low-dose sodium valproate group (VPA, 50 mg/kg) relative to controls ($p > 0.05$). In addition, grooming activity in the VPA 50 mg/kg group was significantly lower than that observed in the VPA 100 mg/kg and VPA 200 mg/kg groups ($p < 0.05$).

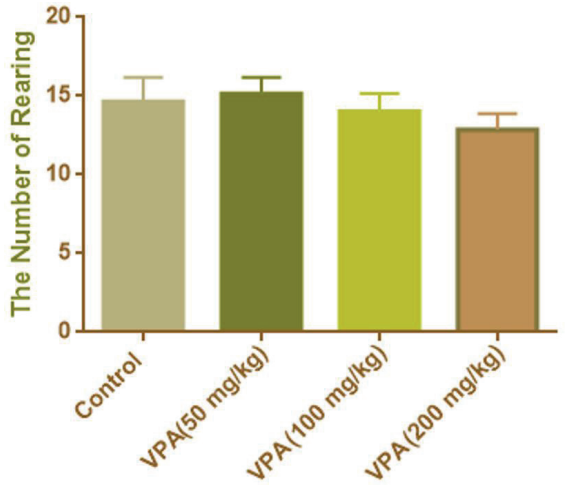

Figure 6. Vertical locomotor activity (rearing behavior) in the open field test. The number of rearing events did not differ significantly among the experimental groups or when compared with the control group ($p > 0.05$).

Vertical locomotor activity (rearing)

No statistically significant differences were observed among the groups. One-way ANOVA indicated no group effect ($F(3,24) = 0.65$, $p = 0.5907$, $R^2 = 0.075$), and all pairwise comparisons were non-significant (all adjusted $p > 0.55$). The corresponding effect size was small ($\eta^2 \approx 0.075$), suggesting a negligible treatment effect on vertical locomotor activity (Figure 6).

Discussion

To the best of our knowledge, this is the first study to investigate the effects of sodium valproate on both anxiety- and depression-like behaviors in the WAG/Rij model of absence epilepsy. Numerous in vivo and in vitro studies have been conducted to elucidate the molecular mechanisms underlying seizure activity in experimental epilepsy models using various pharmacological agents (9-11). Absence epilepsy represents a typical form of idiopathic generalized epilepsy and is most commonly observed during childhood. It is characterized by sudden, brief episodes of impaired consciousness, accompanied by bilateral,

synchronous, and symmetrical spike-and-wave discharges on electroencephalography (EEG), typically at 2.5–3.5 Hz and with amplitudes of 100–1200 μV.

In the present study, WAG/Rij rats were selected as a model of absence epilepsy. This strain was developed through inbred breeding of Wistar albino rats that spontaneously exhibit spike-and-wave discharge (SWD) activity. As a genetic animal model of absence epilepsy, WAG/Rij rats display clinical, pharmacological, and electrophysiological features that closely resemble those observed in human absence epilepsy (12). In addition to epileptic activity, the WAG/Rij model is characterized by depression-like comorbidities associated with absence epileptogenesis. In patients with epilepsy, anxiety and depression occur more frequently than in the general population. Therefore, the WAG/Rij rat model provides a suitable experimental platform for investigating anxiety- and depression-related behaviors accompanying absence seizures.

Previous studies have demonstrated that pharmacological suppression of absence seizures reduces both anxiety- and depression-like behaviors in epileptic rats (6). One of the limited studies investigating the effects of sodium valproate in the WAG/Rij model reported that chronic valproate treatment suppressed the development of absence seizures and significantly attenuated accompanying depression-like behaviors (13). In contrast, other genetic absence epilepsy models, such as GAERS, exhibit pronounced anxiety and anhedonia even before seizure onset, indicating apparent model-specific behavioral differences (14). In a GAERS-based study, sodium valproate was shown to exert sedative effects without exacerbating anxiety-like behavior (15). Findings from acquired epilepsy models are more heterogeneous; in the PTZ-kindling model, valproate effectively suppressed seizures but failed to reverse depression-like behavior when administered alone (16). Similarly, in the hippocampal kindling model, low-dose valproate combined with low-frequency electrical stimulation significantly reduced both anxiety- and depression-like behaviors (17).

The open field test is widely used to assess anxiety-like behaviors in rodents. In the present study, locomotor activity (horizontal movement; number of squares crossed), exploratory behavior (vertical activity; rearing), and grooming responses were evaluated in rats treated with sodium valproate (VPA). A reduction in locomotor activity is generally interpreted as an increase in anxiety-like behavior (18,19). Decreased exploratory behavior may reflect impaired novelty-seeking motivation, reduced interest in new environments, and features associated with anxiety and depressive disorders. Similarly, reduced grooming responses are considered to mimic social withdrawal, loss of interest, and anhedonia, which are core features of depression (20-24).

Self-grooming is an ethologically organized, self-directed behavior that can reflect multiple neurobehavioral states rather than a single affective construct. Depending on context, grooming may increase after novelty or mild stress as a displacement/coping response and may also present as repetitive or stereotyped behavior in some pharmacological or neuropsychiatric models (25-27). Moreover, stress-related grooming has been proposed to contribute to post-stress de-arousal and behavioral homeostasis (28). Accordingly, the increased grooming observed after VPA 100–200 mg/kg in the open field should be interpreted cautiously and may reflect altered stress responsivity, arousal, or repetitive behavioral expression rather than a specific depression-like phenotype. Because we quantified total grooming duration only (without microstructural pattern analysis such as bout number, bout duration, or grooming sequence structure), we cannot distinguish between displacement grooming and other grooming phenotypes. Future studies should incorporate ethological grooming microstructure and additional assays of depression- and anxiety-

related behavior to better triangulate affective state.

Valproate's anti-absence efficacy in WAG/Rij rats has been characterized previously in dose–response designs, with doses up to ~280 mg/kg (i.p.) and an estimated ED50 around 121 mg/kg for reducing spike–wave discharges (29). Functional tolerance to valproate's anti-absence effects at high exposure levels has also been reported in this model (30). More recently, chronic paradigms including valproate have been used to examine comorbidity-relevant outcomes and disease modification in WAG/Rij rats (13), and long-term oral VPA regimens (e.g., 300 mg/kg) have been implemented in WAG/Rij studies targeting epilepsy-related comorbid phenotypes (31). Our findings extend this literature by describing dose-dependent open-field behavioral changes after a 21-day VPA regimen.

Limitation

Relating rodent mg/kg dosing to human therapeutic exposure is inherently limited by species differences in absorption, distribution, metabolism, and sampling time relative to dosing. In clinical practice, typical total valproate therapeutic plasma concentrations are approximately 50–100 μg/mL for epilepsy (32). In rodents, higher peak plasma concentrations can occur shortly after i.p. dosing; for example, 200 mg/kg (i.p.) produced mean plasma levels of ~376 μg/mL at 30 min in a rat kindling study (33), while chronic dosing studies demonstrate pronounced peak–trough fluctuations over time (34). Plasma valproate levels were not measured in the present study, which limits direct comparison to therapeutic ranges; future work should include pharmacokinetic confirmation to strengthen translational interpretation.

Considering the behavioral outcomes observed in genetically absence epileptic WAG/Rij rats, our findings suggest that low-dose VPA reduces anxiety-like behaviors by enhancing locomotor activity, whereas higher doses may preferentially attenuate depression-like behaviors, as reflected by alterations in grooming activity.

Ethical approval

All procedures were approved by the Tokat Gaziosmanpasa University Animal Ethics Committee (Approval No: 51879863-15).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: HA; data collection: HA, OS; analysis and interpretation of results: HA, OS; draft manuscript preparation: HA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Research Article

Predictors of the major and minor ileostomy complications following ileostomy closure in rectal cancer patients: a retrospective cohort study

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ABSTRACT

Aim: This study aimed to investigate the predictors associated with the ileostomy related complications after ileostomy closure among the patients with rectal cancer who underwent temporary diverting ileostomy following total mesorectal excision.

Method: A retrospective study included 151 patients who underwent total mesorectal excision for rectal cancer with ileostomy closure following temporary diverting ileostomy. Patients' demographic characteristics, clinical and laboratory findings, and the major and minor ileostomy complications were evaluated by univariate and multivariate analysis.

Results: The mean age was 61.13 ± 13.33 years old. The population of data included 95 (62.9%) male patients. Adenocarcinoma was diagnosed in 149 (98.7%) patients. The duration of ileostomy was 197.3 ± 136.3 days. The patients who received neoadjuvant therapy were 52.3%. The patients with major ileostomy surgical site complications were more likely to have colorectal anastomosis leakage and intraabdominal pelvic abscess (17.72% vs 0% and 25.32% vs 0%, respectively; $p < 0.001$) whereas patients with minor complications were more likely to have colorectal anastomosis stenosis and intraabdominal pelvic abscess (18.67% vs 5.26% and 20.0% vs 6.58%, respectively; $p < 0.05$). Deep incisional, organ space and superficial SSIs were significantly higher in patients with both major and minor ileostomy complications ($p<0.001$) comparing to those who had no complications. Higher duration of ileostomy significantly increased the risks of major (OR 1.015, 95% CI, 1.007-1.022, $p<0.001$) and minor complications (OR 1.006, 95% CI 1.002-1.011, $p=0.008$).

Conclusion: Ileostomy duration was analyzed as a continuous variable and demonstrated a significant association with SSI risk. While prior literature suggests a 3-month threshold, our data support a progressive increase in risk with longer duration, rather than a strict cutoff.

Keywords: ileostomy, colorectal surgery, surgical site infection

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Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed form of cancer globally, with an increasing incidence in developing countries (1,2). Comprising 11% of all cancer diagnoses, CRC is the second most deadly cancer worldwide (1). Surgery remains the principal way of treatment in cases of early diagnosis, however, surgery may no longer effective in the patients diagnosed with advanced and metastasized CRCs (3,4). In these patients, the effectiveness of neoadjuvant and adjuvant therapies has been applied regarding cancer recurrence, resulting in differences in disease-free survival and overall survival rates in patients with rectal tumors (5,6). Temporary diverting ileostomy is performed frequently in the treatment of numerous CRC cases, including rectal cancer. Patients who underwent temporary diverting ileostomy after total mesorectal excision for rectal cancer have shown reduced rates of morbidity and re-operation secondary to anastomotic leak than the patients without loop ileostomy (7-9). However, the main disadvantage of diverting ileostomy is that it implies some complications such as surgical site infection (SSI), ileostomy site infection, and anastomotic leak (10). The most known complication following an ileostomy closure is SSI, with a reported incidence between 2%–34% (11). Hence, SSI poses a considerable problem in the rectal cancer patients and a significant load to the health care system (10,11).

The overall predictors of post-closure complications for temporary loop ileostomies are likely underreported and poorly characterized among the rectal cancer cases. Improving our understanding of the SSI during the diverting ileostomy, as well as estimating the predictors for ileostomy-related SSI following the surgery may help us to identify the methods to reduce these complications before its closure (7,12). Therefore, this study aimed to investigate the predictors associated with the ileostomy-related SSI after closure among the patients with rectal cancer who underwent temporary diverting ileostomy following total mesorectal excision. Despite its clinical relevance, predictors of SSI following ileostomy closure remain insufficiently defined. This study aims to evaluate risk factors associated with SSI after ileostomy closure and to clarify the impact of ileostomy duration on postoperative outcomes.

Materials and Methods

The study protocol was approved by the Clinical Research Ethics Committee of Bagcilar Training and Research Hospital of Health Science University (date: 12.06.2020, number: 2020.06.1.10.081). All procedures performed in this study involving human participants were following the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Study population

The medical records of 151 patients who applied to Bagcilar Training and Research Hospital of Health Science University between February 2013 and January 2019 were evaluated retrospectively. The rectal cancer patients who were treated with or without neoadjuvant therapy, the clinical examination, radiological imaging, and histopathological findings were included and analyzed in the study. Patients older than 18 years of age, who underwent elective ileostomy closure following total mesorectal excision for a primary diagnosis of rectal cancer with a temporary diverting ileostomy were included. Patients younger than 18 years and those who underwent emergency colorectal excision or elective total mesorectal excision without diverting ileostomy or colon resection with or without a diagnosis of Inflammatory bowel diseases, diverticulitis or benign and malign colon diseases and patients without the procedure of ileostomy closure were excluded from the study.

All patients received perioperative antibiotic prophylaxis according to institutional protocols. This consisted of a second-generation cephalosporin (e.g., cefuroxime

1.5 g intravenously) administered within 30–60 minutes prior to skin incision. In cases with anaerobic risk, metronidazole (500 mg intravenously) was added. No routine postoperative antibiotic continuation was applied unless clinically indicated.

Ileostomy closure was performed using standard surgical techniques, including either hand-sewn or stapled anastomosis, based on surgeon preference and intraoperative findings. Although general surgical principles were consistent across cases, the specific technique was not fully standardized and depended on the operating surgeon.

Surgical site infection (SSI) surveillance was conducted in accordance with Centers for Disease Control and Prevention (CDC) criteria. Patients were followed for a minimum of 30 days postoperatively. SSI assessment was performed through a combination of inpatient monitoring and outpatient follow-up visits.

SSI diagnosis was determined by the treating surgical team based on clinical evaluation, supported by medical record documentation. No independent blinded adjudication was performed.

Variables and outcomes

Demographic, perioperative clinical findings, and laboratory parameters were recorded retrospectively. These included age, sex, comorbidities (hypertension, diabetes mellitus, coronary artery disease), neoadjuvant/adjuvant therapy, ASA score, surgical approach, and tumor characteristics. Complications related to the initial colorectal surgery, including anastomotic leakage, stenosis, and intraabdominal abscess, were defined as events occurring after total mesorectal excision and prior to ileostomy closure. These variables were considered pre-existing clinical factors and were analyzed as potential risk factors for post-closure complications, rather than as outcomes of ileostomy closure.

The primary outcome was the occurrence of surgical site infection (SSI) following ileostomy closure, defined according to the Centers for Disease Control and Prevention (CDC) classification as:

- Superficial incisional SSI
- Deep incisional SSI
- Organ/space SSI

To facilitate clinical interpretation, complications were further categorized into:

- Major complications: conditions requiring invasive intervention, prolonged hospitalization, or associated with significant morbidity (e.g., deep incisional SSI, organ/space SSI, anastomotic leakage, intraabdominal abscess, bowel obstruction, acute renal failure).
- Minor complications: self-limiting or conservatively managed conditions (e.g., superficial SSI, skin irritation, electrolyte imbalance, minor wound infection).

This classification was based on clinical severity and management requirements, rather than infection type alone, to better reflect real-world surgical decision-making.

Importantly, SSI subtypes (superficial, deep, organ-space) were considered components of the outcome definition and were not treated as independent predictors in multivariate models.

Statistical analysis

Statistical analyses were performed using SPSS (version 19.0). Continuous variables were expressed as mean ± standard deviation, and categorical variables as frequencies and percentages.

Univariate analyses were conducted using Chi-square, Fisher's exact test, Student's t-test, or Mann–Whitney U test, as appropriate.

To identify independent predictors of SSI, multivariate logistic regression models were constructed separately for:

- Major complications
- Minor complications

Variables with $p < 0.10$ in univariate analysis and clinically relevant factors (e.g., age, comorbidities, ileostomy duration, neoadjuvant therapy) were included in the multivariate model to control for confounding.

Variables representing components of the outcome (e.g., SSI subtypes) were excluded from regression models to avoid collinearity and misinterpretation. To avoid overlap between predictors and outcomes, variables such as deep incisional SSI and organ-space SSI were not included as independent predictors in multivariate analysis, as they are components of the SSI outcome.

Statistical significance was set at $p < 0.05$. No formal model validation (e.g., ROC curve, calibration) was performed; therefore, findings should be interpreted as exploratory rather than a validated prediction model.

Results

The patients who were diagnosed with rectal cancer (151), 56 (37.1%) were female and 95 (62.9%) were male. The major ileostomy-related surgical site complications were showed in 57.1% of female patients and 49.5% of male patients, while 42.9% of female and 53.7% of male patients showed minor complications without any significant difference (Table 1-4). The mean age of all patients was 61.13 ± 13.33 years old, the patients with major ileostomy-related surgical site complications were 63.32 ± 12.6 and with minor complications was 61.45 ± 13.1. (Figure 1 and Figure 2) The duration of ileostomy was 197.3 ± 136.3 days. The duration of ileostomy closure with major complications was 272.1 ± 135.5 days and with minor complications was 260.55 ± 142.3 days.

Regarding the demographic characteristics of patients, older patients, patients with CAD or HT, the patients with radiological stage III rectum cancer and T3 or N0 stage, and patients having neoadjuvant or adjuvant therapy were more likely to have major ileostomy surgical site complications ($p < 0.05$). It was also determined that the mean age, the distribution of sex, number of patients with DM or HT, ASA scores, any of laboratory findings, histological type of tumor, and M stage did not differ among the patients according to the presence of minor complications (Table 1). However, the patients with CAD, the patients with radiological stage III rectum cancer and T3 or N0 stage, and patients having neoadjuvant or adjuvant therapy were more likely to have minor complications ($p < 0.05$).

Clinical findings of the patients showed that both hospitalization and ileostomy durations were significantly longer among patients with major or minor complications ($p < 0.001$) (Table 2 and Table 3, Figure 1 and Figure 2). Among

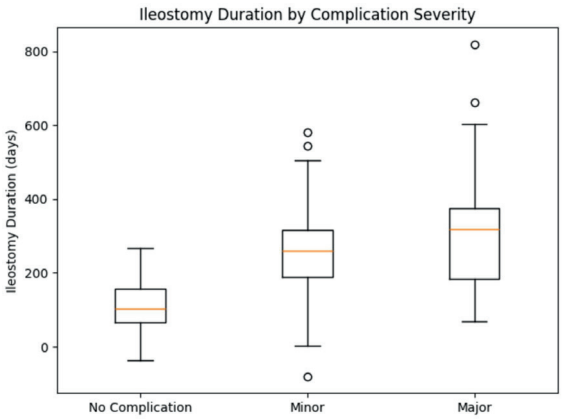

Figure 1. Relationship between ileostomy duration and probability of minor and major complications. The risk increases progressively with longer duration.

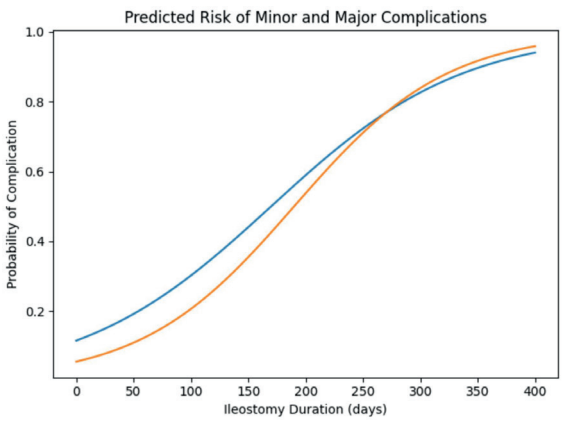

Figure 2. Comparison of ileostomy duration between patients with minor and major complications.

Table 1. Demographic characteristics of patients compared with the presence major and minor ileostomy complications

Variable	Major Complications			Minor Complications		
	None (N=72)	Yes (N=79)	p value	None (N=76)	Yes (N=75)	p value
Age (±SD)	58.74 ± 13.8	63.32 ± 12.6	**0.034**	60.82 ± 13.6	61.45 ± 13.1	0.770
Sex (n, %)						
Female	24 (42.9)	32 (57.1)	0.362	32 (57.1)	24 (42.9)	0.199
Male	48 (50.5)	47 (49.5)		44 (46.3)	51 (53.7)	
Comorbidities (n, %)						
DM	18 (42.9)	24 (57.1)	0.461	20 (47.6)	22 (52.4)	0.679
CAD	13 (28.3)	33 (71.7)	**0.002**	17 (36.9)	29 (63)	**0.030**
HT	30 (37.97)	49 (62.03)	**0.012**	36 (45.6)	43 (54.4)	0.220
ASA (n, %)						
1	41 (56.94)	39 (49.37)		44 (57.89)	36 (48)	
2	24 (33.33)	21 (26.58)	0.078	19 (25)	26 (34.67)	0.571
3	7 (9.72)	15 (18.99)		11 (14.47)	11 (14.67)	
4	0 (0)	4 (5.06)		2 (2.63)	2 (2.67)	
Laboratory Findings						
HGB (±SD)	12.45 ± 2.9	12.77 ± 2.9	0.501	12.27 ± 3.1	12.97 ± 2.7	0.130
ALB (±SD)	4.15 ± 0.9	4.05 ± 0.9	0.324	4.12 ± 0.9	4.08 ± 0.8	0.711
Histology (n, %)						
Adenocarcinoma	68 (49.3)	70 (50.7)		71 (51.5)	67 (48.6)	
Mucinous adenocarcinoma	3 (27.3)	8 (72.7)	0.263	4 (36.4)	7 (63.6)	0.366
Signet-ring cell carcinoma	1 (100)	0 (0)		1 (100)	0 (0)	
Neuroendocrine tumor	0 (0)	1 (100)		0 (0)	1 (100)	
Stage (MRI) (n, %)						
1	52 (72.2)	20 (27.8)		52 (72.2)	20 (27.8)	
2	6 (27.3)	16 (72.7)	**0.001**	9 (40.9)	13 (59.1)	**<0.001**
3	13 (26.0)	37 (74.0)		13 (26.0)	37 (74.0)	
4	1 (14.3)	6 (85.7)		2 (28.6)	5 (71.4)	
Histopathological Stage (n, %)						
T stage						
1	17 (68.0)	8 (32.0)		18 (72.0)	7 (28)	
2	38 (61.3)	24 (38.7)	**0.001**	37 (59.7)	25 (40.3)	**0.001**
3	15 (25.4)	44 (74.6)		19 (32.2)	40 (67.8)	
4	2 (40.0)	3 (60.0)		2 (40.0)	3 (60)	
N stage						
0	58 (61.1)	37 (38.9)	**0.001**	61 (64.2)	34 (35.8)	**<0.001**
1	12 (30.0)	28 (70.0)		14 (35)	26 (65)	
2	2 (12.5)	14 (87.5)		1 (6.3)	15 (93.8)	
M stage						
0	71 (49.3)	73 (50.7)	0.070	74 (51.4)	70 (48.6)	0.276
1	1 (14.3)	6 (85.7)		2 (28.6)	5 (71.4)	
Neoadjuvant (n, %)	20 (25.3)	59 (74.7)	**0.001**	24 (30.4)	55 (69.6)	**<0.001**
Adjuvant (n, %)	23 (28.4)	58 (71.6)	**0.001**	25 (30.9)	56 (69.1)	**<0.001**

±SD: Standard deviation; DM: Diabetes Mellitus; CAD: Coronary artery disease; HT: Hypertension; HGB: Hemoglobin; ALB: Albumi; ASA: American Society of Anesthesiologists; MRI: Magnetic resonance imaging.

Table 2. Clinical findings of patients with major ileostomy complications

	None (N=72)	Yes (N=79)	p value
Post-closure hospitalization duration (day, ±SD)	4.9 ± 1.3	8.9 ± 4.8	**<0.001**
Ileostomy duration (day, ±SD)	115.1 ± 77.3	272.1 ± 135.5	**<0.001**
Surgery type (n, %)			
Laparotomy	32 (44.4)	29 (36.7)	
Laparoscopy	35 (48.6)	43 (54.4)	0.613
Lap to Open Conversion	5 (6.9)	7 (8.9)	
Hypokalemia / Hyponatremia (n, %)	3 (4.17)	12 (15.19)	**0.024**
Anastomosis related complications (n, %)			
Colorectal anastomosis stenosis	6 (8.33)	12 (15.19)	0.194
Colorectal anastomosis leakage	0 (0)	14 (17.72)	**<0.001**
Intraabdominal pelvic abscess	0 (0)	20 (25.32)	**<0.001**
Ileostomy related complications (n, %)			
Skin Irritation	10 (13.89)	21 (26.58)	0.054
Retraction	0 (0)	12 (15.19)	**0.001**
Parastomal Infection	0 (0)	24 (30.38)	**<0.001**
Post-closure Ileostomy Site Infection	7 (9.72)	19 (24.05)	**0.020**
Reoperation (n, %)	2 (2.78)	9 (11.39)	**0.042**
Post-Closure Diarrhea (n, %)	11 (15.28)	9 (11.39)	0.482
Deep Incisional SSI (n, %)	0 (0)	39 (49.37)	**<0.001**
Organ Space SSI (n, %)	0 (0)	28 (35.44)	**<0.001**
Superficial SSI (n, %)	16 (22.22)	38 (48.1)	**0.001**

±SD: Standard deviation, SSI: Surgical site infection.

the patients with major ileostomy surgical site complications, the incidence of hypokalemia/hyponatremia and the rate of reoperation was observed significantly higher (15.19% vs 4.17% and 11.39% vs 2.78%, respectively; $p < 0.05$) while the surgery type and the incidence of post-closure diarrhea did not differ (Table 2). Among the patients with minor complications, the incidence of acute renal failure, postoperative ileus, the surgery type, and post-closure diarrhea also did not differ according to the minor complications (Table 3-4). Patients who had experienced colorectal anastomosis leakage prior to ileostomy closure were more likely to develop major complications after closure and intraabdominal pelvic abscess (17.72% vs 0% and 25.32% vs 0%, respectively; $p < 0.001$) whereas patients with minor complications were more likely to have colorectal anastomosis stenosis and intraabdominal pelvic abscess (18.67% vs 5.26% and 20.0% vs 6.58%, respectively; $p < 0.05$). The patients with major complications were more likely to have prior to closure; retraction, parastomal infection and ileostomy site infection (15.19% vs 0%, $p < 0.01$; 30.38% vs 0%, $p < 0.001$ and 24.05% vs 9.72%, $p < 0.05$, respectively) whereas patients with minor complications were more likely to have post-closure ileostomy stenosis, ischemia and ileostomy leakage (14.67% vs 1.32%, $p < 0.01$; 25.33% vs 3.95%, $p < 0.001$ and 12.0% vs 0%, $p < 0.01$, respectively).

Table 3. Clinical findings of patients with minor ileostomy complications

	None (N=76)	Yes (N=75)	p value
Hospitalization (day, ±SD)	5.62 ± 2.2	8.39 ± 5.0	**<0.001**
Ileostomy duration (day, ±SD)	134.83 ± 95.9	260.55 ± 142.3	**<0.001**
Surgery type (n, %)			
Laparotomy	35 (57.38)	26 (42.62)	
Laparoscopy	37 (47.44)	41 (52.56)	0.239
Lap to Open Conversion	4 (33.33)	8 (66.67)	
Anastomosis related complications (n, %)			
Colorectal anastomosis stenosis	4 (5.26)	14 (18.67)	**0.011**
Colorectal anastomosis leakage	5 (6.58)	9 (12)	0.211
Intraabdominal pelvic abscess	5 (6.58)	15 (20)	**0.015**
Ileostomy related complications (n, %)			
Ileostomy Stenosis	1 (1.32)	11 (14.67)	**0.002**
Ischemia	3 (3.95)	19 (25.33)	**<0.001**
Parastomal Hernia Prolapses	5 (6.58)	2 (2.67)	0.442
Post-Closure Leakage	0 (0)	9 (12)	**0.006**
Reoperation (n, %)	2 (2.63)	9 (12)	**0.027**
Post-Closure Diarrhea (n, %)	12 (15.79)	8 (10.67)	0.353
Acute Renal Failure (n, %)	2 (22.22)	7 (77.78)	0.051
Post-closure Obstruction (Ileus) (n, %)	12 (15.79)	14 (18.67)	0.640
Deep Incisional SSI (n, %)	3 (3.95)	36 (48)	**<0.001**
Organ Space SSI (n, %)	6 (7.89)	22 (29.33)	**<0.001**
Superficial SSI (n, %)	0 (0)	54 (72)	**<0.001**

SSI: Surgical site infection.

The univariate regression analysis of all variables showed that older age (OR: 1.027; 95% CI: 1.002-1.053; P = 0.037) and longer ileostomy duration (OR: 1.015; 95% CI: 1.011-1.020; P < 0.001) and the presence of ileostomy site infection (OR: 2.940; 95% CI: 1.154-7.489; P = 0.024) primarily affected the risk of major complications (Table 5).

The univariate regression analysis of all variables showed that the presence of comorbidity such as CAD (OR: 2.188; 95% CI: 1.073-4.460; P = 0.031), longer ileostomy duration (OR: 1.01; 95% CI: 1.006-1.013; P < 0.001) and ileostomy stenosis (OR: 12.891; 95% CI: 1.6200-102.58; P = 0.016) initially affected the risk of minor complications (Table 6).

Table 4. Frequencies of ileostomy related complications

	N (%)
Major complications	
Ileostomy Stenosis	12 (7.95)
Ischemia	22 (14.57)
Parastomal Hernia Prolapses	7 (4.64)
Acute Renal Failure	9 (5.96)
Post-closure Obstruction	26 (17.22)
Ileostomy Leakage	9 (5.96)
Deep Incisional SSI	39 (25.83)
Organ Space SSI	28 (18.54)
Minor complications	
Skin Irritation	31 (20.53)
Retraction	12 (7.95)
Parastomal Infection	24 (15.89)
Hypokalemia / Hyponatremia	15 (9.93)
Ileostomy Site Infection	26 (17.22)
Superficial Space SSI	54 (35.76)

SSI: Surgical site infection.

Table 5. Unadjusted covariates for major ileostomy complications

Characteristics	Odds Ratio	95% CI	p value
Age	1.027	1.002-1.053	**0.037**
Comorbidities			
CAD	3.256	1.540-6.884	**0.002**
HT	2.287	1.191-4.392	**0.013**
Ileostomy duration	1.015	1.011-1.020	**<0.001**
Stage (MR)	2.747	1.867-4.041	**<0.001**
Histopathological Stage			
T stage	2.479	1.555-3.952	**<0.001**
N stage	3.479	1.915-6.322	**<0.001**
Adjuvant	12.38	0.534-286.77	0.117
Neoadjuvant	7.670	3.721-15.81	**<0.001**
Reoperation	4.500	0.938-21.58	0.060
Hypokalemia / Hyponatremia	4.119	1.113-15.25	**0.034**
Ileostomy Site Infection	2.940	1.154-7.489	**0.024**

CAD: Coronary artery disease; HT: Hypertension, SSI: Surgical site infection.

Table 6. Unadjusted covariates for minor ileostomy complications

Characteristics	Odds Ratio	95% CI	p value
Comorbidities			
CAD	2.188	1.073-4.460	**0.031**
Ileostomy duration	1.010	1.006-1.013	**<0.001**
Stage (MR)	2.496	1.722-3.619	**<0.001**
Histopathological Stage			
T	2.241	1.421-3.535	**0.001**
N	3.991	2.171-7.336	**<0.001**
Adjuvant	6.013	2.965-12.192	**<0.001**
Neoadjuvant	5.958	2.947-12.049	**<0.001**
Reoperation	5.045	1.052-24.196	**0.043**
Colorectal Anastomosis Stenosis	4.131	1.292-13.209	**0.017**
Intraabdominal Pelvic Abscess	3.550	1.219-10.338	**0.020**
Ileostomy Stenosis	12.891	1.6200-102.58	**0.016**
Ischemia	8.256	2.327-29.294	**0.001**

CAD: Coronary artery disease; SSI: Surgical site infection.

Multivariate analysis by adjusted covariates showed that the patients with longer ileostomy duration were more likely to have major (OR: 1.015; 95% CI: 1.007-1.022; P <0.001) and minor (OR: 1.006; 95% CI: 1.002-1.011; P = 0.008) complications. Eventually, the increase in ileostomy duration had an impact on the risks of major and minor complications (Table 7 and Table 8).

Table 7. Adjusted covariates for major ileostomy complications

Parameter	Odds Ratio	95% CI	p value
Age	0.997	0.948-1.049	0.915
Hypokalemia/ Hyponatremia	0.553	0.081-3.761	0.545
Stoma Site Infection	0.417	0.066-2.619	0.350
CAD	2.497	0.644-9.680	0.185
HT	1.268	0.349-4.604	0.718
Stage MR	0.952	0.198-4.587	0.951
T Stage	0.853	0.355-2.048	0.722
N stage	2.177	0.467-10.139	0.322
Neoadjuvant	0.946	0.048-18.693	0.971
Ileostomy duration	**1.015**	**1.007-1.022**	**<0.001**

CAD: Coronary artery disease; HT: Hypertension, SSI: Surgical site infection.

Table 8. Adjusted covariates for minor ileostomy complications

Parameter	Odds Ratio	95% CI	p value
Colorectal Anastomosis Stenosis	2.460	0.530-11.422	0.251
Intraabdominal pelvic abscess	0.709	0.024-21.242	0.843
Stomal Stenosis-Obstruction	3.025	0.209-43.835	0.417
Ischemia	0.001	0.0001-1	0.998
Re-operation	2.844	0.320-25.26	0.348
Ileostomy duration	1.006	1.002-1.011	**0.008**
CAD	1.888	0.717-4.971	0.198
Stage MR	0.403	0.102-1.588	0.194
T Stage	0.982	0.422-2.282	0.966
N stage	4,879	0,90-26,24	0,065
Adjuvant	3.629	0.611-21.56	0.156

CAD: Coronary artery disease; SSI: Surgical site infection.

Discussion

The incisional SSI and intestinal obstruction are the most frequent complications after a diverting ileostomy, both related to low morbidity rates of around 5%, but reported up to 43%, among which are mainly problems with the anastomotic dehiscence, the appearance of incisional hernias (8,13-18). These infectious complications lead to a significant economic burden with increased hospitalization and costs (19). Understanding of the SSI-related morbidities, as well as estimating the predictors for ileostomy-related SSI following the diverting ileostomy closure might be beneficial to reduce these complications, the hospitalization duration, and costs (20). Therefore, we focused on specifically the predictors associated with the ileostomy-related SSI among the patients with rectal cancer who underwent temporary diverting ileostomy closure. Subsequently, we reported that the ileostomy site-related complications including retraction, parastomal, and ileostomy site infections were observed more likely in patients with major ileostomy-related SSI, and complications including ileostomy stenosis, ischemia, and leakage were more likely in patients with minor complications. Deep incisional, organ space and superficial SSIs were significantly higher in patients with both major and minor complications (Table 2 and Table 3).

There are numerous factors associated with a high risk of SSI including obesity, emergent surgery, an open operative approach, preoperative abscess, advanced age (>70 yr), and comorbidities (13,21). We compared these factors in terms of the presence of major complications including ileostomy stenosis, ischemia, parastomal hernia prolapses, post-closure obstruction, post-closure ileostomy leakage, deep incisional SSI, organ space SSI, and also the minor complications including skin irritation, retraction, parastomal infection, post-closure ileostomy site infection, superficial space SSI. We determined that older age and the presence of comorbidities such as CAD, and HT, and longer ileostomy duration primarily affected the risk of major complications. Moreover, the presence of comorbidity and longer ileostomy duration significantly affected the risk of minor complications. Considering the duration of ileostomy and its effects on ileostomy-related SSI, several studies focused on early and delayed ileostomy reversal time and examined the effect of the timing of closure on morbidity and mortality rates (7,18,22-24). In a recent study, the rates of complication variables were found to be more likely among the patients who had ileostomy duration longer than 3 months and also, ileostomy-site complications were observed in 61.1% of the patients who had delayed closure time, too (7). Consistent with these previous findings, we showed that increase duration of ileostomy significantly affected the risks of major and minor complications. The longer waiting period of ileostomy closure was primarily a predictor of post-closure ileostomy-related SSI for the patients who underwent temporary diverting ileostomy with total mesorectal excision.

Ileostomy complications especially encountered after the construction of the loop ileostomy are the retraction of loop ileostomy, ileostomy flux, stomal prolapse, parastomal herniation, parastomal abscess, and severe skin excoriation (17-19,25). After reversal of the ileostomy, complications related to ileostomy are anastomotic leakage or around the site of ileostomy reversal resulting in small bowel fistula, small bowel obstruction, and stitch-related adverse outcomes after ileostomy closure. Furthermore, after the closure of ileostomy and preservation of intestinal stability, the fistulas such as recto-vaginal fistula, pouch-vaginal fistula, and pouch-anal fistula are hardly witnessed (17-21,25). In our data analysis, we evaluated that major complications was more likely affected by deep incisional SSI, organ space SSI, and post-closure obstruction while the minor complications were exaggerated by superficial space SSI, skin irritation, and ileostomy site infection, respectively. Our findings are consistent with previous studies demonstrating that delayed ileostomy closure is associated with increased postoperative morbidity. Similarly, prolonged ileostomy duration may increase local inflammation, bacterial colonization, and technical difficulty during closure. Clinically, these findings support consideration of earlier closure when feasible.

Regarding Aydin and Soylu, the factors such as age, ASA score, presence of chronic lung disease, presence of hyperglycemia, hematocrit and albumin levels, location of disease (colon or rectum), surgery duration, colostomy or ileostomy during the operation, and surgeon volume were associated with the incidence rates of SSI among patients who underwent colorectal surgery (26). Al-Khamis et al. modified a five-item frailty index to use predictor of 30-day postoperative outcomes after colorectal surgery, and to proactively recognize frail patients to instigate interventions to optimize them preoperatively (15). Consistently, we performed a multivariate logistic regression analysis to identify factors associated with major and minor complications. This approach allows assessment of independent associations

but does not constitute a predictive or diagnostic model. As previously mentioned in various aspects of other complications of colorectal diseases, we first tried to build a new diagnostic model to perform clinically adjustable to measurements of ileostomy related complications by identifying the major and minor complications (13-16,20-28). We performed a new diagnostic approach to predict the specific ileostomy complications, other than a common well-known Clavien–Dindo grading system which reflects generally the post-surgical complications (27). Eventually, as we expected based on our clinical practice, deep incisional, organ space, and superficial SSIs were seen to be significantly higher in patients with both major and minor complications.

However, this study has several limitations. First, its retrospective design introduces potential selection and information bias. Second, it represents a single-center experience with a relatively small sample size, which may limit generalizability. Third, variability in surgical technique and perioperative management could not be fully controlled. Finally, no external validation or performance assessment (e.g., ROC analysis) was performed, limiting the predictive applicability of the findings. No model validation (e.g., discrimination or calibration) was performed; therefore, the findings should be interpreted as exploratory associations rather than a validated predictive model. SSI assessment was based on routine clinical evaluation without independent adjudication, which may introduce observer variability. Despite these limitations, this study provides clinically relevant insights into factors associated with postoperative complications that could measure the predictors of ileostomy-related SSI among rectal cancer patients, suggesting a multivariate risk factor analysis for the major and minor complications following total mesorectal excision.

Conclusion

Prolonged ileostomy duration is independently associated with an increased risk of surgical site infection following ileostomy closure. Rather than a strict temporal cutoff, the risk appears to increase progressively over time. These findings highlight the importance of optimizing the timing of ileostomy closure to reduce postoperative complications. Further prospective, multicenter studies are needed to validate these results.

Ethical approval

The Clinical Research Ethics Committee of Bagcilar Training and Research Hospital of Health Science University approved the study protocol (date:12.06.2020, number: 2020.06.1.10.081).

Author contribution

Study conception and design: YA, EY; data collection/processing: YEA, MT, SM, HY; analysis and interpretation of results: YA, YEA, MT, SM, HY, EY; draft manuscript preparation: YA. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Research Article

Subclinical atherosclerosis and related factors in patients with liver cirrhosis: a case–control study

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ABSTRACT

Background: The atherosclerosis and its complications may be less prevalent in patients with liver cirrhosis. However, the mechanisms underlying this observation remain unclear. This study aimed to evaluate the frequency of subclinical atherosclerosis and associated biochemical factors in patients with cirrhosis.

Methods: This case–control study included 49 patients with liver cirrhosis and 28 age- and sex-matched healthy controls. Subclinical atherosclerosis was assessed by Doppler ultrasonography measuring carotid intima–media thickness (CIMT) and the presence of carotid plaques. Laboratory parameters associated with atherosclerosis, including lipid profile, lipoprotein(a), oxidized low-density lipoprotein (oxLDL), insulin, homocysteine, platelet count, fibrinogen, high-sensitivity C-reactive protein (hsCRP), and bilirubin levels, were analyzed. Statistical analyses were performed using Student's t-test or Mann–Whitney U test as appropriate, with $p < 0.05$ considered statistically significant.

Results: Mean CIMT was significantly lower in cirrhotic patients compared with controls (0.664 ± 0.133 mm vs. 0.749 ± 0.091 mm, $p = 0.002$). Carotid plaque was detected in 18.4% of patients and 14.3% of controls. Cirrhotic patients had significantly higher oxLDL levels, whereas total cholesterol, LDL-cholesterol, triglycerides, lipoprotein(a), platelet counts, and fibrinogen levels were significantly lower compared with controls. hsCRP levels were significantly higher in the cirrhosis group. No significant differences were observed in HDL cholesterol, blood pressure, body mass index, or homocysteine levels between groups.

Conclusion: Despite the presence of potential pro-atherogenic factors such as insulin resistance and elevated oxLDL levels, cirrhotic patients demonstrated lower carotid intima–media thickness, suggesting reduced subclinical atherosclerosis. Decreased lipid levels, thrombocytopenia, and hyperbilirubinemia may contribute to this paradoxical finding.

Keywords: liver cirrhosis, subclinical atherosclerosis, carotid intima–media thickness, oxidized LDL

Introduction

Liver cirrhosis is an irreversible disease characterized by chronic hepatocellular injury accompanied by inflammation, fibrosis, and nodular regeneration, ultimately leading to clinical manifestations of hepatocellular insufficiency and portal hypertension (1). According to the World Health Organization (WHO), liver cirrhosis causes over 1.4 million deaths annually worldwide, accounting for approximately 2.4% of global deaths. The age-standardized death rate due to liver cirrhosis in Türkiye was 7.1 per 100,000 population in 2019

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(2). The major causes of mortality in cirrhotic patients are complications associated with hepatocellular failure and portal hypertension (3).

Interestingly, several metabolic and vascular alterations observed in cirrhosis may influence cardiovascular risk and the development of atherosclerosis. Atherosclerosis is a focal, inflammatory, fibrotic, and degenerative disease affecting the intimal layer of medium- and large-sized elastic arteries. It begins in childhood, progresses slowly over decades, and eventually leads to clinical symptoms (cardiovascular and cerebrovascular diseases) and causes morbidity and mortality due to mechanical obstruction of blood flow (4,5). Major risk factors for atherosclerosis include diabetes mellitus, hypertension, smoking, dyslipidemia, obesity, advanced age, an atherogenic diet, physical inactivity, male sex, hyperhomocysteinemia, and prothrombotic conditions (6,7).

Measurement of carotid intima-media thickness (CIMT) using high-frequency (7–12 MHz) Doppler ultrasonography for detecting subclinical atherosclerosis has become the most widely used technique in clinical studies because of its non-invasive nature, reproducibility, and ease of application (8).

Although cirrhosis is associated with several metabolic abnormalities that may theoretically promote atherosclerosis, previous studies have reported conflicting results regarding the actual burden of vascular disease in these patients (9-11). The relationship between cirrhosis and atherosclerosis has not yet been fully clarified. In this study, CIMT, a reliable marker of subclinical atherosclerosis, was measured using Doppler ultrasonography to compare patients with cirrhosis and healthy control subjects. In addition, clinical and laboratory parameters potentially contributing to the development of atherosclerosis in cirrhotic patients were evaluated before the occurrence of overt cardiovascular complications. The aim of this study was to identify major risk factors associated with atherosclerosis in patients with liver cirrhosis.

Materials and Methods

Study design and ethical approval

This study was conducted at the Department of Gastroenterology, Trakya University Faculty of Medicine, between April 2011 and May 2012. The study was designed to investigate the presence of subclinical atherosclerosis and its associated risk factors in patients with chronic liver cirrhosis. Ethical approval was obtained from the Local Ethics Committee of Trakya University (approval date: April 6, 2011). The study was supported by the Trakya University Scientific Research Projects Unit (TÜBAP; project number: 2011-170). All participants were informed about the study both verbally and in writing, and written informed consent was obtained from each participant before enrollment.

Study population

A total of 49 adult patients with clinically, laboratorial, and radiologically diagnosed liver cirrhosis who were followed in the Gastroenterology outpatient clinic of Trakya University Faculty of Medicine were included in the study.

Patients with cirrhosis were excluded if they had any of the following conditions; diabetes mellitus, hyperlipidemia receiving treatment, hypertension receiving treatment, history of cardiovascular disease or cerebrovascular disease, hepatocellular carcinoma, active bacterial infection or history of esophageal variceal bleeding within the last three months.

The control group consisted of 28 healthy adult volunteers with no known acute or chronic disease. The controls were age- and sex-matched to the patient group and were selected from individuals who presented to the internal medicine outpatient clinic with nonspecific complaints but had no pathological

findings on clinical examination or laboratory evaluation. Individuals with diabetes mellitus, hyperlipidemia, hypertension, cardiovascular or cerebrovascular disease, active bacterial infection, or malignancy were excluded from the control group.

Clinical assessment

Demographic data and detailed medical histories of all participants were recorded. Physical examinations were performed and anthropometric measurements were obtained.

Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared (kg/m²). Waist circumference was measured at the midpoint between the iliac crest and the lower rib margin during normal expiration with the participant standing. Arm circumference was measured at the midpoint between the acromion and the olecranon. Blood pressure measurements were obtained using a calibrated aneroid sphygmomanometer according to World Health Organization guidelines.

Measurement of carotid intima-media thickness

CIMT measurements were performed at the Department of Radiology by an experienced radiologist who was blinded to the clinical and laboratory data of the participants. Measurements were obtained using an Esaote MyLab 60 ultrasound device (Esaote, Saint-Germain, France) with a 7.5 MHz linear transducer in B-mode.

Participants were examined in the supine position with the neck slightly extended and the head turned approximately 45° away from the side being examined. Longitudinal images of the carotid artery were obtained using high-resolution Doppler ultrasonography. CIMT was defined as the distance between the lumen–intima interface and the media–adventitia interface of the arterial wall.

Measurements were performed on the far wall of the common carotid artery over a segment of at least 1 cm, and the highest value obtained was recorded. Both right and left carotid arteries were examined, and the arithmetic mean of the measurements was calculated.

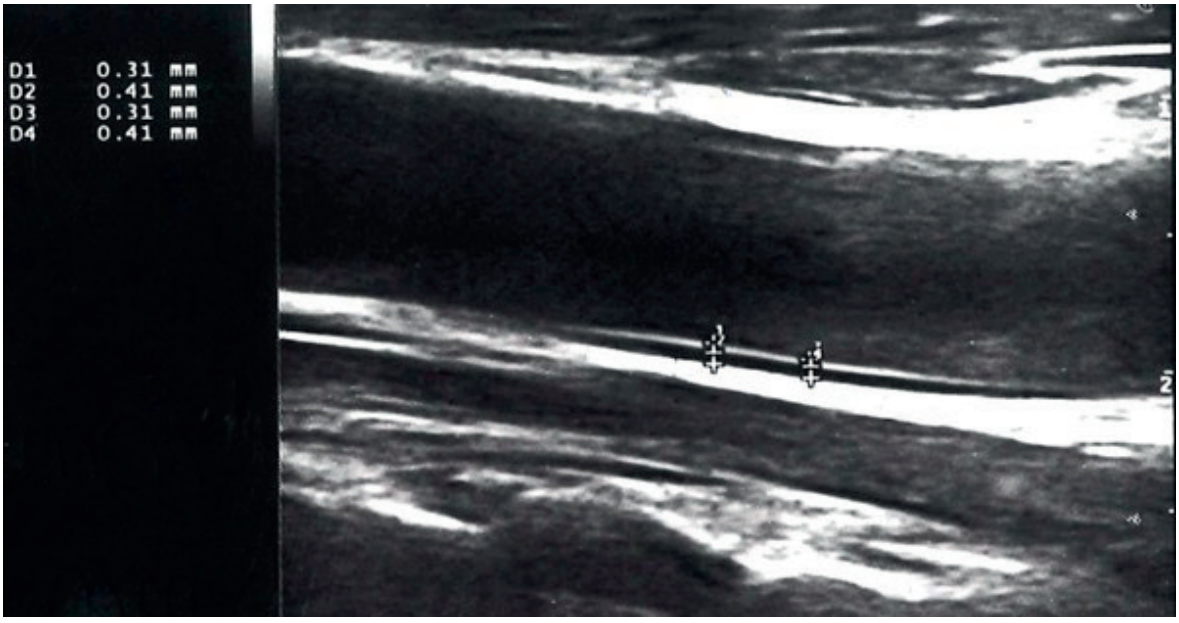

Figure 1. Doppler Ultrasonography image of the thickness of carotid intima media

Carotid plaques were evaluated throughout the common carotid artery and carotid bulb region. A focal protrusion into the lumen greater than 0.5 mm, a thickening exceeding 50% of the surrounding CIMT, or a CIMT measurement greater than 1.5 mm was defined as a plaque. CIMT measurements were not performed at sites where plaques were detected (Figure 1).

Biochemical analysis

Routine laboratory parameters were obtained from hospital medical records or the laboratory information system.

Blood samples were stored at −80°C until the day of study. Homocysteine and insulin levels were measured using the Siemens Immulite 2000 XPi system (Tarrytown, NY, USA). Lp(a) and high-sensitivity C-reactive protein (hsCRP) levels were measured using the Siemens BN2 nephelometric analyzer (Siemens, Tarrytown, NY, USA).

Oxidized low-density lipoprotein (oxLDL) levels were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit (Immundiagnostik, Bensheim, Germany) according to the manufacturer's instructions, and absorbance was measured at 450 nm using a Biotek ELISA reader (Vermont, USA).

Insulin resistance was calculated using the homeostasis model assessment of insulin resistance (HOMA-IR) with the following formula:

HOMA-IR = [Fasting insulin (μU/mL) × fasting plasma glucose (mg/dL)] / 405.

Statistical analysis

All statistical analyses were performed using SPSS software version 19 (SPSS Inc., Chicago, IL, USA). The distribution of continuous variables was evaluated using the Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± standard deviation or median values where appropriate. For comparisons between the patient and control groups, the Student's t-test was used for normally distributed variables, whereas the Mann–Whitney U test was used for non-normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test where appropriate. A p value < 0.05 was considered statistically significant.

Results

A total of 77 individuals were included in the study, consisting of 28 healthy controls and 49 patients with liver cirrhosis. Among the cirrhotic patients, the etiology was hepatitis B virus (HBV) infection in 13 patients and alcohol consumption in 13 patients. The distribution of cirrhotic patients according to the Child–Turcotte–Pugh (CTP) classification is shown in Figure 2. According to the CTP staging system, 27 patients were classified as stage A, 18 as stage B, and 4 as stage C.

Demographic, anthropometric, and blood pressure characteristics of study groups

In the control group, 17 participants were female and 11 were male, whereas in the cirrhosis group 19 were female and 30 were

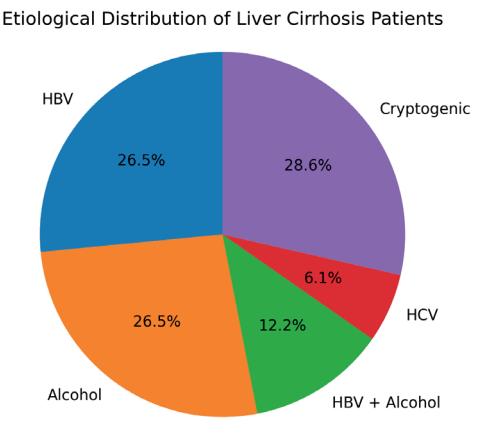

Figure 2. Etiological distribution of liver cirrhosis among the study population. The most frequent causes were cryptogenic cirrhosis (28.6%), hepatitis B virus (HBV) infection (26.5%), and alcohol-related cirrhosis (26.5%), followed by combined HBV and alcohol-related cirrhosis (12.2%) and hepatitis C virus (HCV) infection (6.1%).

male (p=0.06). The mean age was 49.9 ± 7.4 years in the control group and 53.8 ± 10.7 years in the cirrhosis group (p=0.09). Smoking was reported in 32% (n = 9) of the control group and 42% (n = 21) of the cirrhosis group (p=0.35) (Table 1).

The mean body mass index (BMI) was 28.9 ± 4 kg/m² in the control group and 27.3 ± 5.9 kg/m² in the cirrhosis group (p = 0.18). The mean waist circumference was 99.8 ± 10.7 cm in the control group and 101.3 ± 15.4 cm in the cirrhosis group, with no significant difference between the groups (p = 0.99). However, arm circumference was significantly lower in patients with cirrhosis compared with controls (26.5 ± 4.6 cm vs. 29.8 ± 3.2 cm, p = 0.001). The mean systolic blood pressure (SBP) was 115.7 ± 16 mmHg in the control group and 119.2 ± 14 mmHg in the cirrhosis group (p = 0.32). The mean diastolic blood pressure (DBP) was 75.5 ± 12 mmHg and 74 ± 8.8 mmHg, respectively (p = 0.83). No statistically significant differences were observed between the groups regarding blood pressure measurements (Table 1).

Carotid intima–media thickness and carotid plaque findings

The mean carotid intima–media thickness (CIMT) in the healthy control group was 0.75 ± 0.09 mm, whereas the mean CIMT in the patient group was 0.66 ± 0.13 mm (p = 0.002). Carotid plaque was detected in 4 individuals (14.3%) in the control group and 9 individuals (18.4%) in the patient group. (p = 0.65) (Table 2).

Table 1. Comparison of demographic, anthropometric and blood pressure parameters of healthy control and cirrhosis patient groups

Parameter	Control Group (n=28)	Cirrhosis Group (n=49)	p value*
Age (year)	49.9 ± 7.4	53.8 ± 10.7	0.09
Gender (Male/Female)	11/17	30/19	0.06
BMI (kg/m²)	28.9 ± 4	27.3 ± 5.9	0.18
Height (cm)	163.2 ± 10.2	164.9 ± 10	0.50
Weight (kg)	77.5 ± 14.8	75.3 ± 15.7	0.54
Waist circumference (cm)	99.8 ± 10.7	101.3 ± 15.4	0.99
Arm circumference (cm)	29.8 ± 3.2	26.5 ± 4.6	**0.001**
SBP (mmHg)	115.7 ± 16	119.2 ± 14	0.32
DBP (mmHg)	75.5 ± 12	74 ± 8.8	0.83

BMI: Body mass index; SBP: Systolic blood pressure, DBP: Diastolic blood pressure. *Statistical significance level p <0.05.

Table 2. Comparison of doppler ultrasonography parameters of healthy control and cirrhosis patient groups

Parameter	Control Group (n=28)			Cirrhosis Group (n=49)		p value*
CIMT (mm) Mean± SD	0.75 ± 0.09			0.66 ± 0.13		**0.002**
Carotid plaque (n, %)	4 (14.3)			9 (18.4)		0.65
Gender	Male (n=11)	Female (n=17)	p value	Male (n=30)	Female (n=19)	p value
CIMT (mm) Mean± SD	0.75 ± 0.11	0.75 ± 0.08	0.942	0.69 ± 0.14[a]	0.63 ± 0.11[b]	0.138
Carotid plaque (n, %)	3 (27.3)	1 (5.9)	0.114	6 (20)	3 (15.8)	0.711

CIMT: Carotid intima media thickness. *Statistical significance level p <0.05.
[a] p=0.191 vs control male individuals; [b] p=0.0008 vs control female patients.

Table 3. Comparison of biochemical parameters of healthy control and cirrhosis patient groups

Parameters		Control Group (n=28)	Cirrhosis Group (n=49)	p value*
Lipid Parameters	Total Cholesterol (mg/dl)	202.4 ± 33.7	140.2 ± 43.8	**<0.001**
	HDL-Cholesterol (mg/dl)	46.1 ± 9.1	40.6 ± 18.1	0.07
	LDL-Cholesterol (mg/dl)	146.3 ± 31.7	89.2 ± 33.9	**<0.001**
	Triglyceride (mg/dl)	117.5	88	**0.003**
	Lp (a) (mg/dl)	11.5	9.5	**0.005**
	Oxidized LDL (ng/ml)	127.9	588.3	**<0.001**
Glucose Metabolism / Insulin Resistance	FBG (mg/dl)	83 ± 11.8	100 ± 20.4	**<0.001**
	Insulin (μIU/ml)	4.56	14.3	**0.001**
	HOMA-IR	0.96	3.67	**<0.001**
Inflammatory And Thrombotic Markers	hsCRP (mg/dl)	0.33	0.47	**0.009**
	Thrombocytes (x10^3/μL)	244 ± 70.1	106.8 ± 52.4	**<0.001**
	Fibrinogen (mg/dl)	338 ± 73.7	245 ± 86.6	**<0.001**
	Homocysteine (μmol/L)	16.5 ± 8.6	15.7 ± 5.6	0.609
Bilirubin	Total bilirubin (mg/dl)	0.66 ± 0.2	2.47 ± 2.8	**<0.001**
	Direct bilirubin (mg/dl)	0.15 ± 0.7	1.4 ±2	**<0.001**

HDL: High density lipoprotein; LDL: Low density lipoprotein; Lp: Lipoprotein; FBG: Fasting blood glucose; HOMA-IR: Homeostasis model assessment-insulin resistance; hsCRP: High sensitive C reactive protein.
*Statistical significance level p <0.05.

Biochemical parameters

The mean total cholesterol level was 202.4 ± 33.7 mg/dL in the control group and 140.2 ± 43.8 mg/dL in the patient group (Table 3). Total cholesterol levels were significantly higher in the control group than in the patient group ($p < 0.001$). The mean HDL-cholesterol level was 46.1 ± 9.1 mg/dL in the control group and 40.6 ± 18.1 mg/dL in the patient group ($p = 0.07$). The mean LDL-cholesterol level was 146.3 ± 31.7 mg/dL in the control group and 89.2 ± 33.9 mg/dL in the patient group ($p < 0.001$). The mean triglyceride level was 117.5 mg/dL in the control group and 88 mg/dL in the patient group ($p = 0.003$). The mean Lp(a) level was 11.5 mg/dL in the control group and 9.5 mg/dL in the patient group ($p = 0.005$). In contrast other cholesterol levels, the mean oxidized LDL level was 127.9 ng/mL in the control group and 588.3 ng/mL in the patient group, indicating significantly higher oxidized LDL levels in patients with cirrhosis ($p < 0.001$) (Table 3).

The mean fasting blood glucose (FBG) level was 83 ± 11.8 mg/dL in the control group and 100 ± 20.4 mg/dL in the patient group ($p < 0.001$). The mean insulin level was 4.56 μIU/mL in the control group and 14.3 μIU/mL in the patient group ($p = 0.001$). When the HOMA-IR index, used as an indicator of insulin resistance, was evaluated, the mean value was 0.96 in the control group and 3.67 in the patient group ($p < 0.001$). The mean hsCRP level was 0.33 mg/dL in the control group and 0.47 mg/dL in the patient group ($p = 0.009$). The mean platelet count was 244 ± 70.1 ×10^3/μL in the control group and 106.8 ± 52.4 ×10^3/μL in the patient group ($p < 0.001$). Similarly, the mean fibrinogen level was 338 ± 73.7 mg/dL in the control group and 245 ± 86.6 mg/dL in the patient group ($p < 0.001$). The mean homocysteine level was 16.5 ± 8.6 μmol/L in the control group and 15.7 ± 5.6 μmol/L in the patient group ($p = 0.609$). Finally, the mean total bilirubin and direct bilirubin levels were significantly higher in the patient group compared with the control group (both $p < 0.001$) (Table 3).

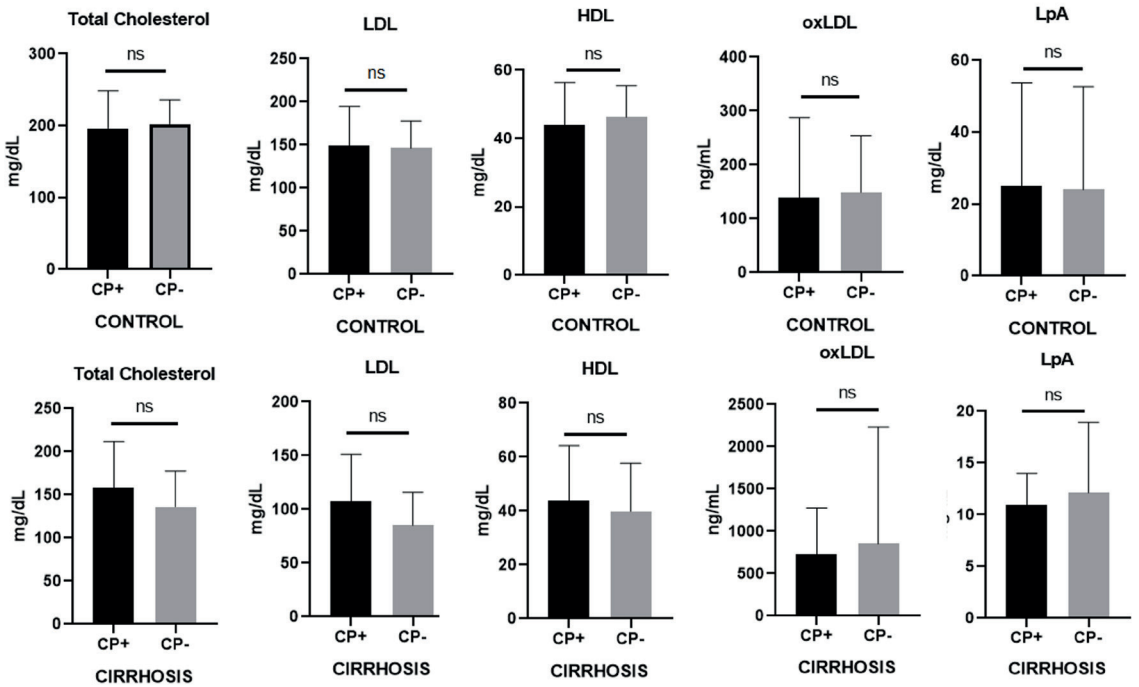

Figure 3. Lipid parameters according to carotid plaque status in control and cirrhosis groups. Comparisons of total cholesterol, LDL-cholesterol, HDL-cholesterol, oxidized LDL (oxLDL), and lipoprotein(a) [Lp(a)] levels according to the presence of carotid plaque (CP+ vs CP−) are shown for both the control group (upper panels) and the cirrhosis patient group (lower panels). Bars represent mean values with standard deviation (ns: not significant).

Comparison of biochemical parameters according to the presence of carotid plaque

Within both the control and patient groups, no statistically significant differences were observed between participants with carotid plaque (CP+) and those without carotid plaque (CP−) in terms of total cholesterol, LDL-cholesterol, HDL-cholesterol, oxidized LDL, and Lp(a) levels (all $p > 0.05$) (Figure 3). In the patient group, neither fasting blood glucose nor insulin levels differed significantly according to carotid plaque status (both $p > 0.05$) (Figure 4).

Platelet and fibrinogen levels according to carotid plaque status are illustrated in Figure 5. As expected, platelet counts were markedly lower in the cirrhosis group than in the control group, regardless of carotid plaque presence. However, no statistically significant differences were observed between CP+ and CP− individuals within either group (all $p > 0.05$). Similarly, fibrinogen levels did not differ significantly according to carotid plaque status in either the control or patient groups.

Discussion

The present case–control study aimed to evaluate subclinical atherosclerosis in patients with liver cirrhosis by assessing CIMT and carotid plaque presence and by examining their relationship with lipid and metabolic parameters. CIMT values which is the main study subject of our study were significantly lower in patients with cirrhosis compared with healthy controls. Beside this, we also found that patients with cirrhosis exhibit metabolic alterations typically associated with increased cardiovascular risk, and the structural markers of subclinical atherosclerosis may remain relatively attenuated in this population.

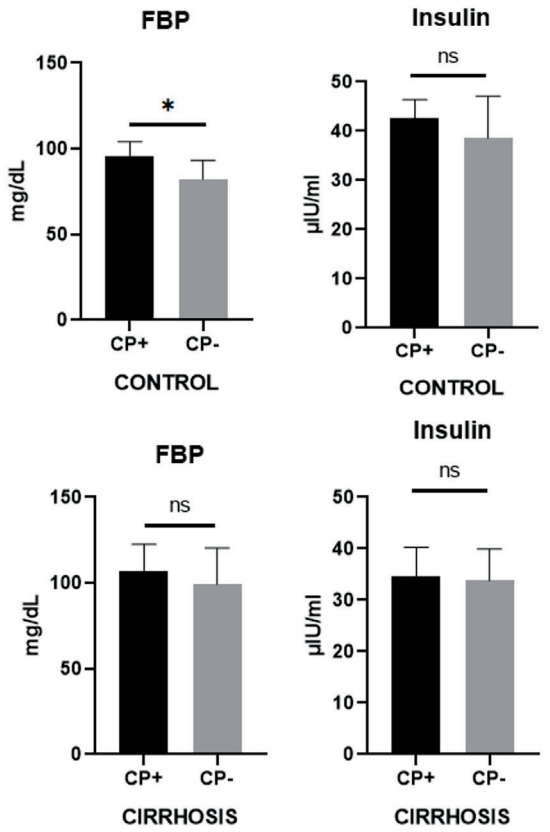

Figure 4. Fasting blood glucose (FBG) and insulin levels according to carotid plaque status. Comparison of FBG and insulin levels according to carotid plaque presence (CP+ vs CP−) in the control group (upper panels) and the cirrhosis patient group (lower panels). Bars represent mean values with standard deviation (ns: not significant).

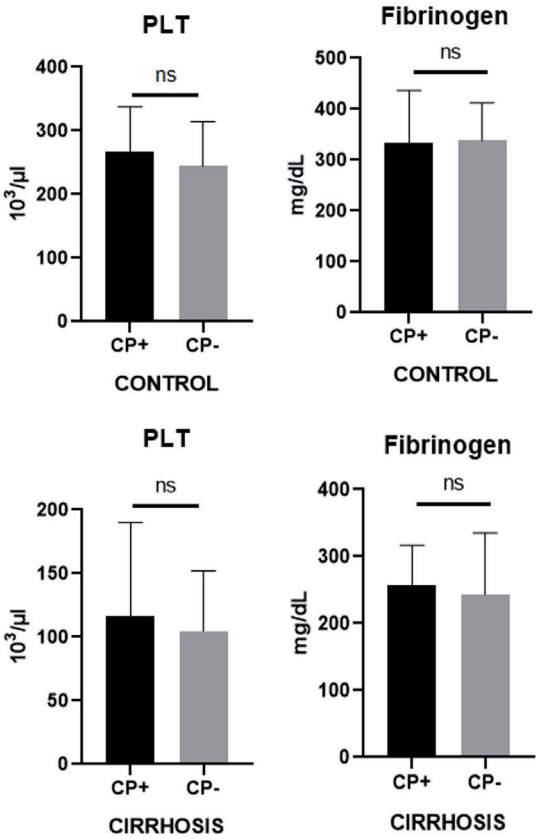

Figure 5. Platelet and fibrinogen levels according to carotid plaque status. Comparison of platelet count (PLT) and fibrinogen levels according to carotid plaque presence (CP+ vs CP−) in the control group (upper panels) and the cirrhosis patient group (lower panels). Bars represent mean values with standard deviation (ns: not significant).

The development of atherosclerosis is strongly influenced by several genetic and environmental risk factors, including dyslipidemia, diabetes mellitus, hypertension, smoking, and metabolic syndrome (12,13). Reduced HDL-cholesterol and elevated triglyceride levels are considered major initiating factors of atherosclerosis, whereas HDL-cholesterol exerts a protective effect (14). Oxidation of LDL particles represents a key step in the initiation of atherosclerosis (15), and a strong inverse association between HDL-cholesterol levels and coronary heart disease has been demonstrated (16). In a study, LDL-cholesterol, HDL-cholesterol, Lp(a), and triglycerides were identified as independent cardiovascular risk factors (17).

Lipid metabolism plays a central role in the pathogenesis of vascular disease, morbidity and mortality worldwide (18). Liver cirrhosis, which represents the final stage of chronic liver disease, profoundly alters lipid metabolism, inflammatory pathways, and hemodynamic regulation (19). Despite the presence of several metabolic abnormalities, numerous studies have reported that atherosclerosis and its clinical complications (cardiovascular and cerebrovascular events) may occur less frequently in cirrhotic patients than in the general

population (10,20,21). These observations have led to the hypothesis that metabolic and hemodynamic alterations associated with cirrhosis—such as hypocholesterolemia, changes in coagulation and fibrinolytic activity, and hormonal or nutritional factors—may modify the development of atherosclerosis. In this context, the present study contributes to the growing body of evidence suggesting that the vascular profile of patients with cirrhosis differs from that of the general population.

Since the cholesterol synthesis largely occurs in the liver, patients with cirrhosis often exhibit reduced lipid levels, and these levels tend to decrease further with disease progression (22). Ghadir et al. reported significantly lower total cholesterol, HDL-cholesterol, and LDL-cholesterol levels in cirrhotic patients compared with controls (23). Kawakami et al. also demonstrated that lipid levels progressively decline with advancing Child–Turcotte–Pugh stages of cirrhosis (24). Consistent with these observations, our study showed that total cholesterol, LDL-cholesterol, HDL-cholesterol, and triglyceride levels were all lower in patients with cirrhosis compared with healthy controls, with statistically significant differences for total cholesterol, LDL-cholesterol, and triglycerides. These findings support the notion that altered hepatic lipid metabolism and reduced cholesterol synthesis in cirrhosis contribute to the relatively hypolipidemic profile observed in these patients.

Lp(a), a molecule structurally similar to LDL-cholesterol, has well-established atherogenic and prothrombotic properties, and elevated levels are associated with increased risk of ischemic heart disease and cerebrovascular events (25,26). Since Lp(a) is primarily synthesized in the liver, its levels are typically reduced in patients with cirrhosis and tend to decline with worsening liver function (27). Several studies have reported progressively lower Lp(a) concentrations with advancing Child–Turcotte–Pugh stages, suggesting that Lp(a) levels may also reflect hepatic synthetic capacity (28,29). In agreement with these findings, we observed significantly lower Lp(a) levels in cirrhotic patients compared with controls (9.5 mg/dL vs. 11.5 mg/dL, $p < 0.005$). This finding supports the hypothesis that impaired hepatic synthesis contributes to the reduced atherogenic lipid profile observed in cirrhosis.

Elevated oxidized LDL levels have been associated with increased coronary lesion burden and higher risk of coronary artery disease (30). Interestingly, previous studies examining oxidized LDL in liver disease are limited, and some reports—particularly in primary biliary cirrhosis—have suggested lower oxidized LDL levels, possibly related to the antioxidant effects of bilirubin (31). In contrast, our study demonstrated markedly higher oxidized LDL levels in patients with cirrhosis compared with healthy controls (588.3 ng/mL vs. 127.9 ng/mL, $p < 0.001$). This finding suggests that despite reduced circulating lipid levels, increased oxidative stress in cirrhosis may contribute to enhanced LDL oxidation, which may represent an alternative pathway influencing vascular alterations in these patients.

Glucose intolerance and diabetes are common metabolic abnormalities in cirrhosis, and hyperinsulinemia and insulin resistance have been reported in up to 80% of affected patients (32). This metabolic disturbance, often referred to as hepatogenous diabetes, differs pathophysiologically from classical type 2 diabetes mellitus and is thought to result from reduced insulin sensitivity in the liver, muscle, and adipose tissue, impaired hepatic insulin degradation, increased pancreatic beta-cell responsiveness to glucose, and the presence of portosystemic shunting (32). Although diabetes may worsen the prognosis of cirrhosis by contributing to hepatic decompensation, it does not appear to increase ischemic cardiovascular events to the same extent observed in the general diabetic population (33). Kim and Choi reported significantly higher fasting insulin and HOMA-IR values in patients with hepatogenous diabetes than in those with type 2 diabetes (34). In line with these reports, our study

demonstrated significantly higher fasting blood glucose, fasting insulin, and HOMA-IR levels in the cirrhosis group compared with controls, indicating increased insulin resistance despite the absence of a parallel increase in CIMT. This finding suggests that, in cirrhosis, insulin resistance may coexist with other metabolic or vascular factors that attenuate the structural expression of subclinical atherosclerosis.

Hemodynamic alterations may also contribute to the distinctive vascular profile of cirrhotic patients. Cirrhosis is characterized by a hyperdynamic circulatory state associated with increased cardiac output, peripheral vasodilation, reduced systemic vascular resistance, and relative arterial hypotension, largely mediated by increased nitric oxide production (3,35). In addition, commonly used medications in cirrhosis, such as diuretics and beta-blockers, may further lower systemic blood pressure. In our cohort, systolic and diastolic blood pressure values did not differ significantly between the cirrhosis and control groups.

Beyond lipid abnormalities and insulin resistance, several inflammatory, hemostatic, and oxidative stress-related markers may influence vascular risk in cirrhosis. Elevated homocysteine, fibrinogen, hsCRP, and Lp(a) have all been recognized as independent risk factors for atherosclerotic vascular disease (36). Studies have reported higher homocysteine levels in cirrhosis (37,38). In our study, however, homocysteine levels were slightly lower in cirrhotic patients and did not differ significantly from controls. In contrast, hsCRP levels were significantly higher in the cirrhosis group, consistent with previous studies showing that low-grade inflammation persists in cirrhosis and may theoretically promote atherogenesis (39,40). Nevertheless, this pro-inflammatory signal was accompanied by markedly lower platelet counts and fibrinogen levels in the cirrhosis group. Elevated fibrinogen has been associated with increased coronary and cerebrovascular risk and with greater CIMT and coronary calcium burden (41,42). In our study, both fibrinogen and platelet counts were significantly lower in cirrhotic patients, supporting the hypothesis that a reduced prothrombotic milieu may counterbalance some of the metabolic and inflammatory drivers of atherosclerosis.

A similar paradox emerged in relation to oxidative stress and bilirubin metabolism. Oxidized LDL is a major mediator of endothelial dysfunction and vascular inflammation and has been linked to increased coronary lesion burden and cardiovascular risk (43). In our study, oxidized LDL levels were markedly higher in cirrhotic patients than in controls, which would ordinarily be expected to favor atherosclerotic progression. However, bilirubin levels—both total and direct—were also significantly higher in the cirrhosis group. Bilirubin has potent antioxidant properties through the biliverdin–bilirubin redox cycle and has been inversely associated with coronary artery disease and myocardial infarction in previous studies (44,45). Thus, our findings suggest that cirrhosis is characterized by the coexistence of both pro-atherogenic and potentially protective influences: increased oxidized LDL, insulin resistance, and hsCRP on the one hand, and decreased total cholesterol, LDL-cholesterol, triglycerides, Lp(a), platelet count, and fibrinogen together with increased bilirubin on the other. Taken together, these data support the interpretation that, in cirrhosis, anti-atherogenic and anti-thrombotic factors may predominate over pro-atherogenic stimuli, which may explain why CIMT was lower in our cirrhotic patients despite the presence of several unfavorable metabolic markers.

This study has several limitations that should be considered when interpreting the findings. First, the sample size was relatively small, which may limit the generalizability of the results and reduce the statistical power for detecting differences in some parameters. Second, the cross-sectional design of the study does not allow causal relationships between cirrhosis-related metabolic alterations and atherosclerosis to be established. Third, although CIMT is a

well-validated surrogate marker of subclinical atherosclerosis, it does not fully reflect the complexity of vascular disease. Additional methods such as coronary artery calcium scoring or arterial stiffness measurements could provide complementary information.

Despite these limitations, the present study provides clinically relevant insights into the vascular profile of patients with cirrhosis. Our findings suggest that cirrhosis is associated with a unique metabolic and hemostatic milieu, characterized by reduced levels of atherogenic lipids, Lp(a), fibrinogen, and platelet counts, together with increased bilirubin levels. These factors may exert protective vascular effects, potentially counterbalancing the pro-atherogenic influences of insulin resistance, inflammation, and elevated oxidized LDL levels. Understanding this complex balance may help clinicians better interpret cardiovascular risk in patients with advanced liver disease.

Conclusion

In conclusion, using carotid intima–media thickness as a marker of subclinical atherosclerosis, our study demonstrated that patients with liver cirrhosis have lower CIMT values compared with healthy controls, despite the presence of several metabolic alterations traditionally associated with cardiovascular risk. The coexistence of both pro- and anti-atherogenic factors in cirrhosis suggests that protective mechanisms related to altered lipid metabolism, thrombocytopenia, hypofibrinogenemia, and increased bilirubin levels may outweigh pro-atherogenic influences, resulting in a relatively attenuated atherosclerotic burden in this population. Further large-scale prospective studies are needed to better clarify the complex relationship between cirrhosis and cardiovascular disease.

Ethical approval

Ethical approval was obtained from the Local Ethics Committee of Trakya University (approval date: April 6, 2011). The study was supported by the Trakya University Scientific Research Projects Unit (TÜBAP; project number: 2011-170).

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: MT, HCÜ; data collection: MT, HCÜ; analysis and interpretation of results: MT, HCÜ; draft manuscript preparation: MT, HCÜ. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Case Report

Metastatic lobular breast carcinoma positive for syndecan-1 mimicking a plasma cell neoplasm: a case report

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ABSTRACT

The metastases of breast cancer to bone marrow can mimic plasma cell neoplasia morphologically due to presence of plasma cell-like neoplastic cells and even positive staining for a carcinoma metastasis with plasma cell marker CD138/ Syndecan-1 may cause confusion in diagnosis. This case report details a 71-year-old female initially suspected of plasma cell myeloma due to hypercalcemia and multiple lytic bone lesions. However, a bone marrow biopsy revealed syndecan-1 positive metastatic lobular breast cancer mimicking a plasma cell neoplasm. Bone marrow aspirate smears and the bone marrow biopsy showed plasmacytoid cells that were strongly positive for syndecan-1, indicating metastatic lobular breast carcinoma. The overexpression of syndecan-1 was a critical marker in identifying the breast cancer cells, emphasizing the diagnostic challenges when syndecan-1 positive metastatic lobular BC presents with plasmacytoid features.

Keywords: bone marrow, lobular breast carcinoma, metastatic breast cancer, plasmacytoid neoplasms, syndecan-1

Introduction

The most frequent cancer in women and the second largest cause of cancer-related deaths globally is BC. Long-term survivors are more likely to experience metastases, even though new treatments have greatly improved patient outcomes. Due to the incredibly complicated pathogenic mechanisms underlying the development and spread of cancer, the classic BC classification method—which evaluates conventional biomarkers and clinical-pathologic features—is unable to account for the variation in each patient's clinical course (1-3).

It is quite uncommon for breast cancer to go to the bone marrow. Invasive ductal carcinoma is the most frequent histology of bone marrow metastases from breast cancer, and it is followed by invasive lobular carcinoma. Fifty to eighty percent of cases had hormone receptors found. Most cases of bone marrow metastasis from cancer cells are asymptomatic. One rare manifestation of metastatic BC is symptomatic bone marrow metastases. To confirm the diagnosis, a bone marrow biopsy was carried out. Therefore, a research area of key relevance is the significance and urgency of identifying target molecules for effective therapy options

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and prognostic markers for bone marrow metastases from BC (4,5).

Increasing evidence suggests that syndecan-1 (CD138), a transmembrane heparan sulfate proteoglycan expressed in epithelial cells, may play a role in breast cancer progression and metastasis. Syndecan-1 is involved in several cellular processes including adhesion, proliferation, and migration. Altered immunohistochemical expression patterns of syndecan-1 in tumor and stromal cells have been associated with different clinical outcomes and may contribute to metastatic dissemination (1,2,6).

In this case report, we present a 71-year-old female patient who underwent a bone marrow biopsy with a prediagnosis of plasma cell myeloma due to the presence of multiple lytic bone lesions on imaging while being examined for hypercalcemia. She was later found to have syndecan-1 positive metastatic lobular breast cancer, which mimicked a plasma cell neoplasm.

Case Report

The diagnostic process in this patient is summarized chronologically for clarity. The patient initially presented with fatigue, back pain, and hip pain, accompanied by hypercalcemia and elevated tumor markers. Radiological imaging revealed multiple lytic bone lesions, raising a strong clinical suspicion of plasma cell myeloma. Bone marrow aspiration and biopsy were subsequently performed and demonstrated plasmacytoid cells with CD138 positivity. However, further immunohistochemical evaluation and radiological correlation revealed a breast lesion, and additional breast-specific markers confirmed the diagnosis of metastatic lobular breast carcinoma involving the bone marrow. This clinical presentation (including hypercalcemia, multiple lytic bone lesions, and plasmacytoid morphology in bone marrow) closely mimicked plasma cell myeloma and therefore represented a significant diagnostic challenge.

A 71-year-old female patient had a medical history of fatigue, back pain, and hip pain that had been present for the past five months. Increases in the calcium concentration (Ca:11.8 mg/dl; NA=8.6-10.6 mg/dL)) and tumor marker CA15-3 level (111U/mL; NA= 0-34.5), CA19.9 level (65.8 U/ml; NA: 0-39) were detected in the serum. There was no cytopenia. Immunoglobulin levels (IgA: 3,04 g/L; NA= 0.7-4, IgG: 12 g/L; NA= 7-16, IgM: 0.99 g/L; NA: 0,4-2,3), creatinine concentration (0,62 mg/dl; NA=0.5-0.9) and erythrocyte sedimentation rate (26 mm/h; NA= <25), thyroid hormone tests (TSH:1.3 ng/dl; NA:0.27-4.20, T3:3.4 ng/dl;NA=2-4.4, T4:1.07 mlU/dl; NA:0.93-1.27), were in normal reference range. In the serum immunoelectrophoresis, the kappa/lambda ratio was intact (0,794g/L) and the monoclonal gammapathy was not detected (IgG:12.3 g/L; NA:7-16g/L, IgA:3.04 g/L; NA:0.7-4, IgM:0.99 g/L; NA:0.4-2.3). On the radiological imaging, there were mottled lucencies, compression fractures and multiple lytic bone lesions, evaluated as a malignant hypercalcemia. Simultaneously, with the preliminary diagnosis of a plasma cell myeloma, the radiological imaging, bone marrow aspiration and tru-cut biopsy were performed on the patient. Aspirated smears showed a large, mature plasma cell-like population with abundant basophilic cytoplasm, round eccentric nuclei, and nucleoli.

In the histological samples of bone marrow tru-biopsy, the plasmacytoid cells with eccentrically located nuclei, which fill the intertrabecular focal area in a nodular fashion, with distinguishable nucleoli and abundant eosinophilic cytoplasm, were observed (Figure 1A, 1B).

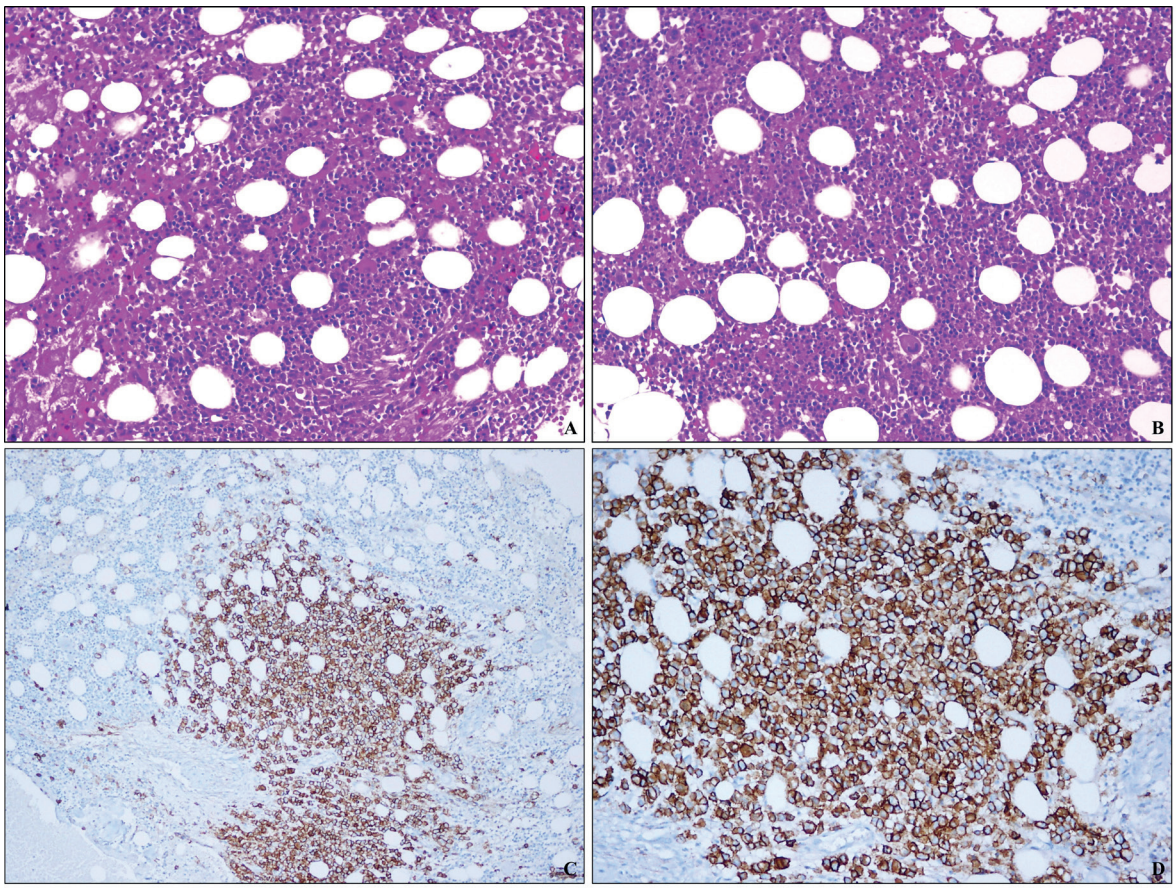

Figure 1. Representative light microscopic images (A, B) showing plasma cell-like neoplastic cells with abundant eosinophilic cytoplasm and eccentric nuclei in the bone marrow (H&E, ×200). Immunohistochemical staining demonstrates strong CD138 positivity in tumor cells (C, D; ×100, ×200).

Following the manufacturer's instructions and standard operating protocols, formalin-fixed, paraffin-embedded tumor tissue was subjected to immunohistochemical indicating using a monoclonal antibody against the CD138 (clone B-A18, 0.10 μg/ml, Cell Marque, Roche, USA), pancytokeratin (clone PCK26, 46.3 μg/ml, Ventana, Roche, USA), mammoglobulin (clone 31A5, 0.05 μg/ml, Cell Marque, Roche, USA), GCDFP-15 (clone EP1582Y, 0.32 μg/ml, Cell Marque, Roche, USA) and GATA-3 (clone L50-823, 1.49 μg/ml, Cell Marque, Roche, USA), cytokeratin 20 (clone SP33, 1.9 μg/ml, Ventana, Roche, USA), TTF-1 (clone SP141, 5,7μg/ml, Ventana, Roche, USA), Napsin A (clone MRQ-60, 1.6 μg/ml, Cell Marque, Roche, USA), PAX-8 (clone MRQ-50, 7 μg/ml, Cell Marque, Roche, USA), estrogen (clone SP1, 1 μg/ml, Ventana, Roche, USA), progesterone (clone 1E2, 1 μg/ml, Ventana, Roche, USA), HER2 (clone 4B5, 6 μg/ml, Ventana, Roche, USA), E-cadherin (clone 36, 0.314 μg/ml, Ventana, Roche, USA) and uroplakin (clone SP73, 0.013 μg/ml, Cell Marque, Roche, USA) antigen. The immunohistochemical panel and diagnostic interpretation are summarized in Table 1 for clarity.

Neoplastic cells observed in the bone marrow biopsy showed a positive reaction with CD138 (Figure 1C, 1D). No staining was observed with both kappa and lambda immunohistochemistry. Simultaneous examination of thorax computed tomography revealed an area of increased density in the subcutaneous tissue showing slightly increased FDG uptake in the retroareolar area of the left breast, and in the

Table 1. Immunohistochemical panel used in the diagnostic work-up

Marker	Clone	Result	Diagnostic implication
CD138 (Syndecan-1)	B-A18	Positive	Plasmacytoid morphology mimicking plasma cell neoplasm
Pancytokeratin	PCK26	Positive	Confirms epithelial origin
Mammoglobulin	31A5	Positive	Supports breast origin
GCDFP-15	EP1582Y	Positive	Supports breast carcinoma
GATA-3	L50-823	Positive	Strong marker of breast origin
CK20	SP33	Negative	Excludes colorectal origin
TTF-1	SP141	Negative	Excludes lung origin
Napsin A	MRQ-60	Negative	Excludes lung adenocarcinoma
PAX-8	MRQ-50	Negative	Excludes renal/gynecologic tumors
Estrogen receptor	SP1	Negative	Triple-negative phenotype
Progesterone receptor	1E2	Negative	Triple-negative phenotype
HER2	4B5	Negative	Triple-negative phenotype
E-cadherin	36	Negative	Consistent with lobular carcinoma
Uroplakin	SP73	Negative	Excludes urothelial origin

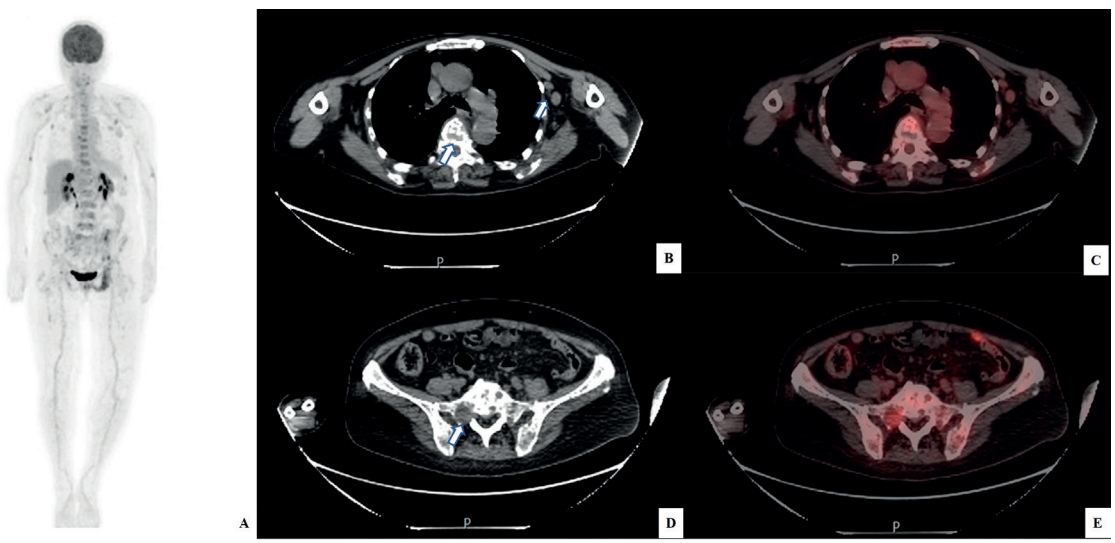

Figure 2. ^{18}F-FDG, PET/CT MIP image (A) revealed multiple FDG-avid metastatic tumor in the skeletal system (B, C); increased FDG uptake was observed in axillary lymph nodes (SUV_{max} 2.8); (D, E) increased FDG uptake was noticed in the right part of the sacrum (SUV_{max} 6.1).

skeletal system, including the sacrum, and in 4-5 lymphadenopathies (Figure 2). The largest of the lymph nodes is 2 cm in diameter and was detected in the left axilla. And while examining the bone marrow biopsy with ultrasound guidance, tru-cut biopsy was collected from the lymph nodes in the left breast and axilla. When a mass was detected in the breast, the immunohistochemistry for pancytokeratin (Figure 3A, 3B), mammoglobulin (Figure 3C), GCDFP-15 (Figure 3D) and GATA-3 were applied to the bone marrow biopsy due to the suspicion of metastasis, resulting in a positive reaction for each staining. The immunohistochemistry for cytokeratin, TTF-1, Napsin A, PAX-8, estrogen, progesterone, HER2, E-cadherin and uroplakin showed negative. Invasive lobular breast carcinoma and breast carcinoma metastasis in the axillary lymph node were detected in the tru-cut biopsy specimens of the patient's breast.

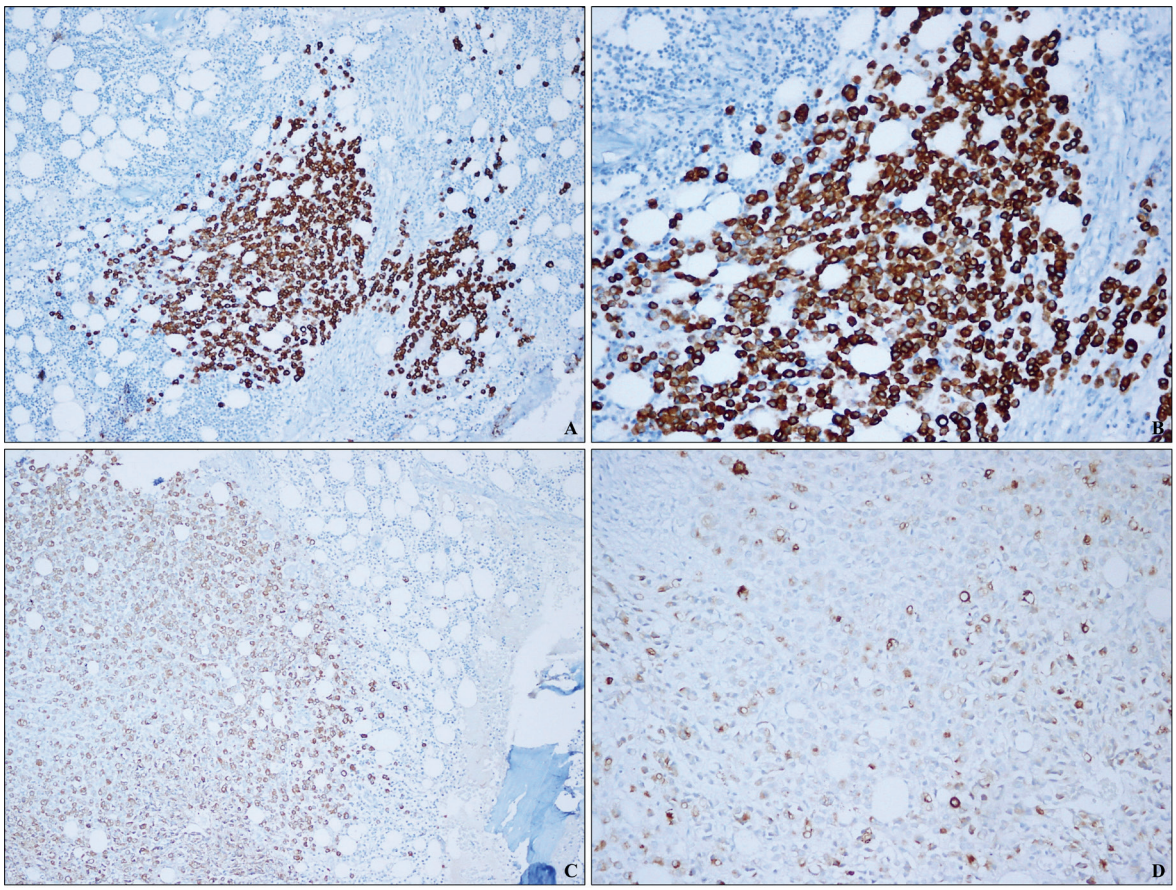

Figure 3. Representative light microscopic images of immunohistochemical staining (A, B) for pancytokeratin detected in tumor cells (x100, x200); (C) for mammoglobulin detected in tumor cells (x100); (D) for GCDFP-15 detected in tumor cells (x200).

In the light of these findings, plasmacytoid-like cells detected in the bone marrow biopsy were evaluated in favor of metastatic breast lobular carcinoma, which stained positively with CD138 and mimicked the plasma cell neoplasia.

Discussion

This case report highlights a unique diagnostic challenge involving a 71-year-old female patient who presented with symptoms of fatigue, back pain, and hip pain over the past five months, accompanied by hypercalcemia and multiple lytic bone lesions. Initially, plasma cell myeloma was suspected due to the radiological findings and the presence of CD138 (syndecan-1) positive cells in the bone marrow biopsy. However, further immunohistochemical analysis revealed that the lesion was a syndecan-1-positive metastatic lobular breast carcinoma mimicking plasma cell neoplasm. This rare presentation underscores the importance of considering metastatic breast cancer (BC), particularly lobular carcinoma, in the differential diagnosis when syndecan-1 is expressed, even when myeloma is strongly suspected.

BC-related deaths are predominantly driven by metastatic dissemination, which closely correlates with the molecular subtype of the originating tumor. Among the various forms of distant spread, bone marrow involvement carries a particularly grave prognosis and markedly restricted survival expectations. This underscores the critical need for reliable biomarkers capable of stratifying patients according to their metastatic

risk, thereby enabling earlier intervention and the development of more targeted therapeutic approaches. Emerging evidence has implicated syndecan-1 as a promising indicator of biologically aggressive BC behavior and unfavorable clinical trajectories (1-3,5). Nevertheless, the available literature predominantly addresses syndecan-1 expression in primary tumor settings, and findings remain inconsistent—likely attributable to heterogeneity in patient cohort selection and variability in methodological approaches. Within the framework of the cancer stem cell model, a distinct cellular population termed cancer-initiating cells is thought to drive both metastatic progression and disease relapse following systemic chemotherapy. Notably, marked upregulation of syndecan-1 has been identified in inflammatory breast cancer, an exceptionally aggressive BC variant (1,2,6). Herein, we report a bone marrow biopsy case initially evaluated under the presumptive diagnosis of myeloma, which was subsequently confirmed as lobular BC metastasis through positive syndecan-1 staining, and contribute this case to the existing literature along with its comprehensive histopathological and clinico-radiological characteristics. Based on our observations, syndecan-1 holds potential as a meaningful prognostic indicator, particularly in triple-negative breast tumors exhibiting an aggressive clinical course.

Primary and metastatic lesions exhibit distinct patterns of immunostaining intensity and location for Syndecan-1. In actuality, the majority of primary BCs exhibit broad cytoplasmic expression; in contrast, all metastatic lesions showed a particular expression pattern in their membrane staining. These results point to a shift in syndecan-1's cellular location during the metastatic phase. This could clarify how this biomarker helps neoplastic cells engraft onto the metastatic site and escape from the original site. Observations in the literature suggest that syndecan-1 plays a part in the intricate interactions between multiple myeloma cells and their bone marrow microenvironment (1,2,4,5). Similarly, in our case, diffuse strong membranous staining was detected in the metastatic lesion. As far as we researched in the English literature, our case was the second case in which this staining was detected in bone marrow localization and the first case reported in our country.

A few studies showed that Syndecan-1 expression in breast carcinoma (6-9) but only one of them (a meeting abstract) reported Syndecan-1 positivity in the bone marrow metastasis of lobular type of breast carcinoma6, which raised the controversy over the morphological similarities with myeloma. In their case report, they showed that the cells were Syndecan-1, cytokeratin 7 and 8/18, mammoglobulin, GATA-3, p120, estrogen receptor and positive (strong, 90%+) positive but cytokeratin 20, TTF-1/ Napsin, PAX-8, uroplakin, E-cadherin, progesterone and HER2 negative (6). Syndecan-1 positivity was observed in our case; however, our patient was triple-negative for estrogen, progesterone, HER2, suggesting a more aggressive type of breast carcinoma.

An additional noteworthy finding in this case is the triple-negative immunophenotype (ER-/PR-/HER2-). Triple-negative breast cancers are generally associated with more aggressive biological behavior, higher metastatic potential, and poorer prognosis compared with hormone receptor–positive tumors. Previous studies have suggested that syndecan-1 overexpression may be more frequently observed in aggressive breast cancer subtypes, including triple-negative tumors (6-9). Therefore, the strong membranous syndecan-1 expression observed in this case may reflect the aggressive metastatic potential of the tumor and may partly explain the unusual bone marrow involvement.

Syndecan-1 expression is downregulated in metastatic lesions, and it localizes selectively to the membrane. These findings corroborate earlier findings in different epithelial cancers and suggest a potential function for syndecan-1 reduction in the metastatic process. Additionally,

there is a correlation between the BC intrinsic subtype of metastatic lesions and the pattern of syndecan-1 expression, with a more diffuse immunostaining pattern in triple negative lesions (with or without hormone receptor positive). Consistent with the strong surface expression, overexpression of syndecan-1 shows promise as a dependable marker for the detection of BC cells. And also, this case report emphasizes that Syndecan-1 positivity in metastatic lobular breast carcinoma with plasmacytoid morphology may be confused with myeloma and definitive diagnosis may be difficult.

Finally, from a practical diagnostic perspective, this case highlights the limitations of relying on CD138 expression alone in the evaluation of plasmacytoid cells within bone marrow biopsies. Although CD138 is widely used as a plasma cell marker, it can also be expressed in epithelial malignancies, including breast carcinoma. Therefore, when plasmacytoid cells are identified in bone marrow specimens, especially in patients presenting with hypercalcemia and lytic bone lesions, a broader immunohistochemical panel should be considered. The inclusion of epithelial markers (such as pancytokeratin) and breast-specific markers (GATA-3, mammaglobin, GCDFP-15) can be crucial for distinguishing metastatic carcinoma from plasma cell neoplasms and preventing potential diagnostic pitfalls.

In conclusion, this case illustrates an important diagnostic pitfall in the evaluation of plasmacytoid cells in bone marrow biopsies. The presence of hypercalcemia, multiple lytic bone lesions, and CD138 positivity may strongly suggest plasma cell myeloma; however, metastatic carcinomas—particularly lobular breast carcinoma—should also be considered in the differential diagnosis. Recognition of this possibility and the use of a comprehensive immunohistochemical panel including epithelial and breast-specific markers are essential to avoid misdiagnosis and ensure appropriate clinical management.

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Ethical approval

This study was conducted according to the Helsinki principles, the patient signed the consent for the participation and nothing offensive was done against the patient's privacy. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the editor of this journal.

Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: BYB; data collection: BYB, EBT, SI; analysis and interpretation of results: BYB, NZC draft manuscript preparation: BYB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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