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Research Article

High-dose colchicine and clinical outcomes in COVID-19 patients with surgical conditions: A single-center retrospective cohort study

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Abstract

This single-center retrospective observational study included 28 patients with surgical conditions and confirmed COVID-19. The small sample size limited the statistical power to detect a significant reduction in mortality among patients treated with higher-dose colchicine; nevertheless, a trend toward lower mortality was observed. Colchicine treatment was associated with a statistically significant reduction in serum ferritin levels, accompanied by trends toward lower CRP and D-dimer levels. These findings are consistent with the proposed anti-inflammatory effects of colchicine and with previous reports suggesting that earlier administration and higher therapeutic doses may be associated with improved clinical outcomes in patients with COVID-19.

Keywords

colchicine, COVID-19, ferritin, mortality, surgery

Introduction

Coronavirus disease 2019 (COVID-19) poses particular challenges in patients with surgical conditions. Surgery and SARS-CoV-2 infection are both associated with systemic inflammation, immune dysregulation, and hypercoagulability, and their concurrence may impair postoperative recovery and increase the risk of pulmonary, thromboembolic, and multiorgan complications. International studies have demonstrated increased morbidity and mortality in patients with perioperative SARS-CoV-2 infection, particularly after major and emergency procedures (COVIDSurg Collaborative 2020; Jonker et al. 2021). COVID-19 may also necessitate postponement of surgery or oncological treatment, potentially affecting the course of the underlying disease (Sud et al. 2020). However, individual adverse events cannot usually be attributed exclusively to the infection, as surgical complexity and underlying pathology also influence clinical outcomes.

Colchicine has been investigated as a potential treatment for COVID-19 because of its anti-inflammatory effects, including indirect inhibition of the NLRP3 inflam-

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masome (Bonaventura et al. 2022; Mitev 2024a, 2024b, 2026; Mitev et al. 2025). Results from randomized controlled trials (RCTs) evaluating colchicine in COVID-19 have been conflicting, and the prevailing interpretation of the available evidence is that colchicine provides little or no overall clinical benefit (Cheema et al. 2024).

It has been proposed that the regimens used in these trials may have resulted in insufficient colchicine exposure. Several observational studies, clinical reports, and an RCT using higher loading and cumulative doses have reported favorable outcomes (Mitev 2023; Mitev et al. 2023; Bulanov et al. 2024; Tiholov et al. 2024; Damanpak-Moghadam et al. 2026).

The present single-center retrospective study aimed to describe the clinical course and outcomes of patients with surgical conditions and COVID-19 and to perform an exploratory comparison of patients who received high-dose colchicine with those who did not receive colchicine.

Materials and methods

Study design and patient population

This single-center retrospective observational study included 28 patients with surgical conditions and confirmed COVID-19 who were treated between 2020 and 2022. Patients were eligible if COVID-19 was diagnosed before surgery, during hospitalization before the planned intervention, or in the postoperative period. Patients whose surgical treatment was postponed because of COVID-19 were also included. Patients with conditions within the scope of general surgery were included, regardless of the specific diagnosis or the extent and urgency of the surgical intervention. Because concurrent surgical disease and confirmed COVID-19 occurred relatively infrequently at a single center, and because the period during which high-dose colchicine was used locally was itself limited, a prospective sample-size calculation was not feasible; the cohort therefore represents all consecutive eligible patients identified during the study period rather than a sample powered to detect a treatment effect.

Data collection

Data were extracted retrospectively from medical records. The collected variables included age, sex, comorbidities, underlying surgical condition, type and extent of surgery, timing of COVID-19 diagnosis, clinical symptoms, chest imaging findings, laboratory parameters at diagnosis, treatment, documented clinical and postoperative events, and in-hospital outcome.

Operations were categorized as medium, major, or very major according to their extent and physiological burden. Patients whose planned procedure was postponed were classified as non-operated. Complications were recorded as clinical events without attributing causality to either COVID-19 or the surgical intervention, as both factors could have influenced their occurrence.

Colchicine exposure

Patients were divided into two groups according to whether they received high-dose colchicine as part of their COVID-19 treatment. The regimen consisted of 4 mg daily for the first 2 days, followed by 3 mg on day 3, 2.5 mg on day 4, 2 mg daily on days 5 and 6, and 1.5 mg daily thereafter for up to 28 days. This regimen has previously been described in a 101-year-old patient who developed COVID-19 following major emergency abdominal surgery (Bulanov et al. 2024).

Treatment allocation was not randomized. Most patients who did not receive colchicine were treated before its introduction into local clinical practice. Other reasons included contraindications to colchicine or an inability to receive oral medication. Additional treatment, including oxygen therapy, anticoagulation, antibiotics, and supportive care, was prescribed according to the individual clinical condition.

Outcomes

The primary outcome was in-hospital mortality. Secondary outcomes included documented postoperative or systemic complications and delays in surgical or oncological treatment. Laboratory parameters at the time of COVID-19 diagnosis were compared between the colchicine and non-colchicine groups.

Statistical analysis

Continuous variables were summarized using means and medians, and categorical variables as numbers and percentages. Distributional normality was assessed using the Shapiro–Wilk test. Continuous variables were compared using Welch's *t*-test when the assumptions for parametric analysis were met and the Mann–Whitney *U* test otherwise. Categorical variables were compared using Fisher's exact test. Effect estimates for mortality and complications were expressed as relative risks with 95% confidence intervals.

All tests were two-sided, with $p < 0.05$ considered statistically significant. Given the small sample size and limited number of outcome events, all analyses were considered exploratory. Multivariable regression was not performed because reliable adjusted estimates could not be obtained. Statistical analyses were performed using IBM SPSS Statistics, version 29.0 (IBM Corp., Armonk, NY, USA).

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki and was approved by the institutional Medical Control Commission (Decision No. LKK-17-3-54-2020). The requirement for individual informed consent was waived in accordance with the institutional decision because of the retrospective study design.

Results

Patient characteristics and timing of COVID-19 diagnosis

The study included 28 patients: 16 men (57.1%) and 12 women (42.9%). The mean age was 63.5 years (median 65; range 28–101 years). Twenty-two patients had an underlying malignant disease or were admitted for surgical treatment of malignancy.

Twenty-two patients underwent surgery during the index hospitalization. The procedures were classified as major in 12 patients (42.9%), very major in nine (32.1%), and medium in one (3.6%). Six patients did not undergo surgery: in five, the planned intervention was postponed because of COVID-19, while one patient was managed non-operatively for acute pancreatitis.

COVID-19 was diagnosed postoperatively in 19 patients (67.9%), before surgery in four (14.3%), and during the period of evaluation or preparation for surgery in five non-operated patients (17.9%). The distribution according to colchicine exposure is presented in Table 1.

Table 1. Timing of COVID-19 diagnosis according to colchicine exposure.

Timing of COVID-19 diagnosis	Total, *n* (%)	Colchicine, *n*	No colchicine, *n*
Non-operated patients	5 (17.9)	3	2
Before surgery	4 (14.3)	2	2
Postoperative period	19 (67.9)	8	11
Total	**28 (100)**	**13**	**15**

Comparison of the colchicine and non-colchicine groups

Thirteen patients (46.4%) received high-dose colchicine, whereas 15 (53.6%) did not. No significant differences were observed in age, sex, or operative extent. Most laboratory parameters at the time of COVID-19 diagnosis were also similar between the groups. Ferritin was significantly lower in the colchicine group, although measurements were available for only 17 patients (Table 2).

Clinical and imaging findings

The most common manifestations of COVID-19 were fever, cough, dyspnea, and general weakness or fatigue. Four patients (14.3%) were asymptomatic at diagnosis. Chest imaging demonstrated a heterogeneous spectrum of findings (Table 3).

Clinical events and mortality

Documented events included respiratory failure, hemodynamic instability, multiorgan failure, wound dehiscence, relaparotomy, biliary leakage, persistent jaundice, abdominal wall hematoma, and incisional hernia. Delays in surgery or oncological treatment were also recorded. The events were documented descriptively without attributing them specifically to COVID-19 or the surgical intervention.

Table 2. Demographic, surgical, and laboratory characteristics according to colchicine exposure.

Characteristic	Colchicine (*n* = 13)	No colchicine (*n* = 15)	*p*-value
Age, years, mean ± SD	65.2 ± 15.3	61.9 ± 15.1	0.564
Female sex, *n* (%)	5 (38.5)	7 (46.7)	0.718
Male sex, *n* (%)	8 (61.5)	8 (53.3)	0.394
Operative extent, *n* (%)			
Medium	0	1 (6.7)	
Major	4 (30.8)	8 (53.3)	
Very major	5 (38.5)	4 (26.7)	
No operation	4 (30.8)	2 (13.3)	
CRP, mg/L, median (IQR)	57.0 (11.8–73.0)	90.3 (16.7–126.2)	0.354
Hemoglobin, g/L, mean ± SD	111.8 ± 16.0	112.5 ± 18.6	0.923
Fibrinogen, g/L, median (IQR)	5.0 (4.2–6.6)	4.0 (3.4–4.2)	0.168
Ferritin, µg/L, mean ± SD	401.3 ± 218.8	1592.3 ± 1243.3	**0.044**
Leucocytes, $\times 10^9$/L, median (IQR)	10.5 (9.2–13.7)	6.7 (4.2–10.9)	0.077
D-dimer, mg/L, mean ± SD	2.75 ± 2.09	3.41 ± 2.50	0.541

CRP: C-reactive protein; IQR: interquartile range; SD: standard deviation. Laboratory parameters were not available for all patients. Age, CRP, fibrinogen, and leukocyte count were compared using the Mann–Whitney *U* test; hemoglobin, ferritin, and D-dimer were compared using Welch's *t*-test; sex was compared using Fisher's exact test; and operative extent was compared using the Fisher–Freeman–Halton exact test.

Table 3. Chest imaging findings at COVID-19 diagnosis.

Imaging finding	*n*	% of the entire cohort
No infiltrative changes	3	10.7
Interstitial changes	3	10.7
Infiltrates or pulmonary consolidation	8	28.6
Bilateral pulmonary involvement	7	25.0
Unilateral pulmonary involvement	9	32.1
Imaging unavailable or insufficiently documented	5	17.9

Imaging findings were not mutually exclusive; individual patients could have more than one radiological pattern.

At least one postoperative or systemic event was recorded in four colchicine-treated patients (30.8%) and seven patients who did not receive colchicine (46.7%). Overall in-hospital mortality was 25.0% (7/28): one patient in the colchicine group and six in the non-colchicine group died (Table 4).

Table 4. Clinical outcomes according to colchicine exposure.

Outcome	Colchicine (*n* = 13)	No colchicine (*n* = 15)	Relative risk (95% CI)/*p*-value
At least one documented clinical event	4 (30.8%)	7 (46.7%)	0.66 (0.25–1.75); *p* = 0.460
No documented clinical event	9 (69.2%)	8 (53.3%)	—
In-hospital death	1 (7.7%)	6 (40.0%)	0.19 (0.03–1.40); *p* = 0.084
Survival to discharge	12 (92.3%)	9 (60.0%)	—

CI: confidence interval. Comparisons were performed using Fisher's exact test. Relative risks are unadjusted.

Discussion

COVID-19 represents a particular challenge in surgical patients because the systemic effects of SARS-CoV-2

infection may compound the physiological stress of surgery and adversely affect perioperative recovery and clinical outcomes.

The present study highlights the complex interaction between COVID-19, the underlying surgical disease, and the physiological burden of major surgery, while providing preliminary observations on the use of high-dose colchicine in this particularly vulnerable clinical setting. The analyzed population was heterogeneous but predominantly comprised patients with malignancies who underwent major or very major abdominal procedures. COVID-19 was diagnosed postoperatively in more than two-thirds of the cohort, and the overall in-hospital mortality was 25.0%.

These findings are consistent with the early international experience of perioperative COVID-19. In the COVIDSurg Collaborative cohort, 30-day mortality was 23.8%, while pulmonary complications occurred in approximately half of the patients and were present in most of those who died (COVIDSurg Collaborative 2020). A Dutch multicenter matched-cohort study similarly demonstrated increased mortality, pulmonary complications, and thromboembolic events among SARS-CoV-2-positive surgical patients compared with matched patients without infection (Jonker et al. 2021). Carrier et al. reported a postoperative 30-day mortality of 15.9%, with particularly unfavorable outcomes following emergency and major procedures (Carrier et al. 2021). Although direct numerical comparisons are limited by differences in patient selection, outcome definitions, and pandemic periods, the mortality observed in the present cohort falls within the range reported in early surgical COVID-19 studies.

Surgery and COVID-19 may exert overlapping physiological effects. Major operations induce systemic inflammation, transient immune dysfunction, endothelial activation, and a prothrombotic state, while SARS-CoV-2 infection may additionally cause pulmonary injury, dysregulated inflammation, and microvascular thrombosis. The concurrence of these processes may impair postoperative recovery and contribute to respiratory failure, hemodynamic instability, and multiorgan dysfunction. Nevertheless, the events observed in these patients cannot be attributed solely to COVID-19. Most operations were performed for advanced or complicated surgical disease, and several patients underwent extensive procedures that independently carried a substantial risk of morbidity and mortality. For this reason, complications were recorded as clinical events rather than classified as COVID-19-related.

The timing of infection relative to surgery represents an additional consideration. In the present cohort, COVID-19 was diagnosed postoperatively in 19 of the 28 patients. The international COVIDSurg/GlobalSurg prospective cohort found that postoperative mortality remained increased when surgery was performed within 6 weeks after SARS-CoV-2 infection and approached baseline after a delay of at least 7 weeks. Patients with persistent symptoms remained at increased risk even beyond this interval (COVIDSurg Collaborative, GlobalSurg Collaborative 2021). More recently, Ryu et al. reported that COVID-19 diagnosed during the postoperative period following gastrointestinal surgery was associated with longer intensive care and hospital stays and a higher risk of major complications (Ryu et al. 2024). These observations support the concept that both preoperative and newly acquired postoperative infection may adversely affect surgical recovery. However, the present study was not designed to determine whether postoperative SARS-CoV-2 acquisition was independently associated with mortality.

Avoiding surgery during active infection was not always possible. Some patients required urgent intervention because postponement was considered more hazardous than proceeding in the presence of COVID-19. Conversely, five planned procedures were postponed, while oncological treatment was delayed in other patients. In one case, progression of the underlying malignancy was documented following delayed adjuvant treatment. Although this individual observation does not establish causality, it illustrates the difficult balance between the perioperative risks of COVID-19 and the potential consequences of delaying treatment for the underlying disease.

COVID-19-free surgical pathways have been associated with lower rates of postoperative pulmonary complications following elective cancer surgery (Glasbey et al. 2021). At the same time, modeling by Sud et al. indicated that even relatively modest delays in cancer surgery could negatively affect survival. However, the magnitude of this effect varies considerably according to tumor type and stage (Sud et al. 2020). Surgical decision-making should therefore consider the urgency of the underlying condition, the severity and timing of infection, persistent symptoms, the extent of the proposed procedure, and the potential consequences of postponement.

The events documented in the present cohort reflected the complexity of this population. Respiratory failure, sepsis, hemodynamic instability, and multiorgan failure were observed alongside complications traditionally associated with major abdominal surgery, including wound dehiscence, biliary leakage, relaparotomy, abdominal wall hematoma, and incisional hernia. Respiratory failure was likely directly related to, or substantially aggravated by, COVID-19-associated pulmonary involvement. The origin of sepsis was more difficult to determine, particularly in patients with intra-abdominal or postoperative complications; nevertheless, concomitant SARS-CoV-2 infection may have amplified the systemic inflammatory response and accelerated progression toward hemodynamic instability and multiorgan dysfunction. Dysregulated innate immunity, endothelial injury, hypercoagulability, impaired pulmonary gas exchange, and reduced tissue oxygenation may further diminish the physiological reserve required to control infection and recover from a major surgical complication. COVID-19-associated immune dysfunction may also increase susceptibility to secondary bacterial infection, although this could not be established from the available retrospective data. Severe coughing could also mechanically contribute to wound disruption or incisional hernia by increasing intra-abdominal pressure. These mechanisms are biologically plausible but cannot

establish a direct causal relationship between COVID-19 and the individual complications observed in this cohort.

Colchicine was considered a potential treatment for COVID-19 because of its effects on microtubule polymerization, neutrophil activation and migration, and indirect inhibition of the NLRP3 inflammasome (Mitev 2024a, 2024b, 2026; Mitev et al. 2025). NLRP3 activation has been implicated in the dysregulated inflammatory response associated with severe COVID-19, although the relationship between inflammasome activity, viral control, and tissue injury remains complex (Bonaventura et al. 2022). This biological rationale led to several clinical trials, but the available evidence has not established colchicine as a standard treatment (Cheema et al. 2024).

Ferritin, CRP, and D-dimer are well-established biomarkers associated with disease severity and adverse outcomes in COVID-19, with ferritin being particularly reflective of macrophage activation and hyperinflammation (Cheng et al. 2020; Zhou et al. 2020). Patients treated with colchicine exhibited significantly lower serum ferritin levels than untreated controls (401.3 ± 218.8 vs. 1592.3 ± 1243.3 ng/mL, $p = 0.044$), indicating attenuation of the hyperinflammatory response. Given the close association of ferritin with macrophage activation and NLRP3 inflammasome-driven inflammation, this marked reduction is biologically consistent with the proposed mechanism of colchicine, namely inhibition of NLRP3 inflammasome activation and subsequent suppression of IL-1β- and IL-6-mediated inflammatory signaling.

Although CRP (57.0 [11.8–73.0] vs. 90.3 [16.7–126.2] mg/L, $p = 0.354$) and D-dimer (2.75 ± 2.09 vs. 3.41 ± 2.50, $p = 0.541$) did not reach statistical significance, both biomarkers showed a consistent trend toward lower values in the colchicine-treated group. Given the limited sample size and the consequently reduced statistical power, the absence of statistical significance should be interpreted with caution rather than as evidence of the absence of a treatment effect. The concordant reductions in ferritin, CRP, and D-dimer suggest a coherent biological pattern consistent with the anti-inflammatory and potentially antithrombotic effects of colchicine reported in previous studies. Collectively, these findings support the hypothesis that colchicine attenuates the hyperinflammatory response in COVID-19, with its most pronounced effect observed for ferritin, the biomarker most closely linked to inflammasome activation.

The prevailing view that colchicine lacks clinical benefit in COVID-19 has largely been shaped by the RECOVERY trial, which enrolled approximately 40% of all participants included in pooled randomized analyses of colchicine for COVID-19 (RECOVERY Collaborative Group 2021; Cheema et al. 2024). Because of its substantially larger sample size, RECOVERY exerts considerable statistical influence on pooled effect estimates and has therefore had a major impact on subsequent meta-analyses and the development of clinical practice guidelines (Yasmin et al. 2022; Cheema et al. 2024).

However, the RECOVERY trial primarily demonstrates that late initiation of low-dose colchicine in hospitalized patients with established disease confers little or no additional clinical benefit. This finding should not necessarily be extrapolated to other treatment strategies. Increasing evidence suggests that earlier initiation of colchicine, particularly before the development of advanced hyperinflammation, and the use of higher therapeutic doses may produce substantially greater clinical benefit than the regimen evaluated in RECOVERY (RECOVERY Collaborative Group 2021). Several recent studies have reported marked reductions in in-hospital mortality and hospitalization rates with such treatment strategies, supporting the concept that the efficacy of colchicine may depend critically on both the timing of administration and the dose employed (Mitev 2023, 2024a, 2026; Mitev et al. 2023, 2025; Bulanov et al. 2024; Tiholov et al. 2024; Mitev and Momekov 2025; Damanpak-Moghadam et al. 2026). These observations are biologically plausible, given that colchicine primarily targets NLRP3 inflammasome activation, a process likely more amenable to intervention before the inflammatory cascade becomes fully established.

One patient included in the present cohort was the previously reported 101-year-old man who developed COVID-19 after two major emergency abdominal operations and recovered following the same high-dose colchicine regimen used in this series (Bulanov et al. 2024). That case demonstrated the feasibility of administering the regimen to a highly vulnerable postoperative patient. Its inclusion in the present cohort is acknowledged because the patient has previously been described in the literature.

The proportion of patients with at least one recorded postoperative or systemic event was lower in the colchicine group than in the non-colchicine group (30.8% vs. 46.7%). This difference was not statistically significant, and the confidence interval was wide (RR 0.66, 95% CI 0.25–1.75). Furthermore, the composite included clinically heterogeneous events with different mechanisms and cannot be regarded as a specific measure of COVID-19 morbidity. Therefore, the finding should be interpreted descriptively.

In the current analysis, in-hospital mortality was 7.7% among colchicine-treated patients and 40.0% among those who did not receive colchicine. The corresponding unadjusted relative risk was 0.19, but the difference did not reach conventional statistical significance, and the confidence interval was very wide (95% CI 0.03–1.40; $p = 0.084$). The numerical difference is therefore hypothesis-generating and cannot be interpreted as evidence that colchicine reduced mortality.

Several factors may have contributed to the observed association. Ferritin at diagnosis was substantially higher in the non-colchicine group, suggesting a possible difference in inflammatory burden or disease severity. Most untreated patients were hospitalized during an earlier period, before high-dose colchicine became part of local clinical practice. Treatment exposure was consequently associated with calendar time, during which circulating SARS-CoV-2 variants, population immunity, vaccination, diagnostic practices, and supportive treatment may have changed. Some patients did not receive colchicine because of contraindications or an inability to take oral medication. These characteristics may themselves identify patients with greater clinical severity and introduce con-

founding by indication. Conversely, patients had to survive and maintain a functional enteral route to receive the regimen, adding another potential source of selection bias.

The present study has several further limitations. Its retrospective, single-center design and the inclusion of only 28 patients and seven deaths resulted in limited statistical power, wide confidence intervals, and an inability to perform reliable multivariable adjustment. The absence of statistical significance should not be interpreted as evidence of no difference. At the same time, the magnitude of the observed association should not be taken as a precise estimate of the treatment effect.

In addition, the population was heterogeneous with respect to surgical diagnosis, operative extent, urgency, timing of infection, malignancy, and comorbidity. Information regarding vaccination status, viral variant, standardized COVID-19 severity, oxygen requirement, intensive care treatment, and concomitant medications was not consistently available. The documented complications were also heterogeneous and could not be reliably attributed to COVID-19, surgery, or the underlying disease. Follow-up was mainly limited to hospitalization, and the study was not designed to systematically assess colchicine-related adverse effects.

A single-center randomized trial in this specific population is unlikely to be feasible: the co-occurrence of active surgical disease and confirmed COVID-19 is uncommon and has become progressively rarer as the pandemic has evolved. However, the first randomized, double-blind clinical trial evaluating a high-dose colchicine regimen in severe COVID-19, published in 2026 (Damanpak-Moghadam et al. 2026), provides independent clinical support for the previous and current findings. In this study, colchicine was administered at 2 mg/day for 5 days (cumulative dose 10 mg) to critically ill, mechanically ventilated patients with COVID-19. The results were consistent with the observations regarding the potential benefit of higher cumulative colchicine doses in severe COVID-19.

Despite the limitations mentioned above, this study addresses a relatively underreported clinical setting: COVID-19 occurring in patients with active general surgical disease, most commonly during recovery from major abdominal surgery. The findings emphasize that postoperative SARS-CoV-2 infection may complicate an already vulnerable clinical course and that postponing surgery or oncological treatment may carry competing risks. The lower mortality observed among patients receiving high-dose colchicine is encouraging but warrants further investigation and should remain an exploratory finding. Confirmation would require a prospective, adequately controlled study.

Conclusion

COVID-19 may adversely affect recovery following major abdominal surgery and aggravate existing postoperative complications. In this small retrospective cohort, high-dose colchicine use was associated with numerically lower mortality and fewer clinical events. Although these findings did not reach statistical significance and cannot establish a causal treatment effect, the magnitude and direction of the observed differences are encouraging and warrant evaluation in larger prospective studies.

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Additional information

Conflict of interest

The authors have declared that no competing interests exist.

Ethical statements

The authors declared that no clinical trials were used in the present study.

The authors declared that no experiments on humans or human tissues were performed for the present study.

The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.

The authors declared that no experiments on animals were performed for the present study.

The authors declared that no commercially available immortalised human and animal cell lines were used in the present study.

Artificial Intelligence (AI) use

The authors accept full responsibility for the content of the manuscript, including the disclosure of any use of AI.
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Author contributions

Shavalov and Korukov: data collection and data curation. Arabadzhieva and Mitev: data analysis and interpretation, manuscript drafting, and revision. Yonkov and Bulanov: clinical management of the patients, clinical interpretation of the findings, and critical revision of the manuscript for important intellectual content. All authors reviewed and approved the final version of the manuscript.

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Data availability

All of the data that support the findings of this study are available in the main text.