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Protective Effect of Oral Antidiabetic Medicines Against Mechanical Ileus Development and Its Impact on Metastatic Colon Cancer Survival

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Abstract

Background

Previous studies have shown that the use of metformin improves overall survival (OS) in colorectal cancer. Furthermore, previous studies have shown that ileus is a poor prognostic factor in colorectal cancer. This study examined the role of metformin and other oral antidiabetic drugs in the development of ileus and their contribution to OS in colorectal cancer, as well as the effect of ileus on OS in metastatic colorectal cancer.

Materials and Methods

In this retrospective study, all patients with metastatic colon cancer followed at the Oncology Clinic of Aydın Adnan Menderes University between 2020 and 2025 were retrospectively screened. Patients who developed ileus and those who did not were compared to examine the potential effect of OAD use on ileus development. Additionally, the impact of the presence of ileus on disease prognosis was evaluated. Multivariate binary logistic regression models were constructed to adjust for clinical confounders.

Results

The mean age of the 244 patients included in the study was 66.19 ± 12.49 years. All patients were clinically Stage IV (100%). OAD use was detected in 20.5% ($n = 50$) of the patients, with metformin being the most common (18.9%, $n = 46$). Ileus developed in 13.5% ($n = 33$) of the cohort. In the comparative analysis, the presence of diabetes mellitus ($p = 0.027$), general OAD use ($p = 0.027$), and specifically metformin use ($p = 0.012$) were significantly higher in patients who did not develop ileus. In the multivariate logistic regression analysis, general OAD use was identified as an independent protective factor reducing the risk of ileus (aOR: 0.214, 95% CI: 0.049–0.935, $p = 0.040$). Similarly, metformin use independently reduced the odds of ileus (aOR: 0.112, 95% CI: 0.015–0.847, $p = 0.034$). Conversely, the presence of lung metastasis was associated with a 2.47-fold independent increase in ileus risk (aOR: 2.475, 95% CI: 1.138–5.383, $p = 0.022$). Kaplan-Meier analysis revealed that the median OS was significantly longer in patients who developed ileus compared to those who did not (24.60 months vs. 17.43 months, $p = 0.046$).

Conclusion

Metformin and general OAD use significantly and independently reduce the risk of ileus development in patients with metastatic colon cancer. Contrary to conventional expectations, metastatic patients presenting with ileus may achieve longer survival times, potentially due to timely palliative surgical interventions that reduce tumor burden.

Introduction

Colon cancer is the third most common type of cancer worldwide (9.9%) (1). Factors contributing to the aetiology of colorectal cancer include dietary factors such as low intake of fruit, vegetables and fibre, and high intake of red meat, saturated fats, caffeine and alcohol; lifestyle factors such as lack of exercise, smoking and obesity; side effects of certain medical or surgical interventions such as pelvic radiotherapy and cholecystectomy; and comorbidities such as diabetes mellitus, acromegaly and inflammatory bowel diseases (2). Some studies have shown that diabetes mellitus increases mortality in patients with colorectal cancer.

There are 530 million people diagnosed with diabetes worldwide (3). Metformin is the most commonly used oral antidiabetic agent in first-line treatment for diabetes or in combination with insulin therapy. Previous studies have demonstrated the protective effect of metformin against colon cancer.

Ileus is observed in 29 per cent of patients with colon cancer (4). Of these, 77 per cent occur in the left colon (5). In cases of colon cancer where acute ileus develops, emergency surgery to perform a colostomy is of critical importance for patient survival.

In addition to metformin's gastrointestinal side effects, such as nausea, vomiting and diarrhoea, its ability to alter bowel motility via mechanisms affecting gastric emptying suggests that this agent may have a protective effect against the development of ileus.

This retrospective study aimed to evaluate the relationship between the use of metformin and other oral antidiabetics and the development of ileus in patients co-diagnosed with metastatic colon cancer and Type 2 Diabetes followed at the Oncology Clinic of Aydın Adnan Menderes University. Furthermore, we aimed to assess the prognostic impact of this condition on overall survival, as well as the effect of ileus on overall survival in all metastatic colon cancer patients, regardless of diabetes status.

Materials and Methods

Study Design and Patient Selection

In this retrospective study, all patients followed with a diagnosis of metastatic colon cancer at the Oncology Clinic of Aydın Adnan Menderes University between 2020 and 2025 were retrospectively screened.

Evaluated Parameters

Patients who developed ileus and those who did not were compared to investigate the potential effect of oral antidiabetic use on ileus development. Additionally, the impact of the presence of ileus on disease prognosis was evaluated.

Statistical Methods

Descriptive statistics were expressed as mean, standard deviation, median, minimum, maximum, frequency, and percentage values. The distribution of variables was evaluated using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Mann-Whitney U test was utilized to analyze continuous independent data with a non-normal distribution. Categorical independent data were analyzed using the Chi-square test, or Fisher's exact test when Chi-square test assumptions were not met. Survival analysis was performed using the Kaplan-Meier method with the log-rank test.

To determine the independent effects of clinical and demographic variables associated with ileus development or carrying potential confounding effects (age, ECOG performance score, primary tumor localization, metastasis sites), **Multivariate Binary Logistic Regression Analysis** was performed. Along with the clinical baseline model, a sensitivity model including variables with a univariate $p < 0.20$ and a secondary model evaluating the independent effect of metformin were constructed. Results were presented as Adjusted Odds Ratios (aOR) and 95% Confidence Intervals (CI). Model fit was evaluated using Nagelkerke R^2 and the area under the ROC curve (AUC). All statistical analyses were performed using SPSS version 28.0, and a p-value < 0.05 was considered statistically significant.

Results

The mean age of the patients included in the study was calculated as 66.19 ± 12.49 years (median: 68, min-max: 1-92). When the general performance status of the patients was evaluated according to the ECOG scale, the vast majority were in the ECOG I group (73%, $n = 178$), followed by ECOG II (14.3%, $n = 35$) and ECOG 0 (8.2%, $n = 20$). Investigation of the metastatic spread profile revealed that liver involvement was the most frequent (75.4%, $n = 184$), lymph node metastasis was the second most common (70.9%, $n = 173$), and lung metastasis was the third most frequent (42.2%, $n = 103$). Anterior abdominal wall/peritoneal metastases were detected in 30.3% ($n = 74$) of the patients.

Regarding the anatomical localization of the primary tumor, the sigmoid colon ranked first with 82% ($n = 200$), followed by the cecum (13.1%, $n = 32$) and the transversum (3.7%, $n = 9$). In histopathological characterization, 98% ($n = 239$) of the cases were diagnosed with adenocarcinoma, while a small group of 2% ($n = 5$) exhibited neuroendocrine differentiation. All patients in the study population were clinically at Stage IV (100%, $n = 244$). Regarding pathological staging details, pTIII was the most dense group (60.4%, $n = 67$), followed by pTIVA (20.7%, $n = 23$) and pTIVB (8.1%, $n = 9$). In pN staging indicating lymph node involvement, the pN0 group (24.3%, $n = 27$) was followed by pNIIB (19.8%, $n = 22$) and pNIB (14.4%, $n = 16$).

In clinical management, 20.5% ($n = 50$) of the patients were found to use oral antidiabetics (OAD). In this group, metformin use ranked first with 18.9% ($n = 46$), while thiazolidinediones (5.3%, $n = 13$) and DPP-4 inhibitors (5.3%, $n = 13$) shared the second place with equal rates. Additionally, an ileus clinical picture developed in 13.5% ($n = 33$) of the patients. At the end of the follow-up period, 63.1% ($n = 154$) of the

cohort was reported as deceased (ex). The baseline demographic and clinicopathological characteristics of the cohort are summarized in Table 1.

Table 1. Analysis of the demographic and clinical-pathological parameters of the study group

		n(%)
Age	**Mean ± SD**	66,19±12,49
	Median (min–max)	68(1-92)
ECOG Score	**0**	20(8,2)
	I	178(73)
	II	35(14,3)
	III	10(4,1)
	IV	1(0,4)
Liver Metastases		184(75,4)
Skeletal Metastases		32(13,1)
Anterior Abdominal Wall Metastases		74(30,3)
Lymph Node Metastases		173(70,9)
Lung Metastases		103(42,2)
Localisation	**Sigmoid**	200(82)
	Caecum	32(13,1)
	Transverse	9(3,7)
	Hepatic flexure	2(0,8)
	Appendix	1(0,4)
Tumour Characteristics	**Adenocarcinoma**	239(98)
	Neuroendocrine	5(2)
Klinik Evre	**Evre IV**	244(100)
pT Stage	**II**	7(6,3)
	III	67(60,4)
	IV	5(4,5)
	IVA	23(20,7)
	IVB	9(8,1)
pN Stage	**0**	27(24,3)
	I	13(11,7)
	IA	9(8,1)

	IB	16(14,4)
	IC	4(3,6)
	II	6(5,4)
	IIA	14(12,6)
	IIB	22(19,8)
Ileus		33(13,5)
Diagnosis of diabetes		50 (20,5)
Use of OADs		50(20,5)
Metformin		46(18,9)
Use of other OADs		31(12,7)
Exenatide		1(0,4)
Sulfonylurea		12(4,9)
Thiazolidinedione		13(5,3)
SGLT-2 inhibitor		1(0,4)
DPP-4 inhibitor		13(5,3)
Exitus		154(63,1)

In the comparative analysis between patients who developed ileus and those who did not, no statistically significant differences were found between the groups regarding age, ECOG performance score, liver metastasis, skeletal metastasis, anterior abdominal wall metastasis, and lymph node metastasis ($p > 0.05$). Similarly, primary tumor anatomical localization, tumor character (histopathological type), pT stage, pN stage distributions, and the use of specific drugs such as Exenatide, Sulfonylurea, Thiazolidinedione, SGLT-2 inhibitors, and DPP-4 inhibitors did not show a significant variation according to ileus status ($p > 0.05$).

Conversely, a significant relationship was identified between the presence of lung metastasis and ileus development; the rate of lung metastasis was 60.6% ($n = 20$) in the group that developed ileus, whereas it was recorded as 39.3% ($n = 83$) in the group that did not ($p = 0.021$). When the diabetic profile and treatment status were evaluated, the presence of a diabetes diagnosis was significantly higher in patients who did not develop ileus ($p = 0.027$). Similarly, general oral antidiabetic (OAD) use ($p = 0.027$) and specifically metformin use ($p = 0.012$) were found to be significantly higher in the non-ileus group. In contrast, the use of other specific OAD classes did not show a significant association with ileus status ($p > 0.05$). Furthermore, a strong correlation was observed between mortality status and the presence of ileus; the mortality rate in the non-ileus group was 66.4% ($n = 140$), while it remained at 42.4% ($n = 14$) in

the ileus group, constituting a statistically significant difference ($p = 0.008$). In conclusion; lung involvement, diabetes/metformin use, and survival rates stand out as the primary parameters where patients diverge clinically according to their ileus status. A complete comparison of patients according to ileus status is provided in Table 2.

Table 2. Comparison of clinical and demographic data between patients who did and did not develop ileus

		Ileus (-)	Ileus (+)	p
		n(%)	n(%)	
Age	Mean ± SD	66,22±12,55	65,97±12,30	0,895
	Median (min–max)	68(1-92)	70(39-85)	
ECOG	0	19(9)	1(3)	0,642
	I	152(72)	26(78,8)	
	II	31(14,7)	4(12,1)	
	III	8(3,8)	2(6,1)	
	IV	1(0,5)	0(0)	
Liver metastases		157(74,4)	27(81,8)	0,358
Skeletal metastases		25(11,8)	7(21,2)	0,163
Anterior abdominal wall metastases		62(29,4)	12(36,4)	0,417
Lymph node metastases		152(72)	21(63,6)	0,323
Lung metastases		83(39,3)	20(60,6)	0,021
Localisation	Appendix	1(0,5)	0(0)	1,000
	Caecum	28(13,3)	4(12,1)	
	Hepatic flexure	2(0,9)	0(0)	
	Sigmoid	172(81,5)	28(84,8)	
	Transverse	8(3,8)	1(3)	
Tumour characteristics	Adenocarcinoma	206(97,6)	33(100)	1,000
	Neuroendocrine	5(2,4)	0(0)	
Clinical stage	Stage IV	211(100)	33(100)	-
pT stage	II	7(8,3)	0(0)	0,635
	III	50(59,5)	17(63)	
	IV	4(4,8)	1(3,7)	
	IVA	16(19)	7(25,9)	
	IVB	7(8,3)	2(7,4)	
pN stage	0	22(26,2)	5(18,5)	0,625
	I	9(10,7)	4(14,8)	

	IA	6(7,1)	3(11,1)	
	IB	11(13,1)	5(18,5)	
	IC	4(4,8)	0(0)	
	II	3(3,6)	3(11,1)	
	IIA	11(13,1)	3(11,1)	
	IIB	18(21,4)	4(14,8)	
Diagnosis of diabetes				0,027
Yes		48	2	
No		163	31	
Use of OADs		48(22,7)	2(6,1)	0,027
Metformin		45(21,3)	1(3)	0,012
Use of other OADs		30(14,2)	1(3,0)	0,091
Exenatide		1(0,5)	0(,0)	1,000
Sulphonylurea		12(5,7)	0(,0)	0,378
Thiazolidinedione		13(6,2)	0(,0)	0,225
SGLT-2 inhibitor		1(0,5)	0(,0)	1,000
DPP-4 inhibitor		12(5,7)	1(3,0)	1,000
Exitus		140(66,4)	14(42,4)	0,008

Kaplan-Meier analysis performed to evaluate the effect of the presence of ileus on overall survival time revealed a statistically significant difference between the groups ($p = 0.046$). According to the analysis data, the median survival time of patients who developed ileus was determined as 24.60 months (95% CI: 0.00–49.53), whereas this duration remained at 17.43 months (95% CI: 14.29–20.58) in the non-ileus group. The total median survival time of the entire study cohort was recorded as 17.97 months (95% CI: 14.85–21.08). Examining the survival curves, especially from the 25th month onwards, the survival probability of the ileus-developing group was higher compared to the non-ileus group, demonstrating that this clinical condition significantly affects survival time ($p = 0.046$). The median survival estimates are presented in Table 3, and the corresponding Kaplan-Meier survival curves are shown in Figure 1.

Table 3. Comparison of patients' demographic, clinical and laboratory data according to the development of ileus

Ileus	Median		p
	Survival time	95% CI	
Absent	17,43	14,29-20,58	0,046
Present	24,60	,00-49,53	
Total	17,97	14,85-21,08	

In the multivariate logistic regression analysis performed to exclude the effects of clinical and demographic confounding factors on ileus development, **general OAD use was sated as an independent protective factor reducing the risk of ileus (aOR: 0.214, 95% CI: 0.049–0.935,** $p = 0.040$**).** Age, ECOG score, sigmoid colon localization, or the presence of anterior abdominal wall/peritoneal metastasis did not lead to an independent increase in ileus risk ($p > 0.05$)

In the Sensitivity Model, which included variables with a univariate $p < 0.20$, the protective effect of OAD use remained significant (aOR: 0.202, 95% CI: 0.046–0.894, $p = 0.035$). In this model, **the presence of lung metastasis was determined to independently increase the risk of ileus by approximately 2.5-fold (aOR: 2.475, 95% CI: 1.138–5.383,** $p = 0.022$**).**

In the secondary model constructed to examine the independent effect of metformin, **metformin use was found to markedly decrease the odds of developing ileus (aOR: 0.112, 95% CI: 0.015–0.847,** $p = 0.034$**).** The results of all multivariable models are summarized in Table 4.

Table 4. Multivariate Logistic Regression Analysis of Factors Influencing the Risk of Developing Ileus

Analytical Models and Variables	Adjusted OR (aOR)	95% Confidence Interval (CI)	p Value
Use of OAD (Yes vs. No)	**0.214**	**0.049 – 0.935**	**0.040**
Age (Increase every 10 years)	**1.028**	**0.757 – 1.398**	**0.858**
ECOG Score (For every 1-point increase)	**1.199**	**0.681– 2.110**	**0.529**
Sigmoid Localisation (Sigmoid vs. Others)	**1.411**	**0.503 – 3.956**	**0.513**
Anterior Abdominal Wall / Peritoneal Metastasis (Present vs. Absent)	**1.302**	**0.580 – 2.920**	**0.522**
SENSITIVITY MODEL (Model AUC: 0.689)			
Use of OAD (Yes vs. No)	**0.202**	**0.046 – 0.894**	**0.035**
Age (Increase of every 10 years)	**0.985**	**0.724 – 1.342**	**0.925**
ECOG Score (Increase of every 1 point)	**1.181**	**0.665 – 2.095**	**0.571**
Skeletal Metastasis (Present vs. Absent)	**1.440**	**0.539 – 3.847**	**0.468**
Lung Metastasis (Present vs. Absent)	**2.475**	**1.138 – 5.383**	**0.022**
SECONDARY METFORMIN MODEL			
Use of Metformin (Yes vs. No)	**0.112**	**0.015 – 0.847**	**0.034**

Discussion

In this study, the relationship between oral antidiabetic (OAD) use and ileus development, alongside the effects of ileus on overall survival (OS) in patients presenting with Stage IV (metastatic) colon cancer, was retrospectively evaluated within a cohort tracked between 2020 and 2025. The most striking findings of our study are that general OAD and specifically metformin use were significantly higher in the group that did not develop ileus ($p = 0.027$ and $p = 0.012$, respectively), and contrary to general oncology expectations, patients who developed ileus had longer median survival times (24.60 months versus 17.43 months, $p = 0.046$).

Previous literature has investigated the effect of metformin therapy on the prognosis of colon cancer and found that metformin positively contributes to overall survival (6, 7). This is thought to be due to metformin's activation of adenosine monophosphate-activated protein kinase (AMPK) and inhibition of the mTOR pathway, which prevents tumor invasion and metastasis, as well as its induction of apoptosis in tumor cells in the presence of hyperglycemia (8). The use of mTOR inhibitors in cancer treatment supports this hypothesis (9). In our study, distinct from the literature, we aimed to examine the

relationship between OADs and ileus—the most common complication in metastatic colon cancer—and its effect on overall survival. The metformin use rate was 21.3% in the non-ileus group, compared to only 3% ($n = 1$) in the ileus group ($p = 0.012$), suggesting that metformin may play a protective role in the bowel motility or tumor microenvironment. The side effects of metformin include gastroenterological symptoms such as nausea, vomiting, and diarrhea. Furthermore, metformin is known to paradoxically accelerate gastric emptying by increasing vasoactive intestinal peptide secretion in the stomach. This motility-altering pharmacological effect of metformin may reduce the risk of mechanical ileus secondary to tumor compression in colon cancer (10, 11).

The most surprising finding obtained in our study, which contradicts general oncological assumptions in the literature, is that patients who developed ileus exhibited better overall survival (OS) (24.60 months vs. 17.43 months, $p = 0.046$). In the study by Yuan et al., the 3- and 5-year OS in patients who developed ileus were found to be 39% and 35%, and no significant relationship was found between ileus and OS (12). Adams et al. reviewed the data of patients operated on for ileus between 1985 and 2019 and compared them with other retrospective studies. These studies differed in many aspects, including patient numbers, country of study, ileus aggregation, tumor localization, disease stage, and types of outcome measures. Of the 15 studies reviewed, seven were limited to colon cancer, while eight were related to colorectal cancer. Out of 26 different multivariate analyses, 14 observed a significantly worse outcome in one or more different outcomes in patients with ileus (13–17), while 12 observed no significant effect (13, 18–21). These studies could not demonstrate a statistically significant effect of ileus on survival. For colon cancer alone, post-ileus outcomes were significantly worse in 7 out of 16 multivariate analyses (13, 14). Therefore, there is no complete consensus in the literature regarding the effect of ileus on oncological outcomes in OS. The higher rates of emergency surgical palliation (tumor resection or diverting stoma) received by Stage IV patients in our cohort may have provided a rapid reduction in tumor burden (debulking effect) and relief from luminal obstruction symptoms, allowing these patients to return to systemic chemotherapy faster and more effectively. Conversely, in the non-ileus group, a insidiously progressing tumor burden or peritoneal carcinomatosis profile may have kept patients away from surgical interventions, thus negatively impacting survival.

The intensity of OAD and metformin use in the non-ileus group sated in our univariate analyses was strongly confirmed by the multivariate logistic regression models performed. Even after adjusting for critical clinical confounders that could affect ileus risk in advanced colon cancer—such as age, performance status (ECOG), primary tumor sigmoid colon localization, and anterior abdominal wall involvement reflecting peritoneal carcinomatosis—**general OAD use independently reduced the risk of ileus by 78.6% (aOR: 0.214**, $p = 0.040$**) and metformin use by 88.8% (aOR: 0.112**, $p = 0.034$**).** This constitutes the most concrete statistical evidence for our hypothesis that metformin may serve as a clinical protective shield against obstructive symptoms via independent mechanical or anti-tumoral effects.

In the adjusted Sensitivity Model, **the presence of lung metastasis was found to be associated with a 2.47-fold independent increase in the risk of ileus (aOR: 2.475, 95% CI: 1.138–5.383**, $p = 0.022$**).** In

our univariate analyses, lung metastasis was observed in 60.6% of patients who developed ileus, compared to 39.3% in those who did not ($p = 0.021$). Hematogenous spread pathways in metastatic colon cancer are related to the anatomical localization and genetic structure of the tumor. The fact that the primary tumor localization in our study was predominantly (82%) in the sigmoid colon supports the tendency of biologically aggressive or specific molecular subtypes of tumors (e.g., BRAF mutation or MSI-H status) to cause both local obstruction (ileus) and early systemic hematogenous dissemination via the systemic venous circulation (caval pathway) directly to the lungs.

Study Limitations

The retrospective and single-center design are the primary limitations of our study. Furthermore, details regarding patients' duration and doses of metformin use, diabetes regulation status (HbA1c levels), and the specific systemic chemotherapy/anti-angiogenic (bevacizumab, etc.) regimens they were receiving at the time of ileus development could not be included in the analysis. Anti-angiogenic therapies are known to increase the risk of bowel perforation and ileus; the interaction of these agents with metformin should be investigated in future studies.

Conclusion

In conclusion, metformin and general OAD use significantly and independently reduce the risk of ileus development in patients co-diagnosed with metastatic colon cancer and Type 2 Diabetes. Contrary to expectations, it should be kept in mind during clinical management that metastatic patients presenting with ileus may achieve longer survival times owing to palliative surgical approaches. Prospective, multicenter studies are needed to elucidate these protective mechanical effects of metformin in metastatic colon cancer at the molecular level.

Declarations

Human ethics and consent to participate

This study involved human participants and was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was granted by the Aydın Adnan Menderes University Faculty of Medicine Non-Interventional Clinical Research Ethics Committee (Decision No. 08; Protocol No. 2026/08; approval date: 8 January 2026; official document No. E-53043469-050.04-787696, dated 14 January 2026). Due to the retrospective nature of the study, the requirement for obtaining informed consent from individual participants was waived by the ethics committee.

Consent for publication

Not applicable.

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Author Contribution

D.Ö. conceived and designed the study, collected and interpreted the data, and drafted the manuscript. G.Ç. and S.Ö. contributed to data collection, data curation, and the literature review. M.N.B. contributed to the study methodology and statistical analysis. Y.Ö. contributed to data interpretation and the preparation of the tables and figures. M.T. supervised the study and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.Initials: D.Ö., Dilara Özgül; G.Ç., Gökhan Çolak; S.Ö., Sercan Özbek; M.N.B., Mehmet Nuri Başer; Y.Ö., Yiğit Özgül; M.T., Merve Turan

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Figures

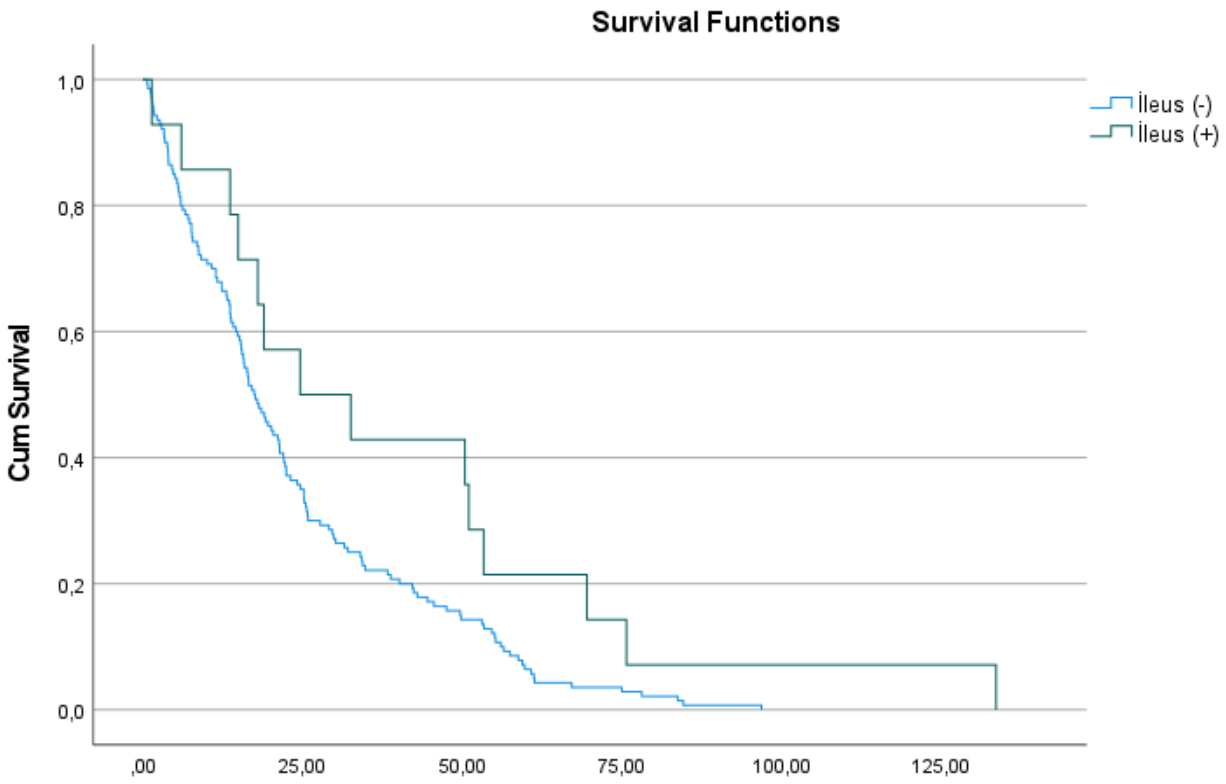


Figure 1

Cumulative survival analysis according to the presence of ileus (Kaplan–Meier survival curve)