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Paper Accepted*

ISSN Online 2406-0895

Original Article / Оригинални рад

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**Factors contributing to survival in hepatic dysfunction
due to colorectal cancer**

Фактори који доприносе преживљавању дисфункције јетре
услед колоректалног карцинома

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Received: July 25, 2022

Revised: September 23, 2022

Accepted: September 29, 2022

Online First: October 5, 2022

DOI: <https://doi.org/10.2298/SARH220725097T>

***Accepted papers** are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.

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Factors contributing to survival in hepatic dysfunction due to colorectal cancer

Фактори који доприносе преживљавању дисфункције јетре услед колоректалног карцинома

SUMMARY

Introduction/Objective Colorectal Cancer(CRC) is currently the third most common cancer in incidence in the United States and accounts for about 8,5% of all cancer related deaths.

Our study aimed to determine the parameters that contribute to the survival of CRC patients with hepatic dysfunction, attention to the positive effects on survival when the most appropriate clinical approaches.

Methods Patients with CRC, diagnosed with hepatic dysfunction, and who were followed up in our inpatient service in the last two years were included in our study. Survival rates were analyzed starting from after the development of hepatic failure.

Results A total of 57 patients were included in the study, 44 (77.2%) were colon carcinoma, and 13 (22.8%) were rectal carcinoma patients, and 14 (24.56%) were female. Bile Duct Dilatation (BD) was detected in 19 (33%) of 57 patients with imaging methods. The median OS was calculated as 4.0 vs. 1.4 months in patients with BD compared to patients without dilatation ($p < 0.001$). Survival times were significantly higher in patients with biliary tract dilatation compared to those without dilatation, and in patients without renal failure compared to those with renal failure.

Conclusion In cancer patients with hepatic dysfunction, those with additional renal failure had shorter survival times and a worse prognosis. The longer survival of patients with bile duct dilatation was attributed to the optimal timing of the Percutaneous Transhepatic Cholangiography (PTC) insertion, close clinical and inflammation marker follow-ups, and early prevention of external biliary drainage, therefore preventing a possible septic complication early on.

Keywords: colorectal cancer; hepatic dysfunction; percutaneous transhepatic biliary drainage; survivability

САЖЕТАК

Увод /циљ Колоректални карцином (ЦРЦ) тренутно је трећи најчешћи рак у Сједињеним Државама и чини око 8,5% свих смртних случајева повезаних са раком. Циљ наше студије био је идентификовати параметре који доприносе преживљавању пацијената са ЦРЦ са дисфункцијом јетре, обраћајући пажњу на позитивне ефекте на преживљавање у најприкладнијим клиничким приступима.

Метод Наша студија је обухватила пацијенте са колоректалним карциномом којима је дијагностикована дисфункција јетре традиционалним тестовима функције јетре и који су примећени у нашој болници у последње две године. Стопе преживљавања анализирани су почевши од развоја затајења јетре.

Резултати У студију је укључено укупно 57 пацијената, 44 (77,2%) су имали карцином дебелог црева, 13 (22,8%) су били пацијенти са карциномом ректума, а 14 (24,56%) су биле жене. Откривена је дилатација жучних канала (БД) код 19 (33%) од 57 пацијената са сликовним методама. Медијан ОС је израчунат као 4,0 наспрам 1,4 месеца код пацијената са БД у поређењу са пацијентима без дилатације ($p < 0,001$). Времена преживљавања је била значајно већа код пацијената са дилатацијом билијарног тракта у поређењу са онима без дилатације, и код пацијената без бубрежне инсуфицијенције у поређењу са онима са затајењем бубрега.

Закључак Пацијенти оболели од рака са дисфункцијом јетре имали су краће време преживљавања и лошију прогнозу код пацијената са додатном бубрежном инсуфицијенцијом. Дуже преживљавање пацијената са дилатацијом жучних канала било је због оптималног времена перкутане трансхепатичке холангиографије, пажљивог клиничког праћења и контроле маркера упале и ране превенције спољне дренаже жучних путева, што омогућава спречавање могућих септичких компликација у раној фази.

Кључне речи: колоректални карцином; дисфункција јетре; перкутана трансхепатична билијарна дренажа; преживљавање

INTRODUCTION

About 149.500 new colorectal cancer (CRC) cases are diagnosed each year in the United States, of which 104.270 are colon cancer, and the remainder are rectal cancer [1]. According to Globocan 2020 data, CRC ranks 3rd after breast and lung cancer according to the frequency of new cases and second after lung cancer in mortality rates [2].

In the evaluation of liver function, aspartate aminotransferase (AST), serum albumin, and prothrombin time are measured, cellular damage is evaluated with alanine aminotransferase (ALT) concentrations, and bile cholestasis is assessed with alkaline phosphatase (ALP), gamma glutamyl-transferase (GGT), and bilirubin levels. Serum bilirubin levels are a specific indicator of severe liver injury and an essential indicator of loss of liver function [3]. Therefore, in our study, when determining liver dysfunction, we considered the elevation of bilirubin (simultaneous total and direct bilirubin) as the main antecedent parameter and accepted it as the first parameter to be evaluated in patient selection. Then, the clinical reflections of the changes in all other liver function tests were evaluated.

The mechanism by which cancer causes liver dysfunction is multifactorial. This may occur through a direct reduction in liver volume, or it may occur with the development of intrahepatic or extrahepatic biliary obstruction [3]. It has also been reported that some cancer-related immunological factors may increase cholestasis and inflammatory damage in the liver. Development of liver dysfunction secondary to metastatic colorectal cancer is considered a poor prognosis and reduces median survival to only a few weeks [4].

Our study aimed to determine the parameters that contribute to the survival of colorectal cancer patients with hepatic dysfunction, regardless of the development of liver metastasis, and to draw the patients' attention to the positive effects on survival when the most appropriate clinical approaches and optimal treatment are performed with the earliest timing.

METHODS

Patients aged 18 years and older who were hospitalized and followed up with liver dysfunction and diagnosed with colorectal cancer in our health center in the last two years were included in the study. The study was conducted per the Declaration of Helsinki. Patient information was recorded by retrospectively scanning the hospital database. Patients who did not meet the inclusion criteria and those who withdrew their voluntary consent during the study were excluded.

The study's ethics committee approval was obtained from the ethics committee of Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital with the number 2022-02/1669 dated 23.02.2022.

In the analyzes, the effects of hemogram, serum glucose, alanine aminotransferase (ALT) and aspartate aminotransferase (AST), total bilirubin, direct bilirubin, alkaline phosphatase (ALP), gamma glutamyltransferase (GGT), albumin, International Normalized Ratio (INR), blood urea nitrogen (BUN), and creatinine parameters, as well as bile duct dilatation, sex, and age parameters on survival after the development of hepatic dysfunction were calculated.

Statistical analyzes were performed using the Statistical Package for the Social Sciences program (SPSS for Windows, Version 24.0, Chicago, IL, USA). Normality analyzes were performed for the distribution of numerical variables. Continuous quantitative variables were reported using the median (interquartile range) (min-max) for non-parametrically distributed and mean (SD) for parametrically distributed variables. Qualitative categorical variables were reported using Pearson's chi-square or Fisher exact test. Survival analyses were performed with Cox regression analysis, while survival curves were created using the Kaplan-Meier method. A p-value of <0.05 was considered significant.

RESULTS:

A total of 57 patients were included in the study by scanning the retrospective database. Of these, 44 (77.2%) were colon carcinoma, and 13 (22.8%) were rectal carcinoma patients, and 14 (24.56%) were female.

The performance statuses were evaluated using the Eastern Cooperative Oncology Group (ECOG) performance status. There were 33 (57.9%) patients with ECOG ≤ 2 and 24 (42.1%) patients with ECOG ≥ 3 .

When the age distributions were categorized as over 50 years old and 50 years old and below, the median overall survival (OS) in the >50 years vs. ≤ 50 age group was higher, with a value close to significance of 4.1 vs. 1.5 months, respectively ($p=0.08$) (Table 1).

The R-value (R factor), an additional factor in determining the possible type of liver injury in patients, was calculated based on serum ALT and ALP levels. Values of 5 and above were considered hepatocellular damage, while values of 2 and below were considered as cholestatic damage. The median R factor was 1.00 (1.00-3.00). While 55 (96.5%) of our patients had cholestatic damage, hepatocellular damage was present in two (3.5%).

When albumin values were similarly categorized as <3 g/dL and ≥ 3 g/dL, the median OS was 2.1 vs. 1.4 months in the group with albumin above 3 mg/dL ($p=0.015$) (Table 1).

In our patients, no pathology supporting chronic renal failure was present in the pre-hepatic dysfunction, both in the past laboratory findings and in the current urinary system ultrasound imaging. When the kidney functions were evaluated, the median OS was 2.72 vs. 1.41 months in the group with serum BUN values of 15 mg/dl and below and in the group with over 15 mg/dl ($p=0.016$). In the group with creatinine values below 1.5 mg/dl, OS was calculated as 2.2 vs. 0.98 months compared to 1.5 mg/dl and above ($p<0.001$) (Table 1).

Bile Duct Dilatation (BD) was detected in 19 (33%) of 57 patients with imaging methods. In the evaluations made according to the patients who developed BD and therefore had

Percutaneous Transhepatic Cholangiography (PTC) and those who did not have PTC, it was determined that 16 (84.2%) of 19 patients underwent PTC procedure. The median OS was calculated as 4.0 vs. 1.4 months in patients with BD compared to patients without dilatation ($p < 0.001$) (Table 1-2, Figure 1).

The patients were followed closely regarding coagulopathy, another consequence of liver failure, and anti-VEGF therapy [5]. However, no thrombosis or bleeding was reported.

When the patients with BD were evaluated according to their subgroups, the median serum ALT levels were calculated as 110 in the dilated group and 36 in the non-dilated group ($p = 0.06$). Other significant variables in bile dilatation were total and direct bilirubin values ($p < 0.001$, Table 1).

In the Spearman correlation analysis performed between numerical variables, the correlation of serum cholestasis enzymes with platelet, neutrophil, and lymphocyte values was evaluated. It was determined that platelet values had a significant positive correlation with bilirubin (total and direct bilirubin) and GGT, and neutrophil and lymphocyte values were also positively correlated with GGT (Table 3).

The HALP score (Calculated by Serum Hemoglobin (g/dL) x Albumin (g/L) x Lymphocyte ($10^9/L$)/Platelet ($10^9/L$) method) was calculated for all patients. The median value was calculated as 1.78 (0.23-16.60). The Cox regression analysis for the calculated HALP score is given in Table 2.

DISCUSSION

Survival in hepatic dysfunction due to cancer is expressed in weeks. Therefore, early identification of factors affecting this survival, initiation of treatment with optimal timing, or early interventions for treatment will increase survival times. Liver biopsy is the gold standard test for detecting liver damage and fibrosis. On the other hand, reasons such as the high cost,

the risk of complications such as bleeding, the pathology results being time consuming, the lack of a practical evaluation method, and the fact that 24 (42.1%) of our patients with liver dysfunction consisted of patients with ECOG performance status of 3 and above, etc. have led to the need to search for methods that can provide rapid results and have an impact on the clinic. For this purpose, some laboratory parameters and clinical findings were evaluated in our patients.

PTC was not implanted in any of our 38 patients who developed hepatic dysfunction but did not have dilated biliary tract. However, PTC was inserted in 16 (84.2%) of our 19 patients with bile duct dilatation. The longer survival of patients with bile duct dilatation was attributed to the fact that PTC fitted with optimal timing, close clinical and inflammation marker follow-ups, and early external biliary drainage could be provided, and therefore, a possible septic picture that could develop was prevented early.

In some studies, the development of sinusoidal obstruction syndrome (SOS) has been shown in patients treated with oxaliplatin-containing regimens [6-8]. In another study by Ward et al., surgery-confirmed SOS was found in 24 of 60 patients who received neo-adjuvant oxaliplatin-based chemotherapy for over 12 weeks [9-10]. In our study, SOS was diagnosed with the revised European Society for blood and marrow transplantation (EBMT) criteria by the presence of two of the following findings in addition to a total bilirubin value ≥ 2 : painful hepatomegaly, $\geq 5\%$ weight gain, and ascites [11]. SOS was detected in a total of 8 patients. All patients with SOS had received oxaliplatin-based treatment. Some reports state adding bevacizumab to the neoadjuvant oxaliplatin-based regimen may reduce the incidence and severity of oxaliplatin-related hepatic sinusoidal injury [10-13]. Of the 57 patients in our study, 16 received combined treatment with bevacizumab. Four (50%) of our patients with SOS had received bevacizumab.

Side effects of regimens containing irinotecan are more frequently associated with steatosis and steato hepatitis [14]. Publications are stating that patients with steato hepatitis have an overall survival difference of approximately 3 months compared to those without [15]. A total of 36 (63.1%) patients received irinotecan treatment at any step. In our study, a total of 32 (56.14%) patients had grade 1 and higher steatosis. Of these patients, 21 had received irinotecan treatment.

We determined that young age is an important parameter of survival. Therefore, patients with poor nutritional support should be considered when evaluating the significant survival difference in albumin values of 3 and above.

Hypoalbuminemia usually indicates severe liver injury with decreased albumin synthesis [16]. Therefore, serum albumin level is included in the Child-Turcotte-Pugh (CTP) classification, a scoring system with prognostic significance in patients with liver cirrhosis [17]. Serum albumin is also decreased in nephrotic syndrome, as a negative acute phase reactant, in widespread systemic inflammation, and in severe nutritional disorders.

Hypoalbuminemia is aggravated as albumin synthesis is also affected by the addition of hepatic dysfunction to these clinical conditions, which are very common in many cancer patients. It was thought that the lower survival rate in patients with hypoalbuminemia was primarily related to liver dysfunction and poor nutritional support in these patients.

Hepatorenal syndrome (HRS) is a clinical picture usually accompanied by acute renal failure in patients with acute or chronic liver disease. Although it is usually seen in patients with advanced cirrhosis, it can also be seen in portal hypertension due to metastatic tumors [18-21]. Since our study was retrospective, although HRS was not diagnosed by considering the diagnostic criteria, it was shown that adding hepatic dysfunction to renal failure reduces patient survival.

Some publications show that the HALP score can be used as a prognostic marker. In a study by Topal U. et al., an indirect relationship between the HALP score and tumor budding in patients with CRC was shown [22]. Another analysis by Yalav et al. found an independent prognostic factor for survival in patients with CRC who underwent curative resection [23]. Our study determined that the HALP score did not make a statistically significant contribution in terms of survival. Therefore, it was thought that there is a need for studies on this subject with more patients and including patients at all stages.

CONCLUSION

Although liver function tests have an important place in cancer patients, early detection of liver dysfunction prolongs the survival of patients. A significant proportion of hepatic dysfunction in CRC patients develops with cholestatic occlusive damage. Therefore, in cases with dilated biliary tract, PTC should not be delayed and should be seen as a priority. Drug toxicities and even non-metastatic liver damage should also be considered since many of these patients receive multiple drug therapies.

Conflict of interest: None declared.

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Table 1: Survival analyzes of demographic characteristics and laboratory parameters

	Median OS (95% CI)	p value
Age, median		
≤ 50	4.1 (01–11.25)	0.08
> 50	1.5 (1.19–1.95)	
Sex		
Male	1.7 (0.91–2.5)	0.470
Female	1.3 (1.1–1.4)	
Glucose		
< 126	1.7 (0.85–2.5)	0.799
≥ 126	1.5 (1.2–1.8)	
Alanine transaminase		
< 40	1.5 (0.74–2.4)	0.443
≥ 40	1.6 (1.1–2.1)	
Aspartate transaminase		
< 40	1.3 (0.45–2.2)	0.108
≥ 40	1.7 (1.2–2.1)	
Alkaline phosphatase		
< 140	1.5 (1.2–1.9)	0.948
≥ 140	1.7 (1.0–2.4)	
Gamma-glutamyl transferase		
< 340	2.7 (1.11–4.34)	0.036
≥ 340	1.6 (1.12–2.04)	
Albumin		
< 3	1.4 (1.1–1.6)	0.015
≥ 3	2.1 (1.0–3.2)	
International normalized ratio		
< 1.5	1.5 (1.0–2.0)	0.61
≥ 1.5	1.3 (0.66–2.0)	
Blood urea nitrogen		
< 15	2.72 (0.43–5.02)	0.016
≥ 15	1.41 (1.09–1.73)	
Creatinine		
< 1.5	2.2 (1.31–3.09)	< 0.001
≥ 1.5	0.98 (0.84–1.12)	
Hemoglobin		
< 11	1.4 (1.1–1.7)	0.211
≥ 11	1.9 (1.1–2.6)	
Bile duct dilatation		
Present	4.0 (0.01–8.59)	< 0.001
Absent	1.4 (1.19–1.63)	

Kaplan Meier survival analysis

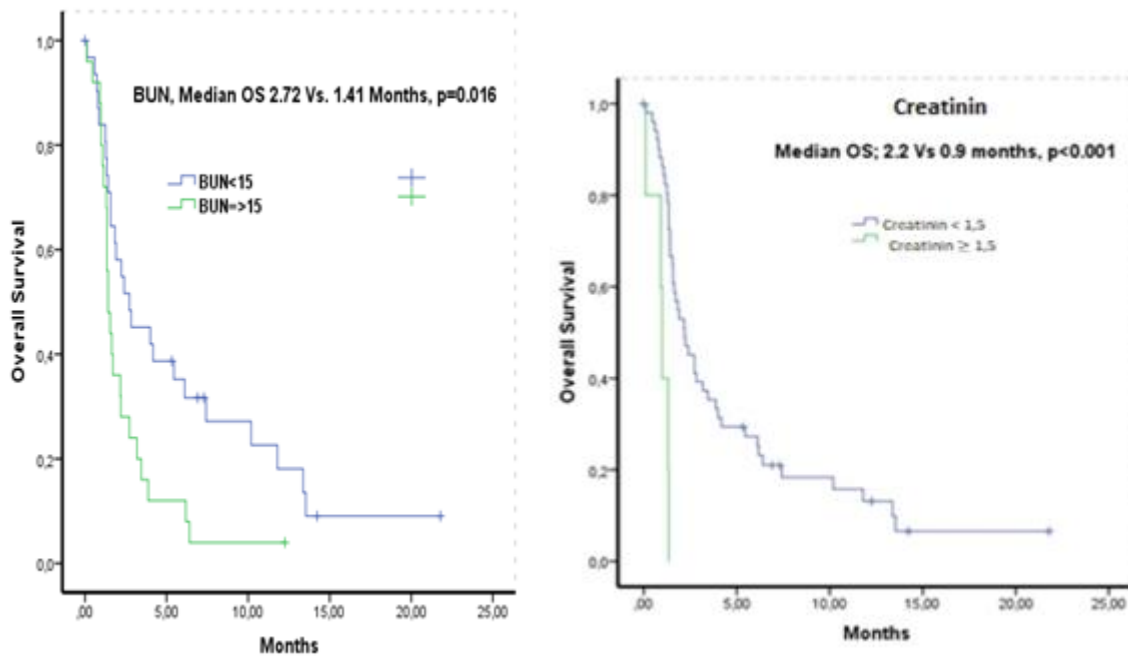


Figure 1. Overall survival related to blood urea nitrogen and creatinine in hepatic dysfunction

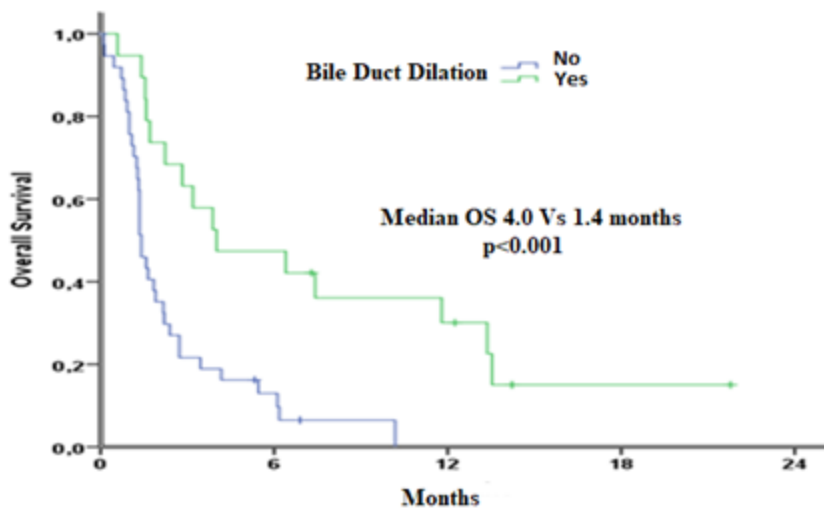


Figure 2: Overall survival in bile duct dilation

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Table 2. Survival analyzes of laboratory parameters (univariate and multivariate analyzes)

Parameters	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Direct bilirubin	0.89 (0.803–0.999)	0.47	1.105 (0.956–1.278)	0.177
Gamma-glutamyl transferase	1.00 (1.000–1.001)	0.37	1.001 (1.000–1.002)	0.002
Blood urea nitrogen	1.02 (1.012–1.047)	0.001	1.032 (1.012–1.053)	0.002
Hemoglobin ≥ 11	0.56 (0.321–1.003)	0.51	0.761 (0.412–1.406)	0.384
Bile duct dilatation, present	3.26 (1.650–6.477)	0.001	0.197 (0.077–0.506)	0.001
HALP score	0.933 (0.827–1.054)	0.250	0.932 (0.819–1.050)	0.281
Cox Regression Analysis				

Table 3. Correlation of numerical variables

		Direct bilirubin	Total bilirubin	Gamma-glutamyl transferase	Lymphocyte	Neutrophil	Platelets
Direct bilirubin	r	1					
	p						
Total bilirubin	r	0.948**	1				
	p	<0.001					
Gamma-glutamyl transferase	r	0.018	-0.021	1			
	p	0.892	0.877				
Lymphocyte	r	0.004	-0.005	0.317*	1		
	p	0.975	0.970	0.016			
Neutrophil	r	-0.172	-0.204	0.268*	0.180	1	
	p	0.202	0.127	0.044	0.181		
Platelets	r	0.338*	0.322*	0.439**	0.289*	0.379**	1
	p	0.010	0.014	<0.001	0.029	0.004	

Spearman correlation analysis