ORIGINAL RESEARCH

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Prognostic Effect of Albumin-Bilirubin Grade on Survival in Advance Gastric Cancer Patients with de-novo Liver Metastasis

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ABSTRACT Objective: We aimed to explore the prognostic effect of albumin-bilirubin scores on survival prior to the treatment of patients with gastric cancer with de-novo liver metastasis. **Material and Methods:** Retrospective screening was conducted on 203 patients who were followed up in our clinic. Two different models have been developed to compare the effect of albumin and bilirubin alone based on the albumin-bilirubin score. Albumin and bilirubin values in Model 1 and albumin-bilirubin grade in Model 2 were included in multivariate analysis. **Results:** Median age of the patients was 63, and 78.8% of the study population was male. There were 57 (28.1%) patients in the albumin-bilirubin grade 1 group, 95 (46.8%) patients inthe albumin-bilirubin grade 2 group, whereas, 51 (25.1%) patients in the albumin-bilirubin grade 3 group. Median progression-free survival accordingto albumin-bilirubin grades 1-2-3 was8.9 (6.1-11.6) months, 4.2 (2.8-5.5) months, and 0.9 (0.7-1.2) months, respectively ($p<0.01$). In univariate analysis, poor prognostic effects of high albumin-bilirubin grade were reflected in bothprogression-free survival and overall survival. Multivariate analyzes revealed that in model 1; albumin <3.5 gr/dL and bilirubin >1.2 gr/dL values were prognostic for both progression-free survival and overall survival. In model 2, albumin-bilirubin grade was an independent prognostic factor for progression-free survival and overall survival. {[H 3.45 (1.98-6.02)] in progression-free survival and [H 4.41 (2.45-7.93)] in overall survival for albumin-bilirubin grade 3}. **Conclusion:** High albumin-bilirubin score (grade) is much more sensitive as compared to low albumin and high bilirubin values alone in showing poor prognosis on progression-free survival and overall survival in patients with gastric cancer with liver metastasis.

Keywords: ALB protein; bilirubin; gastric cancer; prognosis

Although gastric cancer is the fifth most common malignancy worldwide, it is the third leading cause of cancer death owing to its high morbidity and mortality. It has an incidence of 12.5 per 100.000 in our country, comparable to that observed among the Asian population.[1] Local and locally advanced stages can be cured by surgery, neoadjuvant/adjuvant chemotherapies; however, in the metastatic stages, treatment is aimed at palliation, improving quality of life, and prolonging survival.[2] The most common sites of metastasis include lymph nodes, peritoneum, and liver. The worst prognosis is witnessed among the subgroup with liver metastasis, where the survival is approximately three months without treatment with the best supportive care.[3] The prognostic parametersduring the early stages involve age, sex, histological type, tumor size, lymph node involvement, and clinical-stage, but in the metastatic stage, HER2 positivity is the most vital prognostic and predictive known marker.[4]

Albumin-bilirubin (ALBI) score is an integrated version of albumin and bilirubin values into a logarithmic formula. ALBI grades are obtained by grouping the defined value ranges of the score. For the first time in medical oncology practice, patients with hepatocellular carcinoma (HCC) have been shown to be

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predictive for both disease stage and survival as an alternative to the Child-Pugh score, and prognostic significance has been validated for all HCC treatment modalities such as surgery, transplantation, local therapies, and medical therapies.[5-8] After primary liver tumor trials, the impact of ALBI score on survival was also applied for patients with colorectal carcinoma suffering from liver metastases.[9,10]

Studies on gastric cancer of the ALBI score/grade highlighted that preoperative value in early-stage patients is prognostic for postoperative recurrence and survival. In the other clinical trials, preoperative ALBI value is correlated with adjuvant S-1 treatment efficacy.[11,12] However, there is no data regarding the metastatic stage in the literature. The aim of this study was to elucidate the prognostic significance of ALBI score/grade in gastric cancer patients with de-novo liver metastasis.

MATERIAL AND METHODS

STUDY DESIGN AND CATEGORIZATION OF VARIABLES

Our retrospective cross-sectional study employed data from medical files of patients, diagnosed in our clinic between January 2010 and December 2018 (diagnosis was validated histopathologically). Patients detected with liver metastasis by computed tomography, magnetic resonance imaging, or positron emission tomography were considered suitable for the staging of malignancies at the time of diagnosis. Age, gender, performance score (ECOG), body mass index (BMI), HER2 status, and first-line treatment option were obtained from medical files, serum albumin, and bilirubin values at diagnosis were obtained from laboratory records of the hospital automation system.

Patients diagnosed with autoimmune hepatitis, viral hepatitis, and toxic hepatitis were excluded from the study owing to the alteration of albumin and bilirubin levels.

While categorizing the factors that may be prognostic,age was accepted as the cut-off value of 60 years. Those with a performance score of 0-1 were included in one group, and those with a score of 2 or more were classified in the other group. Body mass indexes were grouped according to the original BMI classification. HER2 status data were collected from the pathology archive and categorized as positive for 3(+) with immunohistochemistry (IHC) method or 2(+)with IHC and validated with fluorescein in situ hybridization (FISH) method.

The lower limit value of the albumin (3.5 gr/dL) and the upper limit value (1.2 gr/dL) for bilirubin were accepted as the cut-off. ALBI scores were automatically computed using the logarithmic formula (log^{10} bilirubin x 0.66) + (albumin x -0.085) in the original HCC study (5,6). ALBI group was divided into threegroups according to the value ranges determined in the original study. Values of ≤-2.60 were considered as ALBI grade 1, ALBI grade 2 between -2.60 and -1.39, and ≥-1.39 as ALBI grade 3.[5,6]

The study was approved by the local ethics board according to good clinical practice and applicable laws and declaration of Helsinki.

STATISTICAL ANALYSIS

Progression-free survival (PFS) was calculated using the time interval between the onset of treatment or best supportive care and the date of the first control imaging in which progression was detected. The overall survival (OS) was determined using the date of diagnosis and the date of death or the last clinical follow-up date for patients who did not die. Survival probabilities were analyzed by the Kaplan-Meier method, and the difference between groups was estimated by the log-rank test. In this univariate analysis, variables with p-value <0.05 were included in the multivariate analysis to determine whether there werean independent prognostic factor and survival rates (H) by the Cox-regression method. Two different multivariate analysis models were adopted for the correct evaluation of ALBI grade alone as a much more effective prognostic factor than albumin and bilirubin alone, as applied in a similar study performed previously in patients with liver metastatic colorectal cancer in our clinic (10). In Model 1; only albumin and bilirubin values, and in Model 2; only ALBI grade was included in the multivariate analysis. In all evaluations, a two-tailed p-value <0.05 and confidence interval 95% were considered statistically significant. Statistical analysis of the data was performed using SPSS (Statistical Package for Social Sciences, IBM SPSS Statistics for Windows, Version 23.0, Armonk, NY: IBM Corp.).

RESULTS

PATIENT CHARACTERISTICS

The present study incorporated 203 patients satisfying the inclusion criteria. The median age at diagnosis was 63 (54-73) years, and 78.8% of the patients were male. An ECOG performance score of 2 or more was documented among 107(52.7%), and 35% had a BMIof less than 18.5. HER2 status was positive in the pathological data of 37 patients, whereas HER2 was not reached in the pathology records of 83 patients. While 47 (23.2%) patients were unable to receive chemotherapy and thus, were followed up with palliative support. The rest were capable of receiving first-line treatment in different modalities.

When the laboratory records of the study patients were examined, it was found that the albumin value of 102 (50.2%) patients was lower than the lower limit of 3.5 g/dL, whereas 69 (34%) patients had higher bilirubin levels above the upper limit of 1.2 g/dL. According to the ALBI grade, the study population was distributedas 57 (28.1%) for grade 1, 95 (46.8%) for grade 2, and 51 (25.1%) for grade 3. Table 1 summarizesthe demographic and clinical characteristics of the patients.

TABLE 1: Demographic and clinical characteristics of the patients.

Parameters	All (n=110)
Age, years	
Median (Interquartile range)	63 (54-72)
Gender	
Female	43 (21.2)
Male	160 (78.8)
ECOG-performance score, n (%)	
0-1	96 (47.3)
≥2	107 (52.7)
Body-mass index, kg/m², n (%)	
<18.5	71 (35.0)
18.5-24.9	109 (53.7)
25.0-29.9	21 (10.3)
≥30	2 (1.0)
HER2 status, n (%)	
Positive	37 (18.2)
Negative	83 (40.9)
Unknown	83 (40.9)
First-line treatment, n (%)	
Cisplatin + 5-Flourouracil	40 (36.4)
Cisplatin + 5-Flourouracil + Trastuzumab	35 (31.8)
Docetaxel + Cisplatin + 5-Flourouracil	22 (20.0)
FOLFOX	6 (5.5)
CapeOX	5 (4.5)
Best supportive care	2 (1.8)
Serum albumin, gr/dL, n (%)	
<3.5	102 (50.2)
≥3.5	101 (49.8)
Serum bilirubin, gr/dL, n (%)	
<1.2	134 (66.0)
≥1.2	69 (34.0)
ALBI grade, n (%)	
Grade 1	57 (28.1)
Grade 2	95 (46.8)
Grade 3	51 (25.1)

ECOG: Eastern Cooperative Oncology Group, HER2: Human epidermal growth factor receptor 2, FOLFOX: Fluorouracil + Oxaliplatin + Calcium folinate, CapeOX: Capecitabine + Oxaliplatin, ALBI: Albumin-bilirubin

SURVIVAL ANALYSIS

The median follow-up period in our study was 9.1 months (95% CI, 7.8-10.4). In the last evaluation, 198 (97.5%) patients were found dead. The relationship between the study parameters with PFS and OS is detailed in Table 2, and Figure 1 and Figure 2 illustrate Kaplan-Meier plots stratified by ALBI grade for PFS and OS. The survival analyses, according to serum albumin level, serum bilirubin level, and ALBI grade, are discussed in detail in the subtitles.

PROGRESSION-FREE SURVIVAL (PFS) ANALYSIS

The median PFS for all patients was 4.0 months (95% CI, 3.3-4.7). PFS was 2.2 months in the group with serum albumin value <3.5 gr/dL, 6.9 months in the group with ≥3.5 gr/dL (p <0.01) and 1.5 months in the group with serum bilirubin value ≥1.2 gr/dL, 6.0 months in the group with <1.2 gr/dL (p <0.01). On evaluating PFS, a statistically significant difference between the three groups was revealed according to ALBI grade. PFS was respectively 8.9 months for grade 1, 4.2 months for grade 2, and 0.9 months for grade 3 (p<0.01).

In addition to ALBI grade in univariate analysis for PFS, ECOG performance score, BMI, HER2 positivity status, chemotherapy usage status, trastuzumab

TABLE 2: Association between study subjects and progression-free survival (PFS) and overall survival (OS).

Parameters	Median PFS (95% CI Lower-Upper)	p-value	Median OS (95% CI Lower- Upper)	p-value
Age, years				
<60	5.0 (3.6-6.4)	0.06	9.3 (6.1-12.6)	0.03
≥60	3.7 (3.1-4.3)		5.4 (3.4-7.3)	
Gender				
Female	4.5 (3.5-5.5)	0.12	5.5 (3.9-7.1)	0.06
Male	4.0 (3.1-4.8)		6.8 (4.3-9.2)	
ECOG-performance score				
0-1	9.1 (7.3-10.8)	<0.01	14.3 (12.3-16.3)	<0.01
≥2	2.3 (1.9-2.7)		2.4 (1.9-2.9)	
Body-mass index, kg/m^2				
<18.5	1.1 (0.6-1.6)	<0.01	1.5 (0.8-2.1)	<0.01
≥18.5	6.9 (5.6-8.2)		11.5 (9.9-13.2)	
HER2 status				
Positive	9.8 (5.2-10.7)	<0.01	12.7 (10.0-15.3)	<0.01
Negative	6.9 (3.3-5.1)		7.2 (4.3-10.1)	
Unknown	4.2 (1.7-3.3)		3.0 (1.8-4.2)	
First-line treatment				
Chemotherapy	5.7 (4.8-6.5)	<0.01	9.5 (7.7-11.4)	<0.01
Cis + 5-FU + Trastuzumab	8.0 (6.0-10.0)		12.8 (10.2-15.4)	
Cisplatin based (CF and DCF)	5.0 (3.9-6.1)		7.2 (4.8-9.5)	
Oxaliplatin based (FOLFOX- CapeOX)	5.0 (3.3-6.7)		9.1 (6.5-11.8)	
BSC (no chemotherapy)	1.1 (0.5-1.8)		1.1 (0.5-1.8)	
Serum albumin, gr/dL				
<3.5	2.2 (1.7-2.8)	<0.01	2.4 (1.8-3.1)	<0.01
≥3.5	6.9 (5.2-8.6)		11.6 (9.1-14.0)	
Serum bilirubin, gr/dL				
<1.2	6.0 (5.3-6.7)	<0.01	9.8 (8.1-11.4)	<0.01
≥1.2	1.5 (0.6-2.4)		1.5 (0.9-2.2)	
ALBI grade				
Grade 1	8.9 (6.1-11.6)	<0.01	14.8 (12.0-17.7)	<0.01
Grade 2	4.2 (2.8-5.5)		6.5 (4.7-8.3)	
Grade 3	0.9 (0.7-1.2)		1.0 (0.8-1.2)	
All patients	4.0 (3.3-4.7)	-	6.4 (4.9-7.8)	-

ECOG: Eastern Cooperative Oncology Group, HER2: Human epidermal growth factor receptor 2, FOLFOX: Fluorouracil + Oxaliplatin + Calcium folinate, CapeOX: Capecitabine + Oxaliplatin, BSC: Best supportive care, ALBI: Albumin-bilirubin.

usage status, and serum albumin and bilirubin levels within normal limits or not also affect PFS (Table 3). According to Model 1, multivariate analysis performed with these effective parameters; ECOG performance score, BMI, low serum albumin level (H 1.54 (95% CI, 1.07-2.20)), and high serum bilirubin level (H 1.62 (95% CI, 1.13-2.30)) were considered as independent prognostic factors. According to Model 2, multivariate analysis, ECOG performance score, BMI, as well as ALBI grade 2 and 3 were also found. H for Grade 2 was 1.86 (95% CI, 1.26-2.74), and for Grade 3 H was 3.45 (95% CI, 1.98-6.02) (Table 3).

OVERALL SURVIVAL (OS) ANALYSIS

The median overall survival for all patients was 6.4 months (95% CI, 4.9-7.8). OS was 2.4 months in the group with serum albumin <3.5 g/dL, 11.6 months in

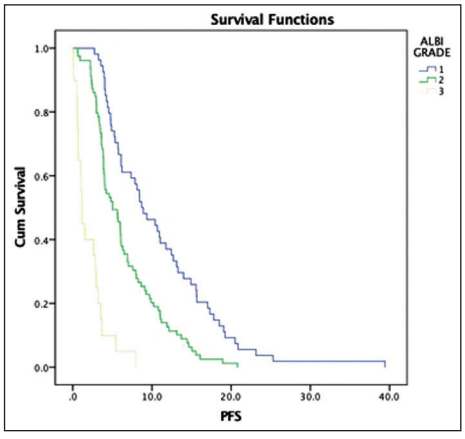

FIGURE 1: Kaplan-Meier plot stratified by ALBI for progression-free survival (PFS).

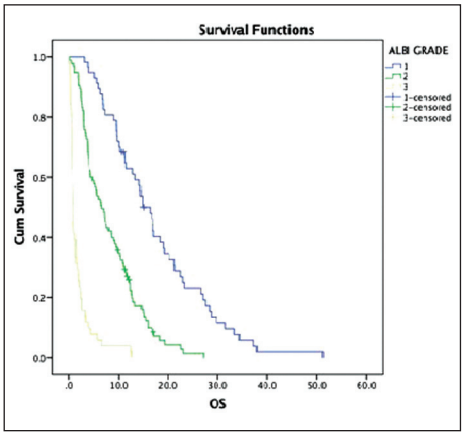

FIGURE 2: Kaplan-Meier plot stratifiedby ALBI for overall survival (OS).

TABLE 3: Univariate and multivariate analysis of prognostic factors for progression free survival (PFS).

	Univariate analysis		Multivariate analysis (Model 1)		Multivariate analysis (Model 2)	
	(95% CI Lower-Upper)	p-value	(95% CI Lower-Upper)	p-value	(95% CI Lower-Upper)	p value
Age, ≥60 years	1.31 (0.99-1.75)	0.06				
Gender, Male	0.76 (0.54-1.08)	0.13				
ECOG, ≥2	9.38 (6.41-13.72)	<0.01	4.73 (2.91-7.69)	<0.01	4.46 (2.74-7.26)	<0.01
BMI, <18.5 kg/m^2	14.0 (9.25-21.36)	<0.01	5.12 (3.14-8.34)	<0.01	4.66 (2.82-7.70)	<0.01
HER2 status, Positive	0.53 (0.36-0.77)	<0.01	1.52 (0.47-4.88)	0.47	1.60 (0.50-5.13)	0.42
Chemotherapy, Yes	0.18 (0.12-0.27)	<0.01	0.74 (0.48-1.15)	0.18	0.75 (0.48-1.18)	0.21
Trastuzumab, Yes	0.50 (0.34-0.74)	0.001	0.48 (0.14-1.62)	0.23	0.43 (0.13-1.47)	0.18
Albumin, <3.5 gr/dL	3.16 (2.34-4.26)	<0.01	1.54 (1.07-2.20)	0.02		
Bilirubin, >1.2 gr/dL	3.16 (2.33-4.29)	<0.01	1.62 (1.13-2.30)	0.007		
ALBI grade,						
Grade 2	2.25 (1.58-3.21)	<0.01			1.86 (1.26-2.74)	<0.01
Grade 3	13.40 (8.50-21.13)	<0.01			3.45 (1.98-6.02)	<0.01

ECOG: Eastern Cooperative Oncology Group, BMI: Body mass index, HER2: Human epidermal growth factor receptor 2, ALBI: Albumin-bilirubin.

the group with ≥3.5 gr/dL (p <0.01) and 1.5 months in the group with serum bilirubin value ≥1.2 g/dL, 9.8 months in group with <1.2 gr/dL (p <0.01). OS evaluated according to ALBI grades was found to be 14.8 months, 6.5 months, and 1.0 months for groups 1, 2, and 3, respectively, and the difference was statistically significant (p<0.01).

In addition to the ALBI grade in univariate analyzes for overall survival, clinical parameters such as age, ECOG performance score, BMI, HER2 positivity status, chemotherapy usage status, trastuzumab usage status, and serum albumin and bilirubin levels (Table 4). According to Model 1 multivariate analysis with these effective parameters, ECOG performance score, BMI, chemotherapy status, low serum albumin level (H 1.70 (95% CI, 1.17-2.47)), and high serum bilirubin level (H 1.65 (%) 95 CI, 1.13-2.39)) as independent prognostic factors. According to the Model 2 multivariate analysis, ECOG performance score, BMI, chemotherapy status, and ALBI grade 2 and 3 were also found. H for Grade 2 was 2.64 (95% CI, 1.74-3.98), and for Grade 3 H was 4.41 (95% CI, 2.45-7.93) (Table 4).

DISCUSSION

In medical oncology practice, prognostic scoring systems are widely applied for survival and treatment options, especially in advanced malignancies. The Child-Pugh score at HCC, IMDC (International Metastatic RCC Database Consortium), and

TABLE 4: Univariate and multivariate analysis of prognostic factors for overall survival (OS).

	Univariate analysis		Multivariate analysis (Model 1)		Multivariate analysis (Model 2)	
	(%95 CI Lower-Upper)	p value	(%95 CI Lower-Upper)	p value	(%95 CI Lower-Upper)	p-value
Age, ≥60 years	1.36 (1.02-1.82)	0.03	1.23 (0.90-1.68)	0.18	1.30 (0.95-1.78)	0.10
Gender, Male	0.72 (0.54-1.02)	0.07				
ECOG, ≥2	16.86 (10.51-27.04)	<0.01	9.76 (5.60-17.01)	<0.01	9.17 (5.22-16.09)	<0.01
BMI, <18.5 kg/m^2	11.90 (8.07-17.56)	<0.01	4.01 (2.48-6.49)	<0.01	3.81 (2.30-6.29)	<0.01
HER2 status, Positive	1.83 (1.25-2.68)	0.002	1.78 (0.55-5.75)	0.33	1.89 (0.58-6.12)	0.28
Chemotherapy, Yes	0.12 (0.08-0.17)	<0.01	0.46 (0.29-0.72)	<0.01	0.44 (0.28-0.70)	<0.01
Trastuzumab, Yes	0.51 (0.34-0.76)	0.001	0.40 (0.11-1.38)	0.14	0.35 (0.10-1.23)	0.10
Albumin, <3.5 gr/dL	3.45 (2.54-4.67)	<0.01	1.70 (1.17-2.47)	0.005		
Bilirubin, >1.2 gr/dL	3.32 (2.44-4.53)	<0.01	1.65 (1.13-2.39)	0.008		
ALBI grade,						
Grade 2	2.99 (2.03-4.38)	<0.01			2.64 (1.74-3.98)	<0.01
Grade 3	16.23 (10.11-26.06)	<0.01			4.41 (2.45-7.93)	<0.01

ECOG: Eastern Cooperative Oncology Group, BMI: Body mass index, HER2: Human epidermal growth factor receptor 2, ALBI: Albumin-bilirubin.

MKSCC (Memorial Sloan Kettering Cancer Center) scores are the best examples of this situation. The present study was designed with the hypothesis that the ALBI score is prognostic in gastric cancer as well as HCC and metastatic colorectal carcinoma.

Exploring the prognostic studies of gastric cancer, albumin, globulin, albumin globulin ratio, neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, prognostic nutritional index have been demonstrated to impart an effect on survival and prognosis, but each study was performed using different cut-offs, and the results could not be entered into clinical use because of varied interpretations.[13-20] The ALBI score/grade is a practical automated method and is easy to use in clinical practice since the intervals obtained in the main HCC study and were authenticated in other studies without changing. As substantiated in our study, the ALBI score/grade is a proven parameter for PFS and OS in gastric cancer patients with liver metastasis.

Albumin is a serum protein synthesized by the liver, reflecting the nutritional status of the body coupled with negative changes in inflammatory conditions. It has been markedto be prognostic alone in various malignancies.[21] Several studies determined the relationship between serum albumin level and survival in both the early stages and metastatic stages in gastric cancer.[13,22] Serum bilirubin level is rarely used as anexclusive marker gastric cancer. In a study conducted in 2017, it was found to be an independent prognostic parameter when evaluated along with the TNM stage and albumin.[23] In our study, although albumin and bilirubin alone were found to be independent risk factors, ALBI grade alone was established to be a much more significant marker with a hazard ratio of 2.5 times higher than the other two parameters.

Although age and sex are a significant predisposing factor in many cancers, both in the early stages and metastatic stages, it is presumed that there may not be an independent prognostic indicator in a poor group of patients with liver metastases in our study.[24] ECOG performance score and BMI are known to have a prognostic effect on survival in many malignancies, especially in the metastatic stage.[13,25] Gastric cancer is one of the cancers that manifests itself with appetite and weight loss, cachexia, and indulgence in performance, and as highlighted in our study, these parameters significantly reduce the survival of patients.

The curative treatment of metastatic gastric cancer is not feasible clinically. Henceforth, the treatment aims to achieve palliation and, if possible, to improve the quality of life and prolong survival. In such a case, chemotherapy seems to be the

most appropriate option. Several clinical studies documented the contribution of first-line chemotherapy in various modalities in the survival of gastric cancer patients.[26] Especially in the case of HER2 positivity, a prominent contribution to both PFS and OS has been achieved by adding an anti-HER2 agent (Trastuzumab).[27] As observed in our study, the patient group receiving chemotherapy has a longer overall survival time in all analyzes. The HER2 positive group treated with trastuzumab has a significantly longer survival time compared to both the HER2 negative/unknown group receiving chemotherapy alone, and the group followed only by palliation. The HER2 status ofa high number of patients is not known in the foreground. This might affect the statistical analysis and might be the reason that HER2 positivity or trastuzumab taking or not is not an independent risk factor in both models.

Our studyhad some limitations. The most obvious of these is that it is a retrospective study and conducted as a single-center experience. Although the result was statistically significant, we believe that prospective validation in a larger, multicenter cohort is essential.

In conclusion, high ALBI grade is an independent prognostic indicator that is more sensitive than low albumin and high bilirubin level alone onestimating poor prognosis on progression-free survival and overall survival in advancedgastric cancer patients with liver metastasis.

Ethics approval and consent to participate

Approval for the study was obtained from the Non-Interventional Clinical Studies Ethics Committee of Trakya University Medical Faculty Hospital on 16.09.2019 with BAEK 2019/340 protocol.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ahmet Küçükarda, İrfan Çiçin;* ***Design:*** *Ahmet Küçükarda, Osman Köstek;* ***Control/Supervision:*** *İrfan Çiçin;* ***Data Collection and/or Processing:*** *Ahmet Küçükarda, Ali Gökyer, Ivo Gökmen, Osman Köstek, Muhammet Bekir Hacıoğlu, Sernaz Uzunoğlu;* ***Analysis and/or Interpretation:*** *İrfan Çiçin, Osman Köstek;* ***Literature Review:*** *Ahmet Küçükarda;* ***Writing the Article:*** *Ahmet Küçükarda, Ali Gökyer, Osman Köstek;* ***Critical Review:*** *İrfan Çiçin;* ***References and Fundings:*** *Ahmet Küçükarda;* ***Materials:*** *Ahmet Küçükarda.*

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