Original Article

The Optimal Treatment Approaches and Prognostic Factors in Elderly Patients with Advanced Stage Biliary Tract Tumors

Metastatik Safra Yolu Kanseri Olan Yaşlı Hastalarda Optimal Tedavi Yaklaşımları ve Prognostik Faktörler

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ABSTRACT

Introduction: There is a lack of evidence of the outcomes in elderly patients advanced stage biliary tract cancer due to the patients aged over 65 years are less than 25% in many prospective trials. We designed a retrospective multicenter study to evaluate the factors affecting treatment and survival in elderly patients with advanced-stage biliary tract cancer.

Materials and methods: A total of 116 patients with advanced stage biliary tract cancer aged ≥65 years were included, and the treatment responses, survival, and toxicity rates were evaluated with respect to age groups

Results: There was no significant difference between age and response to treatment, survival, or toxicity. The median progression-free survival and overall survival were 5.3, and 11.8 months respectively. Multivariate analysis indicated that ECOG PS ($p<0.001$ CI95% 1.5-3.7) and PNI ($p<0.001$ CI 95% 0.14-0.41) were significant independent prognostic factors for PFS. The independent prognostic factors for OS were choice of frontline regimen, NLR and PNI ($p=0.007$ CI 95% 0.71 – 0.94, $p=0.006$ CI 95% 1.2 – 3.1, $p=0.001$ CI 95% 0.35 – 0.91, respectively).

Discussion: This study confirms the general prognostic relevance of inflammatory parameters and the importance of frontline treatment in elderly patients with advanced-stage biliary tract tumors. Additionally, getting older does not indicate that treatment will be avoided or that they will have a worse prognosis and suffer from more toxicities.

Keywords: biliary tract cancer, elderly population, prognostic nutritional index, systemic inflammatory index

ÖZET

Giriş: 65 yaş üzeri hastaların klinik çalışmaların %25'inden daha azını oluşturması nedeniyle biliyer sistem kanseri olan ileri yaş hastaların yönetimi konusunda kanıt eksiği bulunmaktadır. Bu amaçla, metastatik safra yolu kanseri tanılı yaşlı hastalarda tedaviyi ve sağkalımı etkileyen faktörleri değerlendirmek için retrospektif çok merkezli bir çalışma tasarladık.

Gereç ve yöntemler: Çalışmaya 65 yaş ve üzeri, ileri evre safra yolu kanseri tanısı almış, 116 hasta dahil edildi ve yaş gruplarına göre tedavi yanıtları, sağkalım ve toksisite oranları değerlendirildi.

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Bulgular: Median yaşa göre gruplandırılıdğında; yaş ile tedaviye yanıt, sağkalım, toksisite arasında anlamlı bir fark bulunmadı. Tüm populasyonda medyan progresyonsuz sağkalım (PSK) ve genel sağkalım (GSK) sırasıyla 5.3, 11.8 aydı. Multivariate analizde, PSK için bağımsız prognostik faktörler preformans durumu(ECOG PS) (p<0.001 CI95% 1.5-3.7) ve Prognostik nutrisyonel indek (PNI) (p<0.001 CI 95% 0.14-0.41) olarak bulundu. GSK için ise bağımsız prognostik faktörler, birinci sıra tedavi seçimi, Notrofil Lenfosit oranı (p=0,007 CI %95 0,71 – 0,94) ve PNI (p=0,001 CI %95 0,35 – 0,91) olarak bulundu.
Tartışma: Metastatik safra yolu kanseri olan yaşlı hastalarda prognozu etkileyen temel faktöreler inflamatuar parametreler ve birinci basamakta seçilen kemoterapi rejimidir. İleri yaş ile sağkalım, toksiste profili ve tedavi toleransı farklılık göstermemektedir.

Anahtar kelimeler: Safra yolu kanseri, yaşlı populasyon, Prognostik nutrisyonel indeks, sistemik inflamatuvar indeks

Introduction

Biliary tract cancers including intrahepatic cholangiocarcinoma (ICC), extrahepatic cholangiocarcinoma (EHC), and gallbladder cancer (GBC) are rare malignancies with poor survival [1]. The incidence and epidemiology of biliary tract cancer are complex and vary worldwide. It is shown that intrahepatic cholangiocarcinoma is on the rise in the Western world, and gallbladder cancer is on the decline. GBC is also a very rare malignancy with high mortality rates. Fewer than 5000 new cases are diagnosed each year in the United States and the incidence correlates with the prevalence of cholelithiasis [1-3].

Chronic inflammation and the immune response play a big role in the development of biliary tract cancers and biomarkers such as neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the systemic immune-inflammation index (SII) were studied in multiple solid tumors. The prognostic nutritional index [PNI] had an impact on clinical outcomes and low PNI was significantly associated with poor prognosis in patients with BTC in many reports [4-6].

Age-related physiologic changes in the biliary tract can cause more gallstones in elderly patients than young people. It is unclear whether these changings are responsible for the development of GBC. Although the incidence of pancreatic cancer is more frequent in elderly patients; It is not yet clear the correlation between age and biliary tract cancer development [7,8].

BTC is mostly diagnosed in the advanced stage with an estimated five-year survival of 10-20%. Therefore, the major aim is to palliate the symptoms and improve the life quality with longer progression-free survival. However, the cisplatin plus gemcitabine (GC) regimen is the standard frontline regimen, due to potential toxicity and higher comorbidities, physicians can prefer other treatment options for elderly patients [9-12].

In many prospective trials patients aged ≥65 years are less than 25%. Therefore, treatment outcomes and prognostic factors are not well described [11]. The objective of this multicenter study is to determine factors affecting progression-free survival and to evaluate both treatment modalities and their outcomes as real-life experiences in elderly adults with advanced biliary tract tumors.

Material Method

This was a retrospective multicenter study that included a total of 116 patients aged >65 years with advanced biliary tract cancer (ABTC). ICC and ECC, klatskin tumors and GBC patients were included in this study. Data were obtained from patients' charts concerning age, ECOG performance status (PS), tumor location, NLR, PLR, SII, PNI indexes, duration of treatment, and survival outcomes after written informed consent had been obtained from patients.

Treatment responses, survival, and toxicity rates were evaluated together with respect to age groups. Patients with poor performance status and who died related to other reasons were excluded from the study. Common

Terminology Criteria for Adverse Events (CTCAE) v5.0 was used for adverse event evaluation. All procedures performed in studies involving human participants were by the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The Local Ethics Committee of Istanbul Medipol University approved the study with decision number E-10840098-772.02-2913.

Statistical analysis:

Statistical analyses were performed using the statistical analysis was performed using the Statistics Package for Social Sciences software (ver. 24.0; SPSS Inc., Armonk, NY: IBM Corp). The distribution of the study parameters was non-normal distribution, Inflammatory markers were dichotomized at the median as a cut-off value. The relationship between the age group and the clinico-pathological factors was compared using the chi-squared test and Fisher's exact test. Survival analysis and curves were established using the Kaplan-Meier method and compared with the long-rank test. Progression-free survival (PFS) was defined as the time from the diagnosis of advanced stage disease to progression or the last follow-up. Overall survival (OS) was described as the time from diagnosis to the date of the patient's death or last known contact. Univariate and multivariate analyses of prognostic factors related to survival were performed by the Cox proportional hazards model. Multivariate p values were used to characterize the independence of these factors. The 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All p values were two-sided in tests and p values less than or equal to 0.05 were accepted to be statistically significant.

Results:

Between June 2015, and June 2021, a total of 116 patients with ABTCs were included in this study. Sixty-four of the patients (55.2%) were female and fifty-two of them (44.8%) were male with a median age of 70 years (range: 65-89). Sixty-four patients (55.2%) were ≥ 70 years and 52 patients (44.8%) were <70 years. At the initial diagnosis, most patients (77.6%) had ABTC. Forty-eight patients (41.4%) were diagnosed with ICC, twenty patients (10.3%) were ECC, forty-two of patients (36.2%) were GBC, six patients (5.2%) were klatskin tumors respectively. Most patients (n:87) were in good performance status.

In the front-line setting, the gemcitabine monotherapy, cisplatin plus gemcitabine regimen and FOLFOX regimen were preferred in 36 patients (31.0), 38 patients (32.8%), and 15 patients (12.9%), respectively. Eight of the patients (6.9%) were followed up with the best supportive care.

Patients received a median of 4 cycles of chemotherapy (range: 2-12), and 49 of patients (46.7%) could complete the treatment. The objective response rate (ORR) was 12% in all populations. Any grade treatment-related adverse event (AE) was seen in 49 of the patients (42.2%). Grade3 or 4 AEs were detected in 15 patients (12.9%) patients. No deaths due to an AE occurred. 3 of nine patients who were treated with the FOLFIRINOX regimen suffered from grade 3/4 AE while no grade ¾ AE was seen in patients who received single-agent regimens.

There was no significant correlation between treatment regimens and toxicity profile in elderly patients. Additionally, treatment-related any grade of adverse event was seen in 27 patients with <70 years and serious toxicity as grade 3/4 in 22 patients. In the ≥ 70years; the treatment-related adverse event was observed in 22 patients and grade 3 or higher toxicity was seen in 7 patients. ≥ 10% weight loss at the time of diagnosis was statistically significantly higher in patients aged 70 years and older (p=0.038). When the patients were categorized according to age; no significant difference was determined between age groups according to the response to treatment, ECOG PS, tumor localization, presence of jaundice, the choice of front-line treatment, the development of treatment-related AEs, and grade 3 or higher AEs. Although not

Table 1: Patient's and tumour characteristics regarding the age

Characteristics	Total N (%)	<70 years n (%)	≥70 years n (%)	p
Total	116	52 (44.8%)	64 (55.2)	
Initial diagnosis, presence of:				
≥ 10% Weight loss	68 (58.6)	43 (67.2)	25 (48.1)	**0.038**
Jaundice	29 (25)	12 (22.1)	17 (26.5)	0.4
Abdominal Pain	63 (54.3)	28 (51.1)	35 (57.3)	0.1
Gender				
Male	52 (44.8)	31 (48.4)	21 (40.4)	0.3
Female	64 (55.2)	33 (51.6)	31 (59.6)	
ECOG PS*				
0	18 (15.5)	9 (14.1)	9 (17.3)	0.88
1	69 (59.5)	39 (60.9)	30 (57.7)	
2	29 (25.0)	16 (25.0)	13 (25.0)	
Localization of primary tumour		28 (43.8)	20 (38.5)	
Intrahepatic	48	11 (17.2)	9 (17.3)	0.53
cholangiocarcinoma	20	21 (32.8)	21 (40.4)	
Extrahepatic	42	4 (6.3)	2 (3.8)	
cholangiocarcinoma	6			
Gallbladder				
Klatskin				
Initial clinical TNM* stage				
Stage I	2 (1.7)	1 (1.6)	1 (1.9)	0.5
Stage II	8 (6.9)	6 (9.4)	2 (3.8)	
Stage III	16 (13.8)	10 (15.6)	6 (7.2)	
Stage IV	90 (77.6)	47 (73.4)	43 (82.7)	
Presence of PTC* replacement	23 (19.8)	13 (20.3)	10 (19.2)	0.8
Cholangitis	26 (22.4)	14 (21.9)	12 (23.1)	0.8
Choice of the first-line treatment				
Gemcitabine Oxaliplatin	8 (6.9)	4 (6.3)	4 (7.7)	
Gemcitabine cisplatin	38 (32.8)	26 (40.6)	12 (23.1)	
Gemcitabine single agent	36 (31.0)	12 (18.8)	24 (46.2)	**0.055**
FOLFOX*	15 (12.9)	11 17.2)	4 (7.7)	
FOLFIRINOX*	2 (1.7)	1 (1.6)	1 (1.9)	
BSC*	8 (6.9)	4 (6.3)	4 (7.7)	
Other	9 (7.8)	6 (9.4)	3 (5.8)	
Treatment Response				
CR/PR	13 (11.2)	9 (14.1)	4(7.7)	
Stable Disease	36 (31.0)	17 (26.6)	19 (36.5)	0.48
Progressive Disease	67 (57.8)	38 (59.4)	29 (55.8)	
Treatment-Related Any Grade Adverse Event	49 (42.3)	27 (42.4)	22 (42.3)	0.9
Grade 3/4 Adverse Event	15 (57.7)	8 (29.6)	7 (31.8)	0.86

*ECOG PS: Eastern Cooperative Oncology Group Performance Status FOLFOX: (fluorouracil, Leucovorin, Oxaliplatin) *FOLFIRINOX (leucovorin and fluorouracil plus irinotecan and oxaliplatin) * BSC: best supportive care, *TNM: tumour, node, metastasis, *PTC: Percutaneous Transhepatic Cholangiography, *CR: Complete Response, *PR: Partially Response

* p values <0.05 were regarded as statistically significant

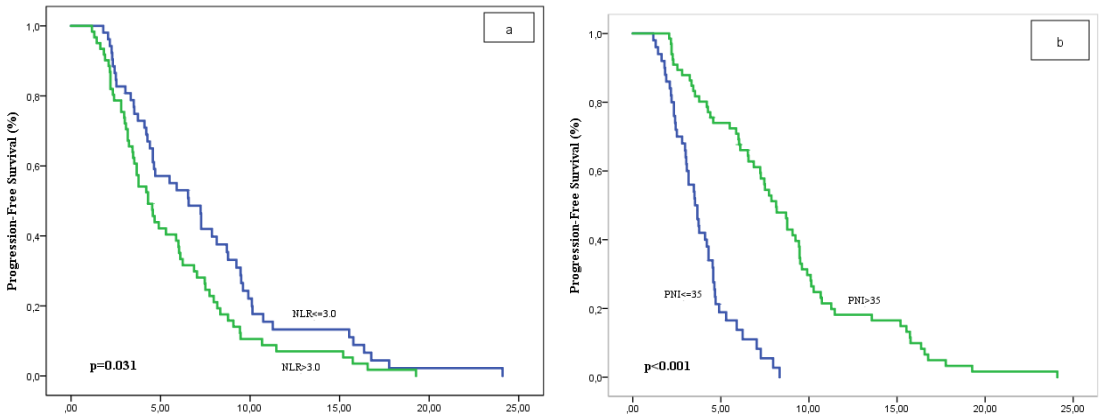

Figure 1 a, b: Progression-free survival curves according to the NLR and PNI.

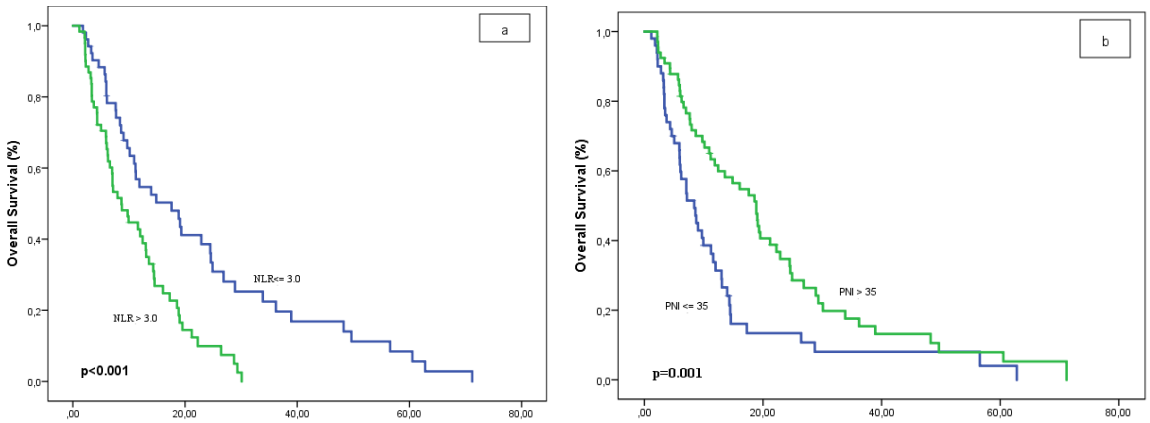

Figure 2 a, b: Overall survival curves according to the NLR and PNI.

statistically significant, the choice of monotherapy tended to be higher in the older population (p=0.055). The baseline patient's and tumor characteristics and the comparison between age groups are summarized in Table 1.

Median NLR, PLR, SII, and PNI values were determined as 3.0, 152.5, 38.5, and 35.0 respectively. The number of patients with NLR >3.0 and PLR >152.5 were 61 (54%) and 56 (48.3%), respectively. The number of patients with SII>38.5 and PNI > 35 was 66 (44.5%) and 66 (56.9%) respectively.

At a median follow-up of 10.0 months, the median PFS time was 5.3 months, while the median OS time was 11.8 months in all patients. Univariate analysis for PFS revealed that ECOG PS (p<0.001), the choice of treatment regimen (p<0.001), NLR (p=0.03) and PNI (p<0.001) were found to be significant prognostic indicators. While not statistically significant, the localization of primary tumor and SII tended to affect the PFS. The PFS did not differ between age groups.

The median PFS was 4.3 months and 6.5 months in patients with NLR>3 and NLR ≤3 respectively (Figure1a). The median PFS was 8.1 months and 3.5 months in patients with PNI >35 and PNI ≤35 respectively (Figure 1b).

The median PFS for patients treated with BSC was 2.2 months, in the gemcitabine monotherapy group it was 4.4 months, in the cisplatin-gemcitabine group it was 7.7 months, in the GEMOX group it was 6 months,

Table 2: Univariate and Multivariate analysis for progression-free and overall survival

	Progression Free Survival		Overall Survival	
	Univariate analysis	Multivariate analysis	Univariate analysis	Multivariate analysis
Factor	p	P (HR; 95% CI)	p	p (HR; 95% CI)
Age (≥70 years vs <70 years)	0.64		0.08	0.2 (0.35; 0.54-1.66)
Gender (male vs female)	0.87		0.9	
ECOG PS (0 vs 1/2)	<0.001	<0.001 (2.4; 1.5–3.7)	0.02	0.6 (1.1; 075-1.62)
Cholangitis (absent vs present)	0.1		0.5	
PTC requirement (absent vs present)	0.2		0.7	
Tumor localization (ICC vs others)	0.55		0.6	
At initial diagnosis				
Presence of ≥ 10% weight loss	0.6		0.5	
Presence of Jaundice	0.7		0.78	
Choice of Treatment (BSC vs others)	<0.001	0.3	0.03	0.007 (0.82; 0.71-0.94)
SII (≤ 38.5 vs >38.5)	0.059	0.64	0.01	0.19 (0.73; 0.46-1.16)
NLR (≤3.0 vs >3.0)	0.03	0.34	<0.001	0.006 (1.9; 1.2-3.1)
PLR (≤ 152.5 vs >152.5)	0.1	0.61	0.07	0.8 (1.1; 0.67-1.55)
PNI (≤ 35 vs > 35)	<0.001	<0.001 (0.24; 0.14–0.41)	0.001	0.01 (0.56; 0.35-0.91)

***** HR: hazard ratio, CI: confidence interval, BSC: best supportive care, ECOG PS: Eastern Cooperative Oncology Group Performance Status PTC: Percutaneous Transhepatic Cholangiography, NLR:neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio, SII:systemic immune-inflammation index, PNI;prognostic nutritional index

and in the FOLFOX group, it was also 7.8 months.

In the univariate analysis for OS, ECOG PS, treatment regimen, SII, PNI, and NLR were found to be prognostic factors (p=0.02, p=0.01, p=0.001, p<0.001, respectively). The median OS treated with BSC was 1.8 months, with monotherapy gemcitabine was 7.0 months, with cisplatin-gemcitabine was 14.5 months, with GEMOX group was 11.2 months and with FOLFOX was 26.4 months, respectively. Multivariate analysis indicated that ECOG PS (p<0.001 HR:2.4; CI95% 1.5-3.7) and PNI (p<0.001 HR:0.24, CI 95% 0.14-0.41) were significantly independent prognostic factors for PFS.

The median OS was 8.6 months and 17.6 months in patients with NLR>3 and NLR ≤3 respectively (Figure 2a). The median OS was 18.8 months and 8.4 months in patients with PNI >35 and PNI≤35 (Figure 2b). The median OS was 9.7 months and 12.4 months in patients with PLR>152.5 and PLR ≤152.5 respectively.

In multivariate analysis the choice of treatment, NLR and PNI were revealed as an independent prognostic factor for OS (p=0.007 CI 95% 0.71 – 0.94, p=0.006 CI 95% 1.2 – 3.1, p=0.001 CI 95% 0.35 – 0.91, respectively). Table 2 summarized the multivariate and univariate analysis for both OS and PFS.

Discussion:

Inclusion of older patients with biliary tract cancer has a limited rate in prospective randomized trials, thus to guide the systemic treatment including BSC has lack of evidence in elderly patients. Also, the term elderly is not well described either. In the current study, we aimed to retrospectively analyze the elderly patients with ABTC to contribute to the literature on decision-making treatment and the choice of regimens and understanding well the prognostic factors affecting survival in these patients.

In Advanced Biliary Cancer-02 (ABC-02) clinical trial, the median OS was 11.7 months in patients treated with cisplatin/gemcitabine. Although age was not a stratification factor, the study concluded that age was not prognostic for PFS and OS in those receiving monotherapy or combination therapy [10,11]. Lewis et al. analyzed 1421 patients diagnosed with hepato-pancreaticobiliary tract tumors. They showed that 10% of patients were over 80 years and 36% had BTC. The median OS was 10 months in this cohort, but there was no significant survival difference between older and younger patients when considered fit enough to have active systemic therapy [12]. Hepatobiliary and Pancreatic Oncology Group of Japan Clinical Oncology Group (JCOG) demonstrated that gemcitabine plus S-1 was non-inferior in OS compared with GC as a first-line treatment for advanced BTC [13]. 354 elderly patients from this study were analyzed in another trial. They reported that there was no significant correlation in OS, efficacy, and adverse events between <75 (non-elderly] and≥ 75 years (elderly) group. In the elderly group, the median OS was 12.7 months for those who received GC [14].

In our population, there was no significant difference in OS and PFS between patients with <70 years and >70 years. The median PFS was 5.3 months, and the median OS was 11.8 months in the overall population. The treatment choice in the frontline setting had a significant impact on PFS (p<0.001) and OS (p=0.01). Better survival outcomes were seen in cisplatin plus gemcitabine and the FOLFOX group (median PFS 7.7 months and 7.8 months respectively). The median OS was superior in patients treated with FOLFOX and cisplatin plus gemcitabine than in other regimens (26,4 months and 14,5 months respectively).

In the ABC-02 study, 66% of patients received at least 3 cycles of gemcitabine for ABTC [10]. In our cohort, the median number of chemotherapy cycles was 4 and 35.3% of patients could complete the planned treatment protocol. Our results were thus compatible with the literature [10-14]. Furthermore, in this study as the patients were categorized according to the median age, there was no significant difference between age and response to treatment, ECOG PS, tumor localization, the development of treatment-related AE, and grade 3 or higher AE. This difference can be explained by the toxicity rate in the total cohort which was lower than in previous trials [10-14] and before treatment 10% dose reduction was done for all patients. Moreover, ORR was significantly correlated with the frontline systemic treatment regimen. As expected, the worse survivals were observed in the BSC group. The OS benefit of the FOLFOX regimen was significantly higher in elderly patients than in other regimens compared with younger patients. However, median PFS time was higher in the cisplatin-gemcitabine group. There was a trend toward choosing monotherapy gemcitabine in patients>70 years old.

In elderly patients, there are some tools to help with geriatric assessment. As American Society of Clinical Oncology (ASCO) guidelines recommend at a minimum, a geriatric assessment of function, comorbidity, falls, depression, cognition, and nutrition.

Cancer and Ageing Research Group (CARG] can be used to estimate the toxicity. Additional tools are recommended to use in the geriatric population [15-21]. In this study, geriatric assessment tools could not be used due to the retrospective design which was another limitation of our study.

Previously studies had shown that higher rates of systemic inflammatory markers such as NLR, and PLR were associated with poor prognosis [22-24]. We illustrated that ECOG PS ($p<0.001$ HR:2.4) and PNI ($p<0.001$ HR:0.24) were significantly independent prognostic factors for PFS; in addition, the choice of treatment ($p=0.007$ CI 95% 0.71 – 0.94), NLR ($p=0.006$ CI 95% 1.2 – 3.1) and PNI ($p=0.001$ CI 95% 0.35 – 0.91) were independent prognostic factors for OS in advance stage elderly BTC. Similar to the literature, we demonstrated a significant relationship between higher NLR and PLR values and worse survival outcomes in the elderly population.

The limitation of our study was the retrospective design which might concern bias and affect results. Another limitation of our study was not to use geriatric assessment tools.

The contribution of our study to the literature was that age should not be a criterion for the choice of treatment. We have shown that being elder had no significant impact on survival outcomes and treatment response. We revealed that the side-effect profile was also not related to age but treatment choice. Although not included in clinical studies, we have shown that inflammatory markers were poor prognostic markers in the elderly population too.

Conclusion

There is a lack of evidence to guide the best treatment regimen in elderly patients with ABTC because age is an exclusion criterion in many trials. Where evidence is available, the survival of older patients with ABTC in receipt of systemic therapy is similar to younger patients. In this multicenter study, we have shown that age was not related to survival and the outcomes of the treatment choice, similarly to the literature. SII which can be used in daily practice was an independent prognostic factor in elderly patients. In our opinion best choice of treatment should be made concerning ECOG PS, not age. To conclude further age-specific studies should be encouraged and real-world observational studies may offer useful comprehensions.

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