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ORIGINAL ARTICLE



A prognostic model in patients with advanced biliary tract cancer receiving first-line chemotherapy

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ABSTRACT

Background: Standard treatment of advanced biliary tract cancer (aBTC) is represented by first-line chemotherapy (CT1). However, some patients do not gain any benefit from CT1, contributing to the overall dismal prognosis of aBTC. The present study aimed to devise a prognostic model in aBTC patients receiving CT1.

Methods: A large panel of clinical, laboratory, and pathology variables, available before the start of CT1, were retrospectively assessed in a multi-centric cohort to determine their prognostic value on univariate and multivariate regression analysis. The variables that showed a significant correlation with overall survival (OS) were computed in a three-tier prognostic score. External validation of the prognostication performance was carried out.

Results: Clinical histories of 935 patients (median OS 10.3 months), with diagnosis dates ranging from 2001 to 2017, were retrieved from 14 institutions. According to multivariate analysis, Eastern Cooperative Oncology Group performance status, carbohydrate antigen 19.9, albumin levels, and neutrophil/lymphocyte ratio were strongly associated with OS ($p < 0.01$). The prognostic score could generate a highly significant stratification (all between-group p values ≤ 0.001) into groups of favorable (comprising 51.5% of the sample), intermediate (39.2%), and poor prognosis (9.3%): median OS was 12.7 (CI_{95%} 11.0–14.4), 7.1 (CI_{95%} 5.8–8.4), and 3.2 months (CI_{95%} 1.7–4.7), respectively. This OS gradient was replicated in the validation set (129 patients), with median OS of 12.7 (CI_{95%} 11.0–14.3), 7.5 (CI_{95%} 6.1–8.9), and 1.4 months (CI_{95%} 0.1–2.7), respectively (all between-group p values ≤ 0.05).

Conclusion: A prognostic score, derived from a limited set of easily-retrievable variables, efficiently stratified a large population of unselected aBTC patients undergoing CT1. This tool could be useful to clinicians, to ascertain the potential benefit from CT1 at the start of treatment.

Abbreviations: aBTC: advanced biliary tract cancer; AC: ampullary carcinoma; ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BTC: biliary tract cancer; Ca19.9: carbohydrate antigen 19.9; CI_{95%}: 95% confidence interval; CT1: first-line chemotherapy; dECC: distal extrahepatic cholangiocarcinoma; ECOG PS: Eastern Cooperative Oncology Group performance status; GC: gallbladder carcinoma; GGT: γ -glutamyl transpeptidase; Hb: hemoglobin; HR: hazard ratio; ICC: intrahepatic cholangiocarcinoma; NLR: neutrophil/lymphocyte ratio; OS: overall survival; pECC: proximal extrahepatic cholangiocarcinoma; PI: prognostic index value; RDW: red blood cell distribution width

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Advanced biliary tract neoplasms; gallbladder neoplasms; cholangiocarcinoma; prognostic factors; prognostic score


Background and rationale

Biliary tract cancer (BTC) comprises epithelial malignancies arising from the different portions of the biliary tree, namely

gallbladder carcinoma (GC), ampullary carcinoma (AC), and intrahepatic (ICC), proximal (pECC), and distal (dECC) extrahepatic cholangiocarcinoma. Age-standardized incidence of BTC

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 Supplemental data for this article can be accessed [here](#).

in Southern Europe (6 cases/100,000 inhabitants/year) is higher than in Central and Northern Europe [1]. In particular, with an incidence of approximately 7–8 cases/100,000/year, BTC represents 1% of all tumor diagnoses in Italy [2]. Diagnosis often occurs at an advanced stage (aBTC), that is no longer amenable to curative surgery, and, even in the resected cases, recurrence rate is high [3]: these malignancies are, therefore, globally characterized by high lethality [4].

However, multi-level differences in biologic features and clinical behaviors are increasingly recognized across aBTC primary sites, as well as within the single primary site [5–9]. In spite of this heterogeneity, the only standard chemotherapy regimen approved in the Western world for aBTC is represented by first-line chemotherapy (CT1) with gemcitabine-platinum salts (cisplatin, oxaliplatin), or gemcitabine monotherapy [10] in unfit patients. Moreover, this option was established quite recently [11], as compared to other malignancies. However, some patients do not derive any benefit from CT1, contributing to the overall dismal prognosis of aBTC.

The purpose of the present study was to develop and validate a new prognostic model for overall survival (OS) from the start of CT1, based on individual clinical, laboratory, and pathology data.

Patients and methods

This study is a multi-center retrospective analysis of aBTC cases conducted by the Cholangiocarcinoma Italian Group Onlus (G.I.C.O.; Gruppo Italiano Colangiocarcinoma Onlus). Inclusion criteria were: histological or cytological diagnosis of aBTC after 2000, and administration of at least one cycle of CT1. Patients with insufficient treatment information were excluded.

Values were collected for an extensive panel of variables, from electronic medical records. Anamnestic and pathology data included sex, primary site, tumor grading, prior biliary stenting, and prior surgery. Inter-center heterogeneity in tumor grading was standardized as follows: well-differentiated tumors were termed as G1, moderately differentiated as G2, poorly differentiated as G3, and undifferentiated or anaplastic as G4; in the case of intratumoral heterogeneity, the maximum grade was recorded; Gx defined a lack of information in the pathology report, such as in the case of certain cytology reports. Values at CT1 initiation were collected for age, disease extension (locoregional, which grouped locally advanced, unresectable disease, and locoregional relapse; distant spread, which grouped initially metastatic disease and recurrence with metastases), number of metastatic sites (no, single, or multiple metastases), Eastern Cooperative Oncology Group performance status (ECOG PS) at the start of CT1. Laboratory analyses, recorded at the medical visit for CT1 initiation or up until two weeks prior to CT1 initiation, included: carcinoembryonic antigen, carbohydrate antigen 19.9 (Ca19.9), hemoglobin (Hb), red blood cell distribution width (RDW), platelets, leucocytes, lymphocytes, neutrophils, monocytes, prothrombin time international normalized ratio, total bilirubin, γ -glutamyl transpeptidase (GGT), alkaline

phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, and lactate dehydrogenase. Several derived indicators, already evaluated either in BTC or malignancies of the same district (hepatocellular carcinoma, pancreatic adenocarcinoma), were also calculated: the neutrophil/lymphocyte (NLR), lymphocyte/monocyte, platelet/lymphocyte, ALT/lymphocyte, albumin/GGT, GGT/ALT, albumin/ALP, GGT/platelet, and Hb/RDW ratios, in addition to the systemic inflammation (neutrophils \times platelets/lymphocytes) and the prognostic nutritional ($10 \times$ albumin + $0.005 \times$ lymphocytes) indexes. Dates of death were retrieved from electronic medical records or administrative files. Data were collected until December 2019 and subsequently analyzed.

OS, defined as the time interval from the first CT1 cycle to death from any cause, was the primary endpoint, and was calculated using the Kaplan–Meyer estimator. OS of patients still under treatment or lost to follow-up were censored at the last follow-up. Confidence intervals were set at 95% (CI_{95%}), and two-sided *p* values < 0.05 were considered statistically significant unless Bonferroni correction was applied for multiple comparisons. Given its retrospective nature, the study did not consider a pre-planned sample size.

A multivariate analysis by backward stepwise elimination was performed on a limited panel of variables. These variables were selected *post hoc*, from those that had displayed a significant correlation with OS on univariate analysis, and were chosen without pre-specified criteria as the most meaningful and clinically relevant. Continuous variables were dichotomized using relevant cut points (e.g. definition of anemia). A prognostic model was devised in the form of a score, and calculated as follows: the value of 1 was assigned to each of the four identified highly-significant independent predictors of OS whenever the case fell in the favorable category (e.g. albumin levels ≥ 3.50 mg/dl), or the respective hazard ratio (HR), rounded to the first decimal place, ascertained by univariate analysis if the patient was identified as being in the unfavorable category (e.g. albumin levels < 3.50). Individual prognostic index values (PI) were derived from the sum of these four values. Patients were then categorized into three groups according to their PI. The form of the model, a three-tier prognostic score (favorable, intermediate, and unfavorable prognosis), had been established in advance, whereas optimal cutoff values were empirically researched to achieve an optimized stratification. In particular, the model aimed to maximize the favorable-prognosis group and to minimize the unfavorable-prognosis one, while maintaining very distinct group-specific survivals. Patients with unavailable data were excluded, according to complete case analysis. Survival analysis employed the log-rank test and Cox regression model. Harrell's c-index, calculated as average from time 0–12 months, as well as areas under the receiver operating characteristic curves for OS events at 6 (AUC₆) and 12 (AUC₁₂) months, were employed as estimators of the discriminatory power of the prognostic index. OS curves for selected subgroups of interest were also calculated. External validation was conducted on a cohort from Modena Cancer Center (Italy) selected with identical criteria. Differences in characteristics between the cohorts were

assessed by Chi-square and Mann–Whitney *U* tests. IBM SPSS Statistics for Windows, version 20 (IBM Corp., Armonk, NY, USA) was used as the main statistical program.

The study protocol followed the principles stated by the World Medical Association's Declaration of Helsinki, and was revised and approved (protocol no 0072135) by the institutional Ethics Committee (Comitato Etico interaziendale AOU Città della Salute e della Scienza di Torino – AO Ordine Mauriziano di Torino – ASL Città di Torino). The validation cohort received approval from the local Institutional Review Board (prot. no AOU 0006255/19). The manuscript was reviewed for adherence to the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) and TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) statements [12,13].

Results

Study population

Clinical histories from 935 patients (training cohort) fulfilling the eligibility criteria were retrieved from 14 Italian medical institutions. The diagnosis period ranged from April 2001 to August 2017. Demographic and baseline clinical, pathological and laboratory characteristics of the study population are listed in Table 1. In particular, median age was 65.9 years; 51.4% were male; the main primary site was ICC in 50.3% of patients, followed by GC in 21.1%, dECC in 14.2%, pECC in 8.2%, AC in 5.9%, and unknown site in 0.3%. Regarding treatment, 562 patients (60.1%) received per intention-to-treat a gemcitabine-platinum salt doublet as CT1, 224 (24.0%) received gemcitabine monotherapy, and 149 (15.9%) received other regimens. Second-line treatment was received by 45.3% of patients. A total of 814 OS events had already

Table 1. Characteristics of the training and validation cohorts.

Variable	Training cohort (n = 935)	Validation cohort (n = 159)	p Value
Age in years			
Median (IQR)	65.9 (58.5–72.1)	67.0 (59.0–75.0)	0.038
≥70 years	312 (33.3)	66 (41.5)	0.046
Sex			
Female	454 (48.6)	85 (53.5)	0.253
Male	481 (51.4)	74 (46.5)	
ECOG PS			
0–1	789 (84.4)	112 (70.4)	<0.001
≥2	84 (9.0)	26 (16.4)	
na	62 (6.6)	21 (13.2)	
Disease extension			
Locoregional	210 (22.5)	19 (11.9)	0.010
Distant spread	720 (77.0)	139 (87.4)	
na	5 (0.5)	1 (0.6)	
Prior R0 surgery			
Yes	236 (25.2)	40 (25.2)	0.945
No	674 (72.1)	114 (71.7)	
na	25 (2.7)	5 (3.1)	
Tumor grade			
Low (G1-G2)	265 (28.3)	23 (14.4)	<0.001
High (G3-G4)	330 (35.3)	18 (11.3)	
Gx or na	340 (36.3)	118 (74.2)	
Laboratory [median, (IQR)]			
CEA (ng/ml)	3.4 (1.6–10.6)	2.6 (1.5–8.7)	0.047
Ca19.9 (U/ml)	119.5 (24.35–822.75)	119.4 (26.7–1234.0)	0.082
Hb (g/dl)	12.6 (11.4–13.9)	12.5 (11.2–13.3)	0.297
Neutrophils (c/μl)	4970 (3507–7330)	5620 (3997–8173)	0.011
NLR	3.05 (2.09–4.55)	3.54 (2.47–5.26)	0.236
Platelets (/μl)	239 (184–319)	251 (200–321)	0.092
Albumin (g/dl)	3.66 (3.20–4.03)	3.70 (3.40–4.10)	0.290
ALT (U/L)	31 (19–54)	33.5 (19–69)	0.017
Primary site			
ICC	470 (50.3)	76 (47.8)	<0.001
pECC	77 (8.2)	15 (9.4)	
dECC	133 (14.2)	10 (6.3)	
GC	197 (21.1)	58 (36.5)	
AC	55 (5.9)	0 (0.0)	
na	3 (0.3)	0 (0.0)	
First-line chemotherapy regimen			
Gem-Pt	562 (60.1)	75 (47.2)	0.003
Gem	224 (24.0)	44 (27.7)	
Other regimens	149 (15.9)	40 (25.1)	
Overall survival in months			
Median (CI _{95%})	10.3 (9.5–11.1)	8.0 (6.7–9.3)	0.052

Values in n (%), unless otherwise specified.

AC: ampullary carcinoma; ALT: alanine aminotransferase; Ca19.9: carbohydrate antigen 19.9; CEA: carcinoembryonic antigen; CI_{95%}: 95% confidence interval; (d/p)ECC: (distal/proximal) extrahepatic cholangiocarcinoma; ECOG PS: Eastern Cooperative Oncology Group performance status; GC: gallbladder carcinoma; Gem: gemcitabine; Hb: hemoglobin; ICC: intrahepatic cholangiocarcinoma; IQR: interquartile range; na: not available; NLR: neutrophil/lymphocyte ratio; nr: not reported; OS: overall survival; Pt: platinum salts.

occurred at the data cutoff, and the median OS of the entire cohort was 10.3 months (CI_{95%} 9.5–11.1). Patients treated with gemcitabine monotherapy (7.5 months, CI_{95%} 6.6–8.4), but not those treated with other treatments (12.4 months, CI_{95%} 10.4–14.4), experienced shorter OS ($p < 0.001$, and $p < 0.12$, respectively) than patients treated with gemcitabine-platinum salts (11.7 months, CI_{95%} 10.8–12.6).

Prognostic factors

Among the several variables that had a prognostic association with OS on univariate regression analysis [Supplementary Table 1], eight of the most relevant were dichotomized and subject to multivariate analysis. ECOG PS ≥ 2 , Ca19.9 > 120 U/l, albumin < 3.50 mg/dl, and NLR > 3.1 retained a high statistical significance ($p < 0.01$), whereas Hb < 12.5 g/dl, prior RO surgery, disease status, and platelet count $> 400,000/\mu\text{l}$ did not (Table 2).

Prognostic model

All of necessary data for a PI to be calculated were available for 421 patients (training set). The distribution of relevant variables in the training and validation sets was not significantly different from their respective original cohorts [Supplementary Table 2].

The resulting equation of the index was: PI = [1 or 3.0 (ECOG PS)] + [1 or 1.5 (Ca19.9)] + [1 or 2.0 (albumin)] + [1 or 1.7 (NLR)]. Values ranged from 4.0 to 8.2, with a median of 5.0. Patients were categorized into three risk groups, with prognoses categorized as favorable (PI ≤ 5.0 , $n = 217$, 51.5% of the training set), intermediate ($5.0 < \text{PI} \leq 6.5$, $n = 165$, 39.2%), and unfavorable (PI > 6.5 , $n = 39$, 9.3%). These groups showed a clear OS gradient, with median values of

12.7 months (CI_{95%} 11.0–14.4), 7.1 months (CI_{95%} 5.8–8.4), and 3.2 months (CI_{95%} 1.7–4.7), respectively, and 1-year OS rates of 55%, 27%, and 13%, respectively. The early and persistent separation of the corresponding survival curves resulted in marked and statistically significant differences (all between-group p values ≤ 0.001) (Table 3; Figure 1).

The c-index, AUC₆, and AUC₁₂ of the prognostic model in the training set were 0.69, 0.68 (CI_{95%} 0.62–0.73), and 0.66 (0.61–0.72), respectively [Supplementary Figure 1]. The model retained its prognostic performance in most of the subgroups explored (primary sites, CT1 regimen, advanced age) [Supplementary Table 3, Supplementary Figure 2]. The mere PI, not categorized in prognostic groups, achieved an AUC₆ of 0.72 (CI_{95%} 0.67–0.77) and an AUC₁₂ of 0.69 (CI_{95%} 0.63–0.74). Patients with ECOG PS of 0, 1, and 2 achieved median OS of 13.1 (CI_{95%} 11.1–15.1), 7.7 (CI_{95%} 6.1–9.3), and 4.0 (CI_{95%} 0.4–7.6) months, respectively. Stratification according to ECOG PS achieved AUC₆ 0.65 (CI_{95%} 0.60–0.71) and AUC₁₂ 0.67 (CI_{95%} 0.62–0.72), similar to those obtained with the risk score ($p = \text{ns}$).

Validation

The validation cohort consisted of 159 clinical histories, diagnosed from November 2000 to March 2018. The median OS in the validation cohort was 8.0 months (CI_{95%} 6.7–9.3) (Table 1). The necessary data were available for 129 patients (validation set). The stratification performed by the prognostic model retained its statistical significance and clinical validity. In particular, patients classified with favorable (51.2% of the validation set), intermediate (33.3%), and unfavorable (15.5%) groups experienced median OS of 12.7 months (CI_{95%} 11.1–14.3), 7.5 months (CI_{95%} 6.2–8.8), and 1.4 months (CI_{95%} 0.1–2.7), respectively. The 1-year OS was 57%, 33%, and 5%,

Table 2. Univariate and multivariate analysis performed on dichotomized variables.

Variable	Discrete categories	Univariate analysis		Multivariate analysis	
		HR (CI _{95%})	p Value	HR (CI _{95%})	p Value
ECOG PS	2–3 vs 0–1	2.95 (2.33–3.72)	< 0.001	2.05 (1.46–2.89)	< 0.001
Ca19.9	≥ 120 U/l vs < 120 U/l	1.52 (1.30–1.78)	< 0.001	1.37 (1.11–1.69)	0.004
Albumin	< 3.50 mg/dl vs ≥ 3.50 mg/dl	1.97 (1.64–2.36)	< 0.001	1.41 (1.13–1.77)	0.002
NLR	< 3.1 vs ≥ 3.1	1.73 (1.49–2.01)	< 0.001	1.51 (1.23–1.87)	< 0.001
Hemoglobin	< 12.5 g/dl vs ≥ 12.5 g/dl	1.52 (1.32–1.75)	< 0.001	1.28 (1.03–1.59)	0.023
Prior surgery	yes vs no	0.66 (0.56–0.78)	< 0.001	Not significant	
Disease status	Distant spread vs locoregional disease	1.30 (1.10–1.54)	0.002	Not significant	
Platelet count	$\leq 400,000/\mu\text{l}$ vs $> 400,000/\mu\text{l}$	1.27 (1.60–2.01)	< 0.001	Not significant	

Ca19.9: carbohydrate antigen 19.9; CI_{95%}: 95% confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; HR: hazard ratio; NLR: neutrophil/lymphocyte ratio.

Table 3. Survival according to prognostic group in the training and validation sets.

Prognostic group	n	% of the sample	Median OS in months (CI _{95%}) [IQR]	HR (comparison with subsequent group)	p Value	1-Year OS	2-Year OS
Training set ($n = 421$)							
Favorable	217	51.5%	12.7 (11.0–14.4) [7.0–18.4]	0.53 (0.43–0.66)	< 0.001	55%	18%
Intermediate	165	39.2%	7.1 (5.8–8.4) [3.7–11.9]	0.54 (0.37–0.77)	0.001	27%	9%
Unfavorable	39	9.3%	3.2 (1.7–4.7) [2.1–8.0]	–	–	13%	0%
Validation set ($n = 129$)							
Favorable	66	51.2%	12.7 (11.0–14.3) [6.8–17.9]	0.66 (0.44–1.00)	0.050	57%	17%
Intermediate	43	33.3%	7.5 (6.1–8.9) [4.1–13.6]	0.30 (0.17–0.53)	< 0.001	33%	14%
Unfavorable	20	15.5%	1.4 (0.1–2.7) [0.8–4.4]	–	–	5%	0%

CI_{95%}: 95% confidence interval; HR: hazard ratio; IQR: interquartile range; OS: overall survival.

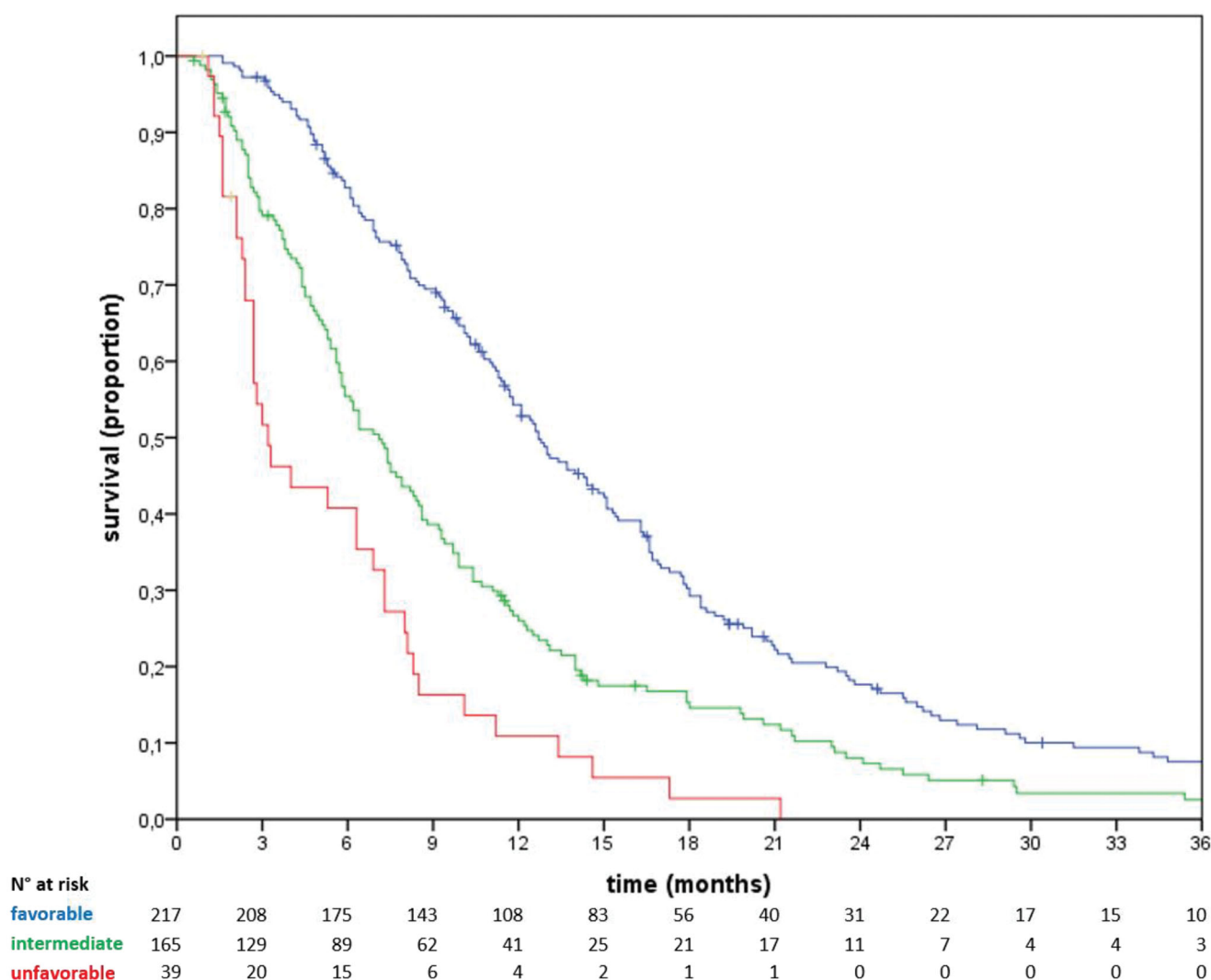


Figure 1. Overall survival in the training set. Blue line, favorable prognosis; green line, intermediate prognosis; red line, unfavorable prognosis.

respectively (Table 3; Figure 2). C-index, AUC_6 , and AUC_{12} values of the model in the validation set were 0.73, 0.75 ($CI_{95\%}$ 0.66–0.84), and 0.69 (0.59–0.78), respectively [Supplementary Figure 1].

Discussion

Against the backdrop of a poor global prognosis, a certain variability in aBTC clinical histories can be demonstrated. Separating clinical trajectories *ex ante* carries the ultimate goal of selecting patients for specific tailored treatments. Indeed, some particularly fragile patients do not benefit from chemotherapy, due to primarily progressive disease, treatment complications and/or clinical deterioration. Conversely, other fitter patients will reach second-line chemotherapy [14,15]. While modeling in pretreated aBTC provided interesting results [16,17], the first-line setting appears even more compelling, considering the high dropout rate between lines of treatment observed in real-world practice [18].

A pattern emerges from the heterogeneous available literature on OS predictors: variables most frequently

associated with prognosis concern the areas of patient general condition (reflected, for example, by age and ECOG PS) [19–22], nutritional status and residual organ synthetic function (albumin, anemia, prognostic nutritional index) [21,23–27], inflammatory status (such as, notably, NLR) [23,25,28–34], biological aggressiveness (tumor grade, prior surgery) [16,23,35], and tumor burden (metastatic disease, carcinoembryonic antigen, Ca19.9) [21,22,26,32,33].

Considering the risks of collinearity and interference related to a high initial number of variables, not all the significant prognosticators on univariate analysis were indiscriminately tested on a multivariate level. Instead, eight relevant prognosticators were chosen, so that all five of the mentioned areas of the disease-patient interaction were covered. Four variables emerged as strong independent predictors of OS, each reflecting, unlike other reports [25], a distinct domain of the tumor-host dyad: ECOG PS, NLR, albumin, and Ca19.9.

By combining these prognosticators, we devised a reliable prognostic estimator. Prognostic modeling in aBTC is heterogeneous, regarding examined population, study design, and final outcome. Firstly, few studies are dedicated to specific

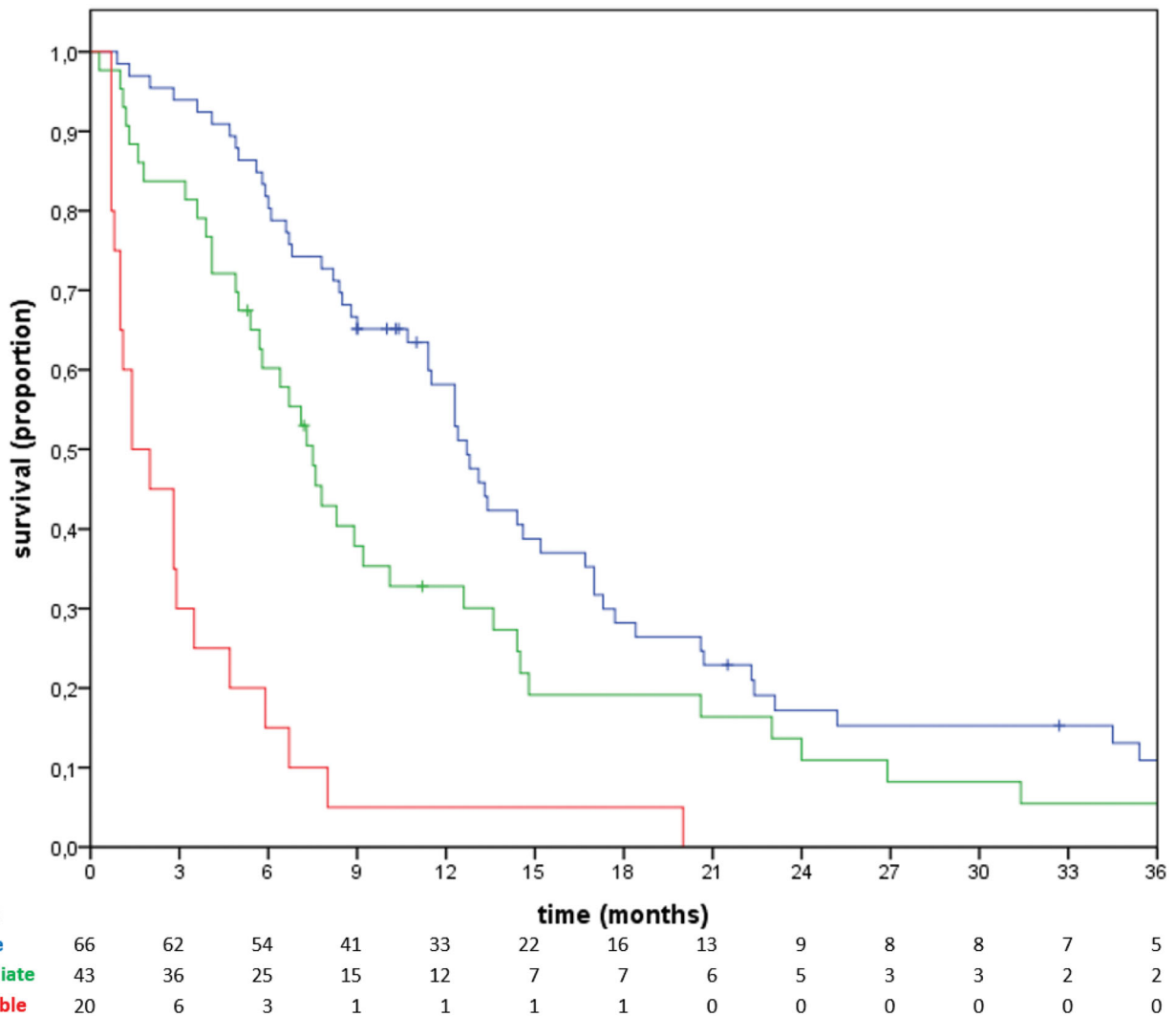


Figure 2. Overall survival in the validation set. Blue line, favorable prognosis; green line, intermediate prognosis; red line, unfavorable prognosis.

primary sites [32,36,37]; conversely, following the consideration that the treatment is not differential according to the primary site, our analysis considered all disease sites together. In particular, our model included AC cases (which, however, only accounted for 5.6% of the sample), similar to other relevant models [26,35,38,39]. While consistent with most of the existing literature in the field, this approach could be theoretically flawed by differences in prognosis and prognostic criteria between primary sites. Indeed, in accordance with other studies [35,40], our analysis suggested poorer outcomes for GC and a trend toward a favorable impact for AC. However, this issue has not yet been unequivocally demonstrated, with studies reporting a particularly unfavorable prognosis to other primary sites [20,41,42], and the majority of the available literature not observing a differential impact of disease site on OS.

Following the paradigm of treatment homogeneity, unlike others [26,32], we included locally advanced, unresectable disease; clinical histories that would not consider CT1, such as surgically cured disease [35], or patients who would never reach active oncologic care [26,32], were excluded. A minority of patients received nonstandard regimens, which lack

level-1 evidence of efficacy. However, given that the intention was to define areas of very high and low benefit from chemotherapy *per se*, we included these patients in the analysis.

The oncology institutions involved in the present study ranged from small peripheral facilities to high-volume, academic centers. This type of multi-center nature added to the real-life blueprint of the work, as not all patients are treated in large hospitals or enrolled in clinical trials.

We developed a prognostic model in the form of a three-tier prognostic score. In contrast to the mere addition of risk factors [37,39], assigning a coefficient to each addend allows accounting for the weight of each prognostic contributor: in previous comparable models [20,25,26,37,43], these coefficients were variably derived from rounded Chi-square values, regression coefficients, or HRs. Among the analogous models with c-index or AUC provided, these parameters ranged from 0.68 to 0.83, and from 0.63 to 0.65, respectively [25,26,43]. Therefore, the discriminatory performance of the prognostic score resulted as being similar to the comparable literature.

Our model, in which ECOG PS was assigned the highest weight, did not outperform this parameter in mere terms of

AUC. However, our attempt was triggered by the specific intent of convenience from the clinician's point of view. In particular, patients identified as having a favorable prognosis would be good candidates for future, intensified regimens (NCT02591030, NCT03768414), or clinical trials. In modeling, we prioritized the maximization of this subpopulation over obtaining higher survivals in smaller groups [25,44]. Favorable-prognosis patients represented more than half of the population and could expect a satisfactory median OS of 12.7 months, and a 75% chance to live longer than 7 months. At the other end of the spectrum, chances of benefitting from chemotherapy were very low for the unfavorable-prognosis group. Importantly, unlike other comparable models [25,43], our prognostic score circumscribed this population, most suited to best supportive care due to an expected median OS of 3.2 months, to less than 10% of patients. However, we could not compare these outcomes with those of patients undergoing palliative care [26], and only a prospective evaluation may ultimately confirm the lack of benefit from CT1. Therefore, we would not recommend referral of these patients to palliation on the sole basis of our work.

Our work has some limitations. Firstly, the retrospective nature of our study entails not-on-purpose data collection, missing information, numerical imbalance between cohorts, and intrinsic patient selection. Important variables such as C-reactive protein levels, cachexia, weight loss, and state and severity of liver disease were not collected. Only a minority of patients in the training cohort could be evaluated for all the necessary variables to the model. However, the sample size remained large (421 patients), and no significant differences were demonstrated regarding relevant variables, including those prognosticators tested on multivariate analysis. Dichotomization of continuous variables introduces a loss of information. To reduce this problem, cut points were chosen to be clinically meaningful (thresholds for anemia, thrombocytosis, hypoalbuminemia), or to approximate consolidated ones (NLR) [22,23,26]; the median value was used for Ca19.9.

However reasoned, some passages of the model construction were made arbitrarily and *post hoc*. This called for further testing on an external validation dataset. This model showed good reproducibility in this population, which trended toward worse prognosis. Prospective validation is required for a higher degree of reliability.

Conclusions

Here, we have proposed a set of easily-retrievable prognostic variables, capable of predicting OS in a large, unselected, real-life population of aBTC patients undergoing CT1. Computation of selected variables into a prognostic score provided a tool to perform prognostic stratification with moderate accuracy. This tool could result in being useful to the clinician, in order to ascertain the potential benefit from CT1 during the clinician-patient discussion at the start of treatment.

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Disclosure statement

The authors declare no conflict of interest with the subject of the present study.

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