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The prognostic nutritional index predicts survival and response to first-line chemotherapy in advanced biliary cancer

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Abstract

Background: An accurate risk-stratification is key to optimize the benefit-to-risk ratio of palliative treatment in advanced biliary cancer. We aimed at assessing the impact of the prognostic nutritional index (PNI) on survival and treatment response in advanced biliary cancer (ABC) receiving first-line chemotherapy.

Methods: Medical records of ABC treated with standard chemotherapy at the Modena Cancer Centre were retrospectively reviewed for variables deemed of potential interest, including the PNI. Univariate and multivariate analyses were performed to investigate the association between the covariates and overall survival (OS).

Results: 114 ABC fulfilled the inclusion criteria and made up the training cohort. A PNI cut-off value of 36.7 was established using the receiver operating characteristic (ROC) analysis. At both the univariate and the multivariate analysis, low PNI value (<36.7) was associated with shorter OS (P = .0011), together with increased NLR (P = .0046) and ECOG >1 (P < .0001). The median OS was 5.4 vs 12.1 months in the low- vs high PNI-group. Moreover, a PNI value >36.7 resulted in a higher disease control in patients treated with gemcitabine/platinum combination (61.4% vs 34.3%). These results were validated in an independent cohort of 253 ABC.

Conclusions: We demonstrated and externally validated a prognostic role for the PNI in ABC treated with first-line chemotherapy. Although the PNI turned out to be predictive in the subset of patients receiving platinum/gemcitabine combination, future prospective confirmation is needed.

KEYWORDS

biliary tract cancer, chemotherapy, cholangiocarcinoma, gallbladder cancer, prognosis, prognostic nutritional index, response prediction, survival

Abbreviations: ABC, advanced or metastatic biliary tract cancer; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BTC, biliary tract cancers; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; dCCA, distal cholangiocarcinoma; DCR, disease control rate; eCCA, extrahepatic cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; ESR, erythrocyte sedimentation rate; GBC, gallbladder carcinoma; GOT, glutamic oxaloacetic transaminase; GPT, glutamate-pyruvate transaminase; iCCA, intrahepatic cholangiocarcinoma; LDH, lactate dehydrogenase; mOS, overall survival; pCCA, perihilar; PNI, prognostic nutritional index.

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1 | BACKGROUND

With approximately 340 000 new cases estimated in 2018 in the world, biliary tract cancers (BTC) account for slightly less than 2% of new cancer diagnoses.[1] These cancers are relatively rare in the West, with approximately 12 000 estimated new cases in the US[2] and 4900 in Italy,[3] annually. Nevertheless, their incidence is increasing worldwide, especially that of intrahepatic cholangiocarcinoma (iCCA).[4,5] Primary sclerosing cholangitis is the most established predisposing factor in Western countries, while hepatobiliary fluke infestation and hepatolithiasis are well-documented risk factors in the East.[6] BTC comprise a heterogeneous group of tumours arising from the biliary tree, including iCCA, extrahepatic cholangiocarcinoma (eCCA) (further divided into perihilar [pCCA] and distal cholangiocarcinoma [dCCA]) and gallbladder carcinoma (GBC).[7] Surgery is the only potentially curative option though feasible in only 10%-20% of cases and associated with recurrence rates as high as 40%-60%.[8] Moreover, the vast majority of patients presents with unresectable advanced disease at diagnosis.[9] Palliative chemotherapy is the standard treatment for recurrent, unresectable advanced or metastatic biliary tract cancer (ABC) resulting in median overall survival (mOS) hardly exceeding 12 months.[10,11] In the literature, several clinical and biochemical factors have been described as prognostic factors in ABC, such as Eastern Cooperative Oncology Group performance status (ECOG PS), primary tumour location, disease status, number of metastatic sites, haemoglobin, bilirubin, LDH and neutrophil-to-lymphocyte ratio.[12-16] Nevertheless, none of these has been convincingly validated and the power of single factors in predicting survival is limited.[17,18] Additionally, growing research interest is headed to novel biomarkers with potential predictive and prognostic value such as non-coding RNAs and exosomal proteins,[19-21] though this research field is still in its infancy. Hence, there remains an unmet need for a more accurate patients' stratification to inform clinical decision making as well as a rationale trials design. In this context, the prognostic nutritional index (PNI), which is a multiparametric indicator based on serum albumin and peripheral lymphocyte count,[22] has been shown to account for both the immune-inflammatory and nutritional status of patients.[23] Interestingly, the PNI has demonstrated to correlate with survival across several gastrointestinal cancers, including BTC.[24-28] In the present study, we sought to assess and validate the impact of this index on survival and treatment response in two independent cohorts of ABC undergoing standard first-line chemotherapy.

Key points

- We showed that the prognostic nutritional index (PNI) is an independent predictor of survival in a cohort of advanced biliary cancer (ABC) treated with first-line chemotherapy.
- More interestingly, we were able to demonstrate, for the first time, a predictive role for the PNI in patients receiving cisplatin/gemcitabine combination.
- We externally validated and propose the PNI as a readily available and inexpensive tool to improve the risk-stratification of patients both in daily practice and clinical trials.

2 | MATERIALS AND METHODS

2.1 | Patient population

Consecutive patients with unresectable locally advanced or metastatic BTC treated with first-line chemotherapy from 1st January 2002 to 31st February 2018 were retrospectively identified from the Modena Cancer Centre database (training cohort).

A retrospective validation cohort with unresectable locally advanced or metastatic BTC treated with first-line chemotherapy was consecutively recruited by the following Institutions: University of Turin, Candiolo Cancer Institute, AO Ordine Mauriziano, City of Health and Science Hospital of Turin, Alba Hospital, University of Pisa.

Patients with mixed hepatocellular-cholangiocellular carcinoma were not eligible.

Chemotherapy regimen and schedule was administered based on physician´s discretion.

Pretreatment demographics, clinical and laboratory data were retrieved through electronic medical records review. In

particular, the following variables were collected and analysed: age, gender, ECOG PS, weight and height, PNI, first-line regimen. Haematological and biochemical parameters were retrieved the day before the start of treatment: blood cell count (cell/μL), haemoglobin (gr/dL), platelet count (cell/μL), erythrocyte sedimentation rate (ESR, mm/h), bilirubin (mg/dL), alkaline phosphatase (ALP; IU/L), lactate dehydrogenase (LDH, U/L), alanine aminotransferase (ALT; IU/L), aspartate aminotransferase (AST; IU/L), albumin (g/dL), carbohydrate antigen 19-9 (CA 19-9) (U/mL) and carcinoembryonic antigen (CEA) (ng/mL).

The study protocol was reviewed and approved by the local Area Vasta Emilia Nord Ethics committee (Protocol number 183/2019) and was conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

2.2 | Statistical analysis

The aim of this analysis was to examine the association between the PNI index values and OS in patients with unresectable locally advanced or metastatic BTC treated with first-line chemotherapy.

Albumin and lymphocyte blood levels were retrieved the day before the start of treatment.

The PNI was calculated as follows: 10 × serum albumin concentration (g/dL) + 0.005 × peripheral lymphocyte count (number/mm^2).[20] The cut-off point of the PNI was determined to be 36.7 by receiver operating characteristic (ROC) analysis (Figure 1).

Categorical variables were compared with the Fisher's exact test. The OS was defined as the time interval between the first day of treatment until the day of death from any cause or last follow-up visit. OS was estimated by the Kaplan-Meier method and curves were compared by the log-rank test. Unadjusted and adjusted hazard ratios (HRs) by baseline characteristics (PNI, ECOG PS, NLR) were calculated using the Cox proportional hazards model. The predictive value and the discrimination ability of the final model were assessed with the Harrell's concordance index (C-index).

MedCalc package (MedCalc® version 16.8.4) was used for statistical analysis.

3 | RESULTS

3.1 | Training cohort

A total of 114 patients with ABC treated with first-line chemotherapy were identified for our analysis and included as a training cohort. Among them, 66 (58%) patients were categorized as the PNI-high group, while the remaining 48 (42%) patients as the PNI-low group.

At the time of database lock in February 2019, after a median follow-up time of 15.3 months, 106 patients had progressed and 104 died. No patients were lost to follow-up.

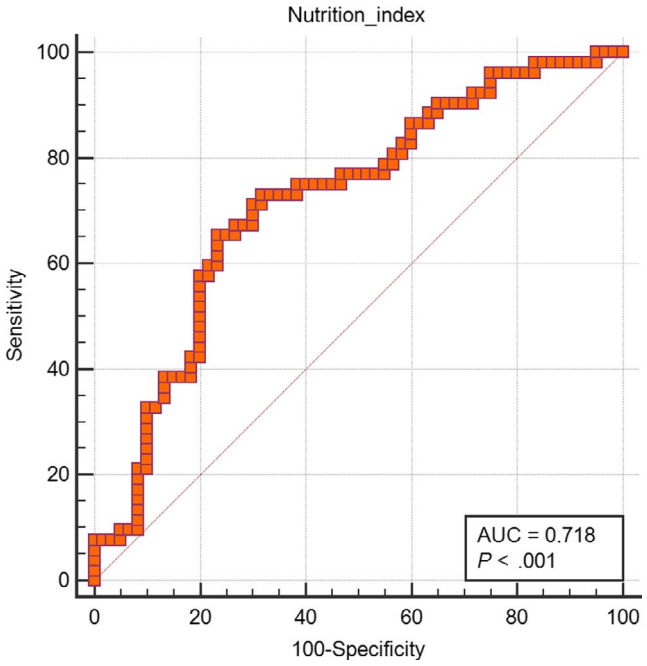

FIGURE 1 Receiver operating characteristic curve analysis for the prognostic nutritional index

Patients' median age was 67.5 years (range 29-80 years), 60 (52.6%) were female and 93 (81.6%) had an ECOG ≤1. The most common primary tumour site was iCCA (52.6%), followed by GBC (33.4%) and eCCA (14%). Overall, 52.6% of the patients (n = 60) received a platinum/gemcitabine doublet as first-line treatment, while 47.4% (n = 54) of them were treated with other regimens. Other baseline clinico-pathological and laboratoristic characteristics are summarized in Table 1.

The mOS of the whole population was 8.1 months (95% CI: 7.0-10.4) and the median progression-free survival (mPFS) was 3.9 months (95% CI: 3.0-40.5) (Figure 2).

3.2 | Prognostic and predictive value of the PNI

At the univariate analysis for both OS and PFS, high PNI was associated with longer mOS (12.1 vs 5.4 months, HR 0.32; 95% CI: 0.2-0.5; $P < .0001$) and mPFS (5.2 vs 2.6 months, HR 0.53, 95% CI: 0.34-0.82, $P = .0048$) respectively (Figure 3).

Across tumour sites, the PNI retained prognostic value in both iCCA and eCCA subgroups with mOS of 6.6 and 13.3 months ($P < 0.0001$) and 4.6 vs 10.5 months ($P = 0.0034$) for the low- compared to high-PNI group respectively. Contrariwise, the PNI does not reach statistical significance among GBC (5.3 vs 7.7 months; $P = .5516$).

In addition, the following covariates turned out to be correlated with a poor prognosis: a 1-unit increase in CA19.9 ($P = .0063$), CEA (= 0.0004), LDH ($P = .0360$), alkaline phosphatase ($P = .0308$), monocyte count, ($P = .0124$), neutrophil/lymphocyte ratio (NLR) (HR 1.16; 95% CI: 1.08-1.25; $P < .0001$), neutrophil count ($P = .0013$) and ECOG >0 (HR 3.31; 95% CI: 1.35-8.12; $P < .0001$). No difference was

TABLE 1 Patients characteristics in the training cohort (n = 114)

Parameter	N (%)
Age, years (median, range)	67.5 (29-80)
Gender	
Female	60 (52.6)
Male	54 (47.3)
Performance status	
ECOG 0-1	93 (81.6)
ECOG Š2	21 (18.4)
Primary tumour site	
iCCA	60 (52.6)
pCCA	10 (8.7)
dCCA	6 (5.3)
GBC	38 (33.4)
Disease status	
Recurrent	14 (12.3)
Locally advanced	14 (12.3)
Metastatic	86 (75.4)
Number of metastatic sites	
0	13 (11.4)
1	59 (51.7)
2	29 (25.4)
3	11 (9.6)
Metastatic sites	
Liver	78 (68.4)
Abdominal lymph node (M1)	25 (22)
Peritoneum	20 (17.5)
Lung	21 (18.4)
Others	14 (12.3)
First-line chemotherapy regimen	
Platinum/gemcitabine	60 (52.6)
Gemcitabine	28 (24.6)
Fluoropyrimidine monotherapy	8 (7)
Fluoropyrimidine-based doublet	4 (3.5)
Other regimens	14 (12.3)
Laboratory tests (median, range)	
ALC, cells/μL	1670 (610-3460)
Albumin, gr/dL	3.7 (2.1-37)
CEA, ng/mL	2.6 (0.2-2029)
CA19.9, U/mL	245.6 (0.6-91.2)
NLR	3.46 (0.9-23.3)
ALP, U/L	208.5 (46-1995)
LDH, U/L	372 (229-2910)
ANC, cells/μL	5940 (1690-5330)
AMC, cells/μL	585 (210-2230)

Abbreviations: ALC, absolute neutrophil count; ALP, alkaline phosphatase; AMC, absolute monocyte count; ANC, absolute neutrophil count; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; dCCA, distal cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gallbladder cancer; iCCA, intrahepatic cholangiocarcinoma; LDH, lactate dehydrogenase; NLR, neutrophil/lymphocyte ratio; pCCA, perihilar cholangiocarcinoma.

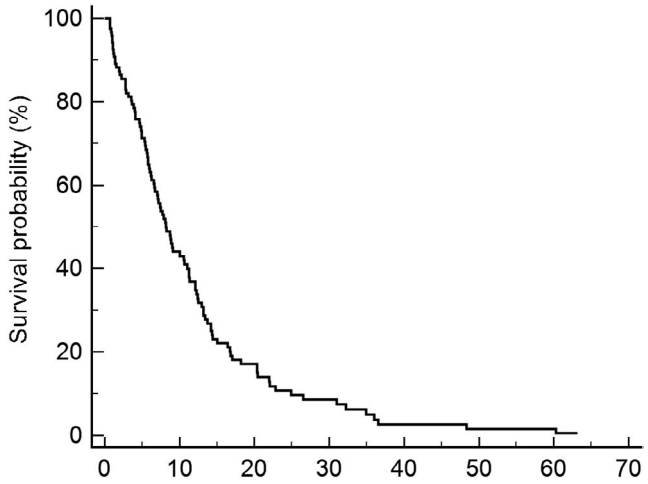

FIGURE 2 Overall survival in the training cohort. [Colour figure can be viewed at wileyonlinelibrary.com]

found for the following covariates: glutamic oxaloacetic transaminase (GOT), glutamate-pyruvate transaminase (GPT), total bilirubin, haemoglobin and type of treatment (gemcitabine/platinum vs other treatments) (Table 2).

Following adjustment for clinical covariates positive after Bonferroni correction (NLR, CEA, ECOG, CA 19-9 and PNI), multivariate analysis confirmed PNI-low (HR 2.12; 95% CI: 1.34-3.32; P = .0011), together with 1-unit increase in NLR (HR 1.11; 95% CI: 1.03-1.20; P = .0046) and ECOG >1 (HR 2.38; 95% CI: 1.72-3.29; P < .0001) as independent prognostic factor for OS (Table 2).

When assessed by treatment regimen, a PNI >36.7 retained a favourable prognostic value in patients treated with gemcitabine/platinum combination (mOS 14.2 vs 4.8 months, HR 0.05, 95% CI: 0.02-0.15, P < .0001), but not in those patients receiving other regimens (8.6 vs 6.1 months, HR 0.65, 95% CI: 0.38-1.11, P = .1151).

With regards to a potential relationship with other variables, the PNI was found to be correlated with the erythrocyte sedimentation rate, age and tumour markers (CEA and CA19.9), whilst no association was recorded with reactive C protein and body mass index. In addition, the PNI trended towards a lower value in eCCA compared to iCCA (36.67 vs 38.79, P = .1768). (Figure S1).

Finally, a high PNI value resulted in a higher disease control compared to the low PNI in patients treated with platinum plus gemcitabine: disease control rate (DCR) was 61.4% in the high-PNI group vs 34.3% in the low-PNI group (P < .01). On the contrary, no difference in DCR was observed both in the whole population (P = .1378) and in patients treated with regimens different from platinum/gemcitabine doublet (P = .1151).

3.3 | Validation cohort

A total of 253 patients diagnosed with ABC were retrieved from an Italian multicenter database and made up the validation cohort. Baseline clinical and laboratoristic characteristics are summarized in Table 3.

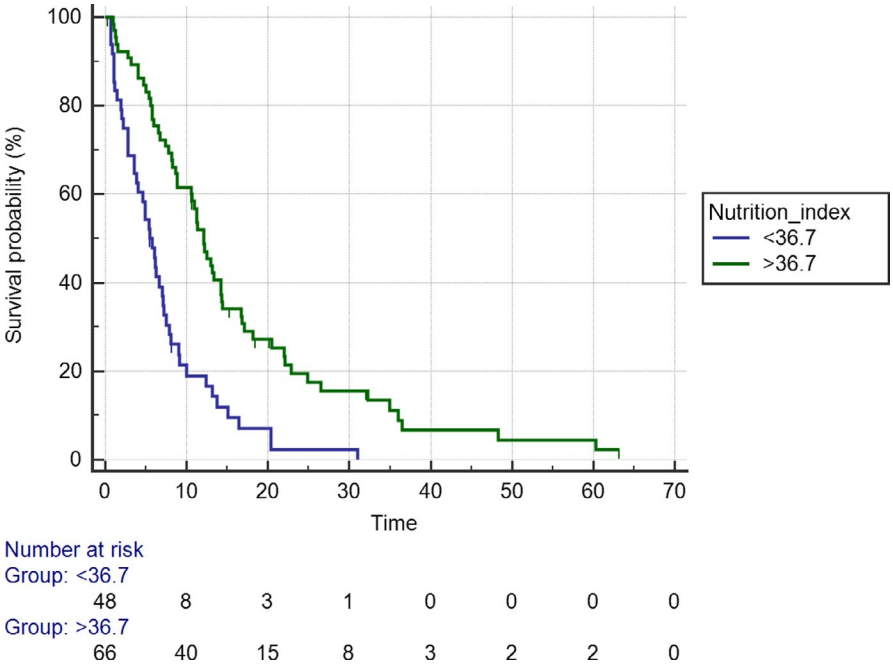

FIGURE 3 Overall survival by prognostic nutritional index in the training cohort

At the time of database lock in February 2019, after a median follow-up time of 18.5 months, 233 patients had progressed and 232 died. No patients were lost to follow-up.

Globally, 131 (52%) patients were categorized as the PNI-high group, while the remaining 122 (48%) patients as the PNI-low group.

The mOS and mPFS of the population were 9.9 (95% CI: 8.3-11.4) and 4.8 months (95% CI: 3.7-5.7) respectively. In keeping with what observed in the training cohort, patients with PNI-low had a mOS of 6.9 months, whereas patients with a PNI-high had a mOS of 13.5 months (HR 2.1, 95% CI: 1.60-2.77, $P < .0001$). Moreover, in the

TABLE 2 Univariate and multivariate analysis for overall survival in the training cohort

	Univariate analysis			Multivariate analysis		
Covariate	HR	95% CI	*P*-value	HR	95% CI	*P*-value
NLR	1.1655	1.08-1.25	<.0001	1.1171	1.03-1.20	.0046
ECOG PS 2 vs 0-1	3.3143	1.35-8.12	<.0001	2.3792	1.71-3.29	<.0001
PNI > 36.7	0.3284	0.20-0.52	<.0001	2.1194	1.34-3.32	.0011
CEA	1.0011	1.00-1.00	.0004	—	—	—
CA19-9	1.0000	1.00-1.00	.0063	—	—	—
ANC	1.0001	1.00-1.00	.0013	—	—	—
AMC	1.0008	1.00-1.00	.0124	—	—	—
LDH	1.0006	1.00-1.00	.0360	—	—	—
ALP	1.0006	1.00-1.00	.0308	—	—	—
Locally advanced versus metastatic disease	0.9843	0.8734-1.1174	.8741	—	—	—
Bilirubin	1.0025	0.99-1.00	.1211	—	—	—
GOT	1.0039	0.99-1.00	.1221	—	—	—
GPT	0.9994	0.99-1.00	.6168	—	—	—
Hemoglobin	0.9991	0.99-1.00	.6101	—	—	—
Platinum/gemcitabine vs other regimens	0.7447	0.52-1.04	.0899	—	—	—

Abbreviations: ALP, alkaline phosphatase; AMC, absolute monocyte count; ANC, absolute neutrophil count; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; NLR, neutrophil/lymphocyte ratio; PNI, prognostic nutritional index.

low-PNI group mPFS was 3.4 months compared to 6.3 months of the high-PNI group (HR 1.62, 95% CI: 1.24-2.11, P = .0003) (Figure 4). Still, according to the results of the training cohort, the PNI displayed a prognostic significance in both iCCA (P = .0002) and eCCA (P = .0003), but not in the GBC subset (P = .1740).

By performing the same multivariate analysis of the training cohort (NLR, CEA, ECOG, CA 19-9 and PNI), PNI (P = .0053), CA19-9 (P = .0145), ECOG PS (P < .0001) and NLR (P = .0009) were found to be independent prognostic factors for OS (Table 4).

The model had a C-index of 0.82.

4 | DISCUSSION

This study highlights that the PNI is an independent predictor of survival in two independent cohorts of patients (training and validation) with BTC treated with first-line chemotherapy.

The results of our analysis are aligned with those coming from a number of previous experiences evaluating the prognostic role of the PNI. This was first shown to correlate with increased morbidity and mortality among patients undergoing gastrointestinal surgery for a variety of underlying disorders, including cancer.[20] Accordingly, accumulating evidence has been suggesting the PNI as a negative predictor of outcome in advanced cancer patients.[29,30] In the context of patients with resectable BTC, Akgul and colleagues[31] showed that those with a lower preoperative PNI (< 40) were at increased risk of death (HR, 1.71; P = .008) and had a worse survival (5-year OS 24.6% vs 47.5%, P < .001) compared to patients with a PNI >40. With regards to ABC treated with first-line chemotherapy, the prognostic significance of the PNI was assessed only in the study by Zhang et al.[28] The authors reported that low PNI (PNI <47.1) was associated with shorter OS (5 vs 10 months, P = .0056) in 173 patients with CCA. Of note, only patients with iCCA were included in that analysis. In contrast, in our study we evaluated both iCCA and eCCA and we can speculate that the inclusion of patients with different tumour location within the biliary tree may have accounted for a different PNI cut-off value.

It is worthwhile to note that in our study the prognostic role of the PNI was confirmed both in iCCA and eCCA but it does not reach statistical significance in the GBC subgroup.

We can speculate that the different prognostic value of the PNI observed across tumour types, underlines not just the inherent biological heterogeneity of BTC,[32] but also a different immune-inflammatory response elicited by tumours arising in various parts of the biliary tree. Again, differences in the albumin level and lymphocyte count between CCA and GBC, may be attributable to an underlying cirrhosis, which is a well-known predisposing factor for CCA.

These hypothesis-generating findings warrant further investigation in tumour-specific subsets of BTC.

By incorporating both lymphocytes and albumin the PNI provides a picture of the complex interplay existing between nutrition, inflammation and immunity in cancer and of their potential prognostic and predictive implications. Indeed, lymphocytes are known to

TABLE 3 Patients characteristics in the validation cohort (n = 253)

Parameter	N (%)
Age, years (median, range)	66.7 (38-87)
Gender	
Female	133 (52.6)
Male	120 (47.4)
Performance status	
ECOG 0-1	113 (45)
ECOG Š2	18 (7)
Not available	122 (48)
Primary tumour site	
iCCA	115 (45)
eCCA	49 (19)
GBC	75 (29)
Ampullary tumor	14 (7)
Number of metastatic sites	
0	87 (34)
1	72 (28)
2	57 (22)
3	23 (9)
Metastatic sites	
Liver	122 (40)
Abdominal lymph node (M1)	78 (26)
Peritoneum	37 (12)
Lung	31 (10)
Others	37 (12)
First-line chemotherapy regimen	
Platinum/gemcitabine	131
Gemcitabine	72
Fluoropyrimidine monotherapy	8
Fluoropyrimidine-based doublet	12
Other regimens	30
Laboratory tests (median, range)	
ALC, cells/μL	1730 (400-5700)
Albumin, gr/dL	3.55 (2.02-4.97)
CEA, ng/mL	3.5 (0.5-5748.41)
CA19.9, U/mL	130.64 (0.8-206600)
NLR	2.92 (0.49-17.53)
ALP, U/L	282 (27-4315)
LDH, U/L	322 (116-2107)
ANC, cells/μL	5260 (680-1800)
AMC, cells/μL	650 (60-2180)

Abbreviations: ALC, absolute neutrophil count; ALP, alkaline phosphatase; AMC, absolute monocyte count; ANC, absolute neutrophil count; CA19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; dCCA, distal cholangiocarcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; GBC, gallbladder cancer; iCCA, intrahepatic cholangiocarcinoma; LDH, lactate dehydrogenase; NLR, neutrophil/lymphocyte ratio; pCCA, perihilar cholangiocarcinoma.

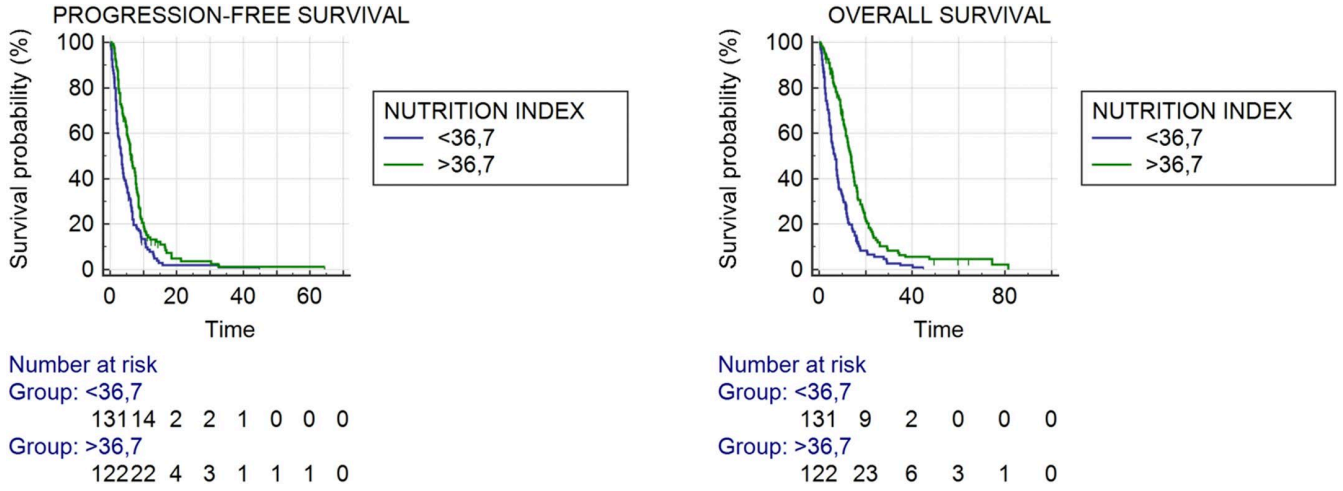

FIGURE 4 Median overall survival and median progression-free survival by prognostic nutritional index in the validation cohort

TABLE 4 Multivariate analysis for overall survival in the validation cohort

	Multivariate analysis		
Covariate	**HR**	**95% CI**	***P*-value**
NLR	1.0096	1.03-1.16	.0009
ECOG PS 2 vs 0-1	1.7971	1.42-2.26	<.0001
PNI >36.7	1.5505	1.33-2.11	.0053
CA19-9	1.00	1.00-1.00	.0145

Abbreviations: CA19-9, carbohydrate antigen 19-9; ECOG PS, Eastern Cooperative Oncology Group performance status; NLR, neutrophil/lymphocyte ratio; PNI, prognostic nutritional index.

reflect both the nutritional and inflammatory status of a given patient, in addition to be major players of the cell-mediated immunity.

On the other hand, albumin can be regarded as a surrogate of nutritional status and can be negatively affected by systemic inflammation. Hypoalbuminaemia has been associated with higher mortality rates in several cancer types and of shorter OS in patients receiving first-line chemotherapy in ABC.[33] In a considerable proportion of cancer patients, it exists a vicious cycle leading to systemic inflammation, malnutrition and immunodepression that can impair patients' prognosis. This is particularly remarkable for BTC since they are known to arise from a background of chronic biliary duct inflammation and are characterized by an immunosuppressive milieu with reduced activation of lymphocytes with anti-tumour activity.[34]

Interestingly, we highlight that the PNI is a predictive factor of response to platinum-based combination. Indeed, patients in the low-PNI group were less likely to respond to treatment (DCR 34.3% vs 61.4%) than those in the high-PNI group. Contrariwise, no difference was recorded in patients who received regimens other than platinum-based.

To this end, it is well-known that systemic inflammation and malnutrition may alter protein binding, impair the activity of cytochrome P450 3A4 and reduce the volume of distribution of cytotoxics through the increase in catabolic processes and induction of acute phase response.[35-37] Ultimately, this leads to increase in toxicity and decrease in the efficacy of chemotherapy. This could be particularly remarkable for platinum compounds that unlike pyrimidine analogues (gemcitabine and 5-fluorouracil) are substrates of the cytochrome P450 isoenzymes CYP2E1 and CYP3A4.[38]

Limitations of the present study are its relatively small sample size, its retrospective nature and the lack of central radiological review assessment. Moreover, these findings need to be prospectively confirmed in larger patient populations.

We proposed and externally validated the PNI as an easy-to-use prognostic and predictive tool taking into account patients nutritional status, systemic inflammatory response as well as immune fitness. Its ready availability and low-cost, make the PNI a promising tool to be implemented in daily management and clinical trials design for patients with ABC.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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