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Prognostic factors for progression-free and overall survival in advanced biliary tract cancer

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Background: Biliary tract cancer is an uncommon cancer with a poor outcome. We assembled data from the National Cancer Research Institute (UK) ABC-02 study and 10 international studies to determine prognostic outcome characteristics for patients with advanced disease.

Methods: Multivariable analyses of the final dataset from the ABC-02 study were carried out. All variables were simultaneously included in a Cox proportional hazards model, and backward elimination was used to produce the final model (using a significance level of 10%), in which the selected variables were associated independently with outcome. This score was validated externally by receiver operating curve (ROC) analysis using the independent international dataset.

Results: A total of 410 patients were included from the ABC-02 study and 753 from the international dataset. An overall survival (OS) and progression-free survival (PFS) Cox model was derived from the ABC-02 study. White blood cells, haemoglobin, disease status, bilirubin, neutrophils, gender, and performance status were considered prognostic for survival (all with $P < 0.10$). Patients with metastatic disease {hazard ratio (HR) 1.56 [95% confidence interval (CI) 1.20–2.02]} and Eastern Cooperative Oncology Group performance status (ECOG PS) 2 had worse survival [HR 2.24 (95% CI 1.53–3.28)]. In a dataset restricted to patients who received cisplatin and gemcitabine with ECOG PS 0 and 1, only haemoglobin, disease status, bilirubin, and neutrophils were associated with PFS and OS. ROC analysis suggested the models generated from the ABC-02 study had a limited prognostic value [6-month PFS: area under the curve (AUC) 62% (95% CI 57–68); 1-year OS: AUC 64% (95% CI 58–69)].

Conclusion: These data propose a set of prognostic criteria for outcome in advanced biliary tract cancer derived from the ABC-02 study that are validated in an international dataset. Although these findings establish the benchmark for the prognostic evaluation of patients with ABC and confirm the value of longheld clinical observations, the ability of the model to correctly predict prognosis is limited and needs to be improved through identification of additional clinical and molecular markers.

Key words: biliary tract cancer, ABC-02, prognostic model, advanced disease, cisplatin and gemcitabine, performance status

introduction

Biliary tract cancer is an uncommon cancer in developed countries with ~1500 new cases in the UK and 9000 new cases in the United States per year although the incidence is increasing [1] (http://www.cancerresearchuk.org/cancer-info/cancerstats/). Most patients are inoperable at presentation and the majority relapse following surgery; therefore, therapy is mainly palliative. The National Cancer Research Institute (UK) ABC-02 study demonstrated a survival advantage for patients receiving cisplatin and gemcitabine (CisGem) compared with gemcitabine alone and this combination has become the international standard of care in advanced disease [2].

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In a preliminary analysis of prognostic factors in ABC-02, a multivariable analysis across 16 variables suggested that Eastern Cooperative Oncology Group performance status (ECOG PS) and the presence of metastatic disease were significant prognostic indicators of progression-free survival (PFS) and overall survival (OS), as were neutrophilia and anaemia [3]. Notably, the location of the tumour within the biliary tract (cholangiocarcinoma, gall-bladder or ampulla of Vater) did not appear to influence outcome. Miyakawa et al. evaluated a surgical series of 5584 patients [4] and demonstrated a trend for improved survival in ampullary cancers compared with bile duct and gall-bladder cancers. In patients with advanced disease, the neutrophil lymphocyte ratio [5], ECOG PS [6], PFS after first-line chemotherapy of >6 months [6], previous surgery on the primary tumour [6], primary tumour location [7], and the number of sites of advanced disease [7] have been considered prognostic factors.

We present multivariable analyses from the ABC-02 study and validate proposed prognostic factors with a dataset of 10 studies in advanced biliary tract cancer (ABC) [8–17]. The objective was to define potentially new prognostic factors for ABC to add to the evidence established by previous contributors [5–7]. This manuscript is consequent on a collaboration of the International Biliary Tract Cancer Collaborators.

methods

We investigated several baseline characteristics: age, sex, metastatic status, site of primary (bile duct, gall-bladder, or ampulla), type of tumour (adenocarcinoma versus other), ECOG PS, previous therapy, white blood cell (WBC) count ($\times 10^9$/l), platelets ($\times 10^9$/l), haemoglobin (g/dl), neutrophils ($\times 10^9$/l), and bilirubin (μmol/l). All blood values were analysed as continuous variables.

The main analysis on the ABC-02 trial included all 410 patients. A secondary analysis was done by restricting ABC-02 dataset to 177 patients who received cisplatin plus gemcitabine and who had baseline ECOG PS 0 or 1, because this is the standard treatment for ABC and preliminary data from ABC-02 suggested patients with ECOG PS 0-1 benefit more from the addition of cisplatin to gemcitabine [3].

Initial screening of the entire set of candidate baseline covariates was done by evaluating the prognostic performance of each variable among patients in ABC-02. This was investigated by calculating the true-positive rate (TPR) and the false-positive rate (FPR). TPR was defined as the percentage of patients with an event of interest that had a certain variable or had a value of a certain variable above a specific cut-off and FPR is the percentage of patients without an event of interest who had a certain variable or had a value of a certain variable above a specific cut-off. The likelihood ratio (LR) test [calculated as a ratio (TPR/FPR), therefore the higher the LR, the stronger the prognostic performance of a specific factor]. The prognostic performance of each baseline variable was examined on its own according to the following events of interest: having a PFS event within 6 months of randomization and death within 1 year from randomization.

All baseline variables were simultaneously included in a Cox proportional hazards model, and backward elimination was used to produce the final model (using a significance level of 0.10), in which the selected variables were associated independently with outcome (each had a P value of <0.10 after adjustment for the other factors in the model). A prognostic score was then generated from the linear predictor of the variables from the final Cox model [using the hazard ratio (HR) estimate for each factor]. This analysis was implemented for PFS (time from randomization to progression or death, whichever happened first) and OS (time from randomization to death).

This score was validated externally using a dataset composed of 10 independent international datasets. For each patient in the validation dataset, the prognostic score was obtained and patients were classified by the event of interest. Prognostic test performance was examined by calculating the TPR and LR at fixed FPR values, and also by using receiver operating curves (ROCs). Prognostic performance was also investigated by assessing the association between prognostic scores and outcome of interest.

The Cox models derived using all patients in ABC-02 and the models including patients with ECOG PS 0 and 1 who received CisGem were also validated using each individual independent dataset separately as a validation dataset. A further sub-analysis was also carried out to assess the value of a derived neutrophil lymphocyte ratio (dNLR) as a prognostic factor in the context of the Cox models because this variable has been shown to be prognostic and potentially predictive of treatment benefit. [5, 18] The models derived from the backward selection were fitted without the variable neutrophils and using the variable dNLR instead. To assess the prognostic performance of such models, the linear predictor generated from these models was then applied to the external dataset as described above; dNLR was calculated as neutrophils/(WBC − neutrophils). The Stata version 12 statistical software package (Stata Corporation, College Station, TX) was used to analyse the data.

results

description of the training and validation datasets

ABC-02 included 410 patients; of those, 204 patients received CisGem chemotherapy. The validation dataset included 753 patients and of those there were 394 PFS events at 6 months since randomization and 440 deaths at 1 year since randomization. A total of 5 patients were followed up for <6 months and did not have a PFS event and 17 patients were followed up for <12 months and did not die.

Supplementary Appendix Table S1, available at *Annals of Oncology* online, summarizes each of the 10 different validation datasets. The medians and percentages of the key relevant factors considered in this analysis were similar in the training and validation datasets (Table 1). The median survival time in the entire ABC-02 cohort was slightly less than in the validation dataset (9.3 versus 10.0 months) and the percentage of deaths slightly higher (96% versus 88%).

prognostic performance of individual baseline characteristics in ABC-02

Table 2 provides data on the prognostic performance of each baseline characteristic separately. The best factor for 1-year death is an ECOG PS of 2 which had a TPR of 17%, an FPR of 5%, and an LR of 3.4 (among patients who died within 1 year, the proportion of those with ECOG PS = 2 was 3.4 times greater than among those who did not die within 1 year). The best factor for the 6-month PFS was also ECOG PS 2 (TPR of 16%, FPR of 9%, and LR of 1.78). None of the other factors presented a TPR considerably higher than the FPR.

prognostic model from ABC-02

Table 3 provides the results for OS and PFS multivariable Cox model selected by backward selection using a significance level of 0.10 for removal from the model. The resulting OS model comprised haemoglobin, disease status, bilirubin, neutrophils, gender, WBC, and ECOG PS which were all identified as independent

Table 1. Description of training and validation datasets

Dataset characteristics	Training dataset ABC-02	Validation dataset Combined validation datasets
Number of patients	410	753
Relevant factors		
Haemoglobin (g/dl), median (range) [*N*]	12.7 (7.8–16.9) [322]	12.6 (8.0–16.8) [737]
Neutrophils ($\times 10^9$/l), median (range) [*N*]	5.8 (1.9–25.6) [323]	5.8 (1.8–24.0) [671]
Bilirubin (μmol/l), median (range) [*N*]	11.0 (3.0–98.0) [323]	12.0 (0.0–102.0) [734]
White blood cell count (×109/l), median (range) [*N*]	8.6 (3.0–28.2) [323]	8.1 (3.1–24.8) [544]
dNLR, median (range) [*N*]	2.2 (−2.4 to 36.6) [323]	2.3 (0.7–21.8) [473]
M stage, *N* (%)		
Locally advanced	121 (30%)	183 (24%)
Metastatic	289 (70%)	538 (71%)
Unknown	0 (0%)	32 (4%)
Gender, *N* (%)		
Female	216 (53%)	372 (49%)
Male	194 (47%)	333 (44%)
Unknown	0 (0%)	48 (6%)
Performance status, *N* (%)		
0	130 (32%)	230 (31%)
1	228 (56%)	360 (48%)
2	52 (13%)	33 (4%)
Unknown	0 (0%)	130 (17%)
Overall median survival time in months (IQR)	9.3 (4.8–16.6)	10.0 (5.6–17.7)
Total number of deaths (%)	395 (96%)	664 (88%)
Total number of PFS events (%)	398 (97%)	722 (96%)

dNLR is calculated as neutrophils/(WBC − neutrophils).
NR, not reached; dNLR, derived neutrophil lymphocyte ratio; IQR, interquartile range; PFS, progression-free survival.

risk factors for OS (all with a significance level of <0.10). The resulting PFS model comprised the same variables as the OS model except the variable gender.

In the main dataset comprising all patients, higher values of neutrophils [PFS, HR 1.19 (95% CI 1.07–1.31); OS, HR 1.16 (95% CI 1.05–1.29)] and bilirubin [PFS, HR 1.01 (95% CI 1.00–1.02); OS, HR 1.01 (95% CI 1.00–1.02)] were associated with increased risk of having a PFS event and risk of death. Higher values of haemoglobin [PFS, HR 0.90 (95% CI 0.83–0.97); OS, HR 0.86 (95% CI 0.79–0.93)] and higher values of WBC [PFS, HR 0.89 (95% CI 0.81–0.98); OS, HR 0.92 (95% CI 0.83–1.01)] were associated with a decreased risk of having a PFS event and risk of death. Patients with metastatic biliary tract cancer [PFS, HR 1.48 (95% CI 1.15–1.91); OS, HR 1.56 (95% CI 1.20–2.02)] and patients with ECOG PS 2 [PFS, HR 1.61 (95% CI 1.10–2.36); OS, HR 2.24 (95% CI 1.53–3.28)] had worse PFS and OS. Male patients [OS, HR 1.28 (95% CI 1.01–1.60)] were also identified as having a worse OS but not PFS.

Supplementary Appendix Table S2, available at *Annals of Oncology* online, shows the final model derived by backward selection when ABC-02 was restricted to patients receiving CisGem who were ECOG PS 0 or 1. The resulting OS and PFS models only included haemoglobin, disease status, bilirubin, and neutrophils. On analysis of the restricted dataset, similar results to above were obtained for haemoglobin, neutrophils, bilirubin, and disease status.

assessment of prognostic performance of ABC-02 models

The prognostic performance using the above factors selected by Cox regression modelling is provided in supplementary Appendix Table S4, available at *Annals of Oncology* online, and in Figure 1A and B. The ROC curves and the LR for values of the prognostic score for 6-month PFS and 1-year OS do not suggest a particularly good performance because the TPRs are close to the FPRs, and all LR values are below the recommended level of 10 for a strong prognosis. The area under the curve (AUC) ROC curves were modest [6-month PFS: 62% (95% CI 57–68), 1-year OS: 64% (95% CI 58–69), Supplementary Appendix Figure S1A and B, available at *Annals of Oncology* online]. Although the results of the ROC analysis show the models are of a limited use as a prognostic marker in a clinical setting, the Kaplan–Meier plots (supplementary Appendix Figure S2A and B, available at *Annals of Oncology* online) show an association between risk scores and OS/PFS. The 12-month survival rate for the low-score group was 51% (95% CI 42–59) compared with 22% (95% CI 15–29) for the high-score group (supplementary Appendix Table S5, available at *Annals of Oncology* online). Similar findings were obtained when the models restricted to patients treated with CisGem who were ECOG PS 0 and 1 were applied to the validation dataset (supplementary Appendix Figure S3A and B, available at *Annals of Oncology* online).

Table 2. Prognostic performance of individual baseline characteristics for overall (1 year) and progression-free survival (6 months) among patients in ABC-02 ($N = 410$)

Characteristic positive-marker level	One-year overall survival			Six-month progression-free survival		
	TPR% (242 events)	FPR% (165 non-events)	LR	TPR% (201 events)	FPR% (206 non-events)	LR
Age, years	$n = 242$	$n = 165$		$n = 201$	$n = 206$	
≥60	65	62	1.05	63	65	0.97
≥65	44	43	1.02	41	46	0.89
≥70	24	18	1.33	21	21	1.00
≥75	10	7	1.43	10	7	1.43
Sex	$n = 242$	$n = 165$		$n = 201$	$n = 206$	
Men	48	48	1.00	49	47	1.04
Women	52	52	1.00	51	53	0.96
M stage	$n = 242$	$n = 165$		$n = 201$	$n = 206$	
Locally advanced	22	40	0.55	25	34	0.74
Metastatic	78	60	1.3	75	66	1.14
Bile duct	$n = 242$	$n = 165$		$n = 201$	$n = 206$	
Yes	60	58	1.03	61	57	1.07
No	40	42	0.95	39	43	0.91
Ampulla	$n = 242$	$n = 165$		$n = 201$	$n = 206$	
Yes	5	5	1.00	5	4	1.25
No	95	95	1.00	95	96	0.99
Type of tumour	$n = 242$	$n = 165$		$n = 201$	$n = 206$	
Adenocarcinoma	90	95	0.95	91	93	0.98
Other	10	5	2.00	9	7	1.29
Performance status	$n = 242$	$n = 165$		$n = 201$	$n = 206$	
0	27	39	0.69	24	39	0.62
1	56	56	1.00	60	52	1.15
2	17	5	3.4	16	9	1.78
Previous therapy	$n = 242$	$n = 165$		$n = 201$	$n = 206$	
Yes	72	80	0.9	73	78	0.94
No	28	20	1.4	27	22	1.23
WBC count × 10^9/l	$n = 195$	$n = 125$		$n = 159$	$n = 161$	
≥6	89	78	1.14	89	81	1.1
≥8	65	50	1.3	64	55	1.16
≥10	40	25	1.6	40	28	1.43
Platelets × 10^9/l	$n = 195$	$n = 125$		$n = 159$	$n = 161$	
≥2.50	73	60	1.22	73	63	1.16
≥3.00	53	39	1.36	51	45	1.13
≥3.50	39	27	1.44	36	34	1.06
Haemoglobin, g/dl	$n = 194$	$n = 125$		$n = 158$	$n = 161$	
≥12.5	52	65	0.8	50	63	0.79
≥13.5	27	40	0.68	27	38	0.71
≥14.5	9	14	0.64	7	16	0.44
Neutrophils × 10^9/l	$n = 195$	$n = 125$		$n = 159$	$n = 161$	
≥4	85	70	1.21	84	74	1.14
≥5.5	63	45	1.4	64	48	1.33
≥7	40	22	1.82	42	25	1.68
Bilirubin, μmol/l	$n = 195$	$n = 125$		$n = 159$	$n = 161$	
≥10	63	54	1.17	64	55	1.16
≥15	35	31	1.13	39	29	1.34
≥20	16	14	1.14	18	13	1.38

The TPR indicates the percentage of patients with an event, with the given characteristic; the FPR is the percentage of patients without an event, with the given characteristic; and the LR is calculated as TPR/FPR, indicating the strength of the prognostic factor.
FPR, false-positive rate; LR, likelihood ratio; TPR, true-positive rate; WBC, white blood cells.

The assessment of the prognostic performance of the ABC-02 models using each external dataset in turn (supplementary Appendix Table S3, available at *Annals of Oncology* online) suggested that the prognostic performance result obtained is dependent on the dataset used, with the highest ROC area obtained for the OS model derived from the patients receiving

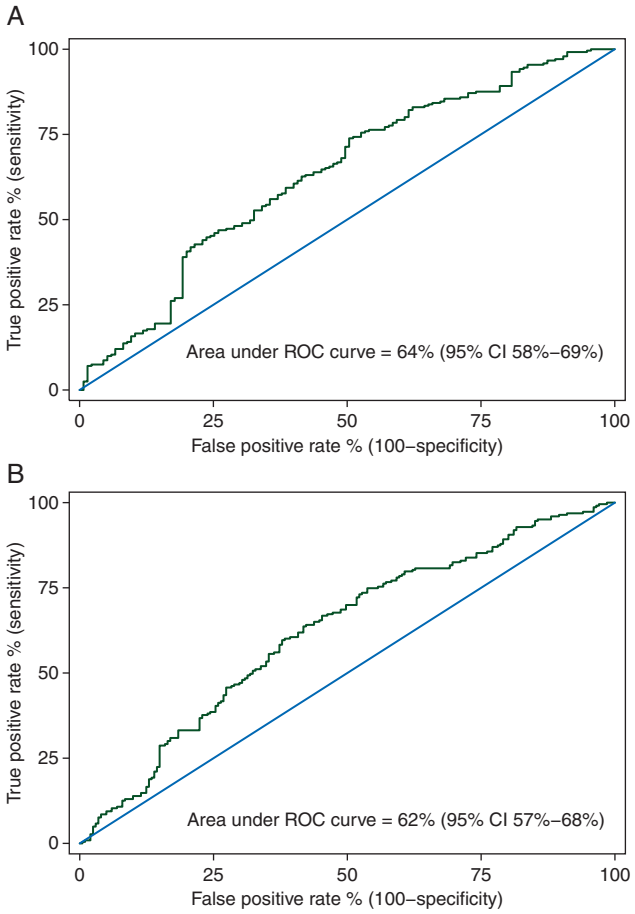

Figure 1. (A) ROC curve for overall survival; (B) ROC curve for progression-free survival.

Table 3. Overall and progression-free survival multivariate cox model selected by backward selection using a significance level of 0.10 for removal from the model

Factor	Overall survival	Progression-free survival
	Adjusted HR (95% CI) *N* = 322, *N* deaths = 307	Adjusted HR (95% CI), *N* = 322, *N* PFS events = 310
Neutrophils (×10^9/l)	1.16 (1.05–1.29)	1.19 (1.07–1.31)
P	0.005	0.001
Disease status		
Locally advanced	1	1
Metastatic	1.56 (1.20–2.02)	1.48 (1.15–1.91)
P	0.001	0.003
Bilirubin (μmol/l)	1.01 (1.00–1.02)	1.01 (1.00–1.02)
P	0.059	0.046
Performance status		
0	1	1
1	1.28 (0.99–1.64)	1.23 (0.96–1.58)
2	2.24 (1.53–3.28)	1.61 (1.10–2.36)
P	*P* < 0.001	0.042
Haemoglobin (g/dl)	0.86 (0.79–0.93)	0.90 (0.83–0.97)
P	*P* < 0.001	0.009
WBC (×10^9/l)	0.92 (0.83–1.01)	0.89 (0.81–0.98)
	0.08	0.02
Gender		
Female	1	–
Male	1.28 (1.01–1.60)	–
P	0.037	–

HR, hazard ratio; CI, confidence interval; WBC, white blood cells.

CisGem with ECOG PS 0 and 1 using the dataset from Moehler et al. [AUC 84% (95% CI 69–99)] [16].

The use of dNLR [19] instead of WBC and neutrophils does not improve the level AUC obtained. The AUC for OS models using dNLR was 63% (95% CI 57% to 70%) and for PFS models was 63% (95% CI 57% to 68%) and this is very similar to the results reported in Figure 1A and B (which relates to the use of WBC and neutrophils in the model).

discussion

The ABC-02 study established the standard of care for ABC and a set of clinically plausible prognostic factors were assembled from ABC-02 and validated in a similar population of patients with ABC in this study. The current analysis supports previous evidence that a prognostic model of neutrophils, disease status, bilirubin, ECOG PS, haemoglobin, WBC, and gender are prognostic factors for PFS and OS whereas age, bile duct or ampulla localization, type of tumour, previous therapy, and platelets were not. Although the model seems sensible to clinicians, our findings suggest the model generated from ABC-02 had limited prognostic value, falling short of the recommended level of LR >10 [20].

Our study agrees with previous investigators [5] who suggested that neutrophils and disease status are important risk factors for PFS and OS. We found no evidence that any localization was prognostic in contrast to Peixoto et al. [7]. Our model had modest prognostic value, the strongest factor being ECOG PS. In a parallel analysis of ABC-02, Grenader et al. suggested that the dNLR was more predictive of outcome than ECOG PS, perhaps reflecting the inaccuracy of a clinical ECOG PS in estimating the biological impact of a large disease burden [18]. Interestingly, in our data, the NLR was not found to be a more accurate prognostic factor than WBC as has been previously suggested [5]. More accurate tools to assess ECOG PS, particularly in the elderly appear to improve our ability for estimation in cancer patients [21]. Interest in inflammation influencing cancer outcome is increasing, in part because of the potential impact of the Glasgow Prognostic Score, based primarily on C-reactive protein and albumin [22]. These data have stimulated research to elucidate a mechanism to link inflammation and malignancy, already established in part for ABC [23]. They also have potential implications for therapy, described in pancreatic cancer for ruxolitinib [24] as well as the increasing impact of programmed cell death 1 receptor inhibition in cancer therapy [25].

Clinical criteria have formed the basis for our evaluation of prognosis but, increasingly, we should be linking these to genotype. Multiple novel technologies have proposed not only prognostic groups but also targetable genetic abnormalities in ABC [26]. Similarly, markers of resistance to chemotherapy

(e.g. ERCC-1 for cisplatin) [27] and the applicability of hENT-1 data for gemcitabine [28] in ABC may define better which patients to treat. We anticipate that ultimately prognostic factors will become closely linked with targetable genotype in order to present all management options for patients with ABC.

The limitations of this study include the incomplete data and different treatment regimen in the validation dataset. This is reflected when the studies are inspected individually (supplementary Appendix Table S3, available at *Annals of Oncology* online); however, when the datasets are combined, there are few differences between ABC-02 and the external dataset (Table 3). Validation methodologies using external datasets are uncommon, so this is a strength in our study as we considered internal validation methodologies not sufficiently credible. The strengths of the data are derived from the quality of the outcome data of patients included in clinical studies and the size of the sample in a rare disease group.

In conclusion, although the predictive value of the models generated from ABC-02 and validated in an international dataset was limited, the factors included form the basis for potential stratification in ongoing studies. Clinicians may consider these data helpful in guiding practice without defining the standard of care.

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disclosure

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A randomized study of KRAS-guided maintenance therapy with bevacizumab, erlotinib or metronomic capecitabine after first-line induction treatment of metastatic colorectal cancer: the Nordic ACT2 trial

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Background: Maintenance treatment (mt) with bevacizumab (bev) ± erlotinib (erlo) has modest effect after induction chemotherapy in metastatic colorectal cancer (mCRC). We hypothesized the efficacy of erlo to be dependent on KRAS mutational status and investigated this by exploring mt strategies with bev ± erlo and low-dose capecitabine (cap).

Patients and methods: Included patients had mCRC scheduled for first-line therapy, Eastern Cooperative Oncology Group (ECOG) 0–1 and no major comorbidities. Treatment with XELOX/FOLFOX or XELIRI/FOLFIRI + bev was given for 18 weeks. After induction, patients without progression were eligible for randomization to mt; KRAS wild-type (wt) patients were randomized to bev ± erlo (arms wt-BE, $N = 36$ versus wt-B, $N = 35$), KRAS mutated (mut) patients were randomized to bev or metronomic cap (arms mut-B, $N = 34$ versus mut-C, $N = 33$). Primary end point was progression-free

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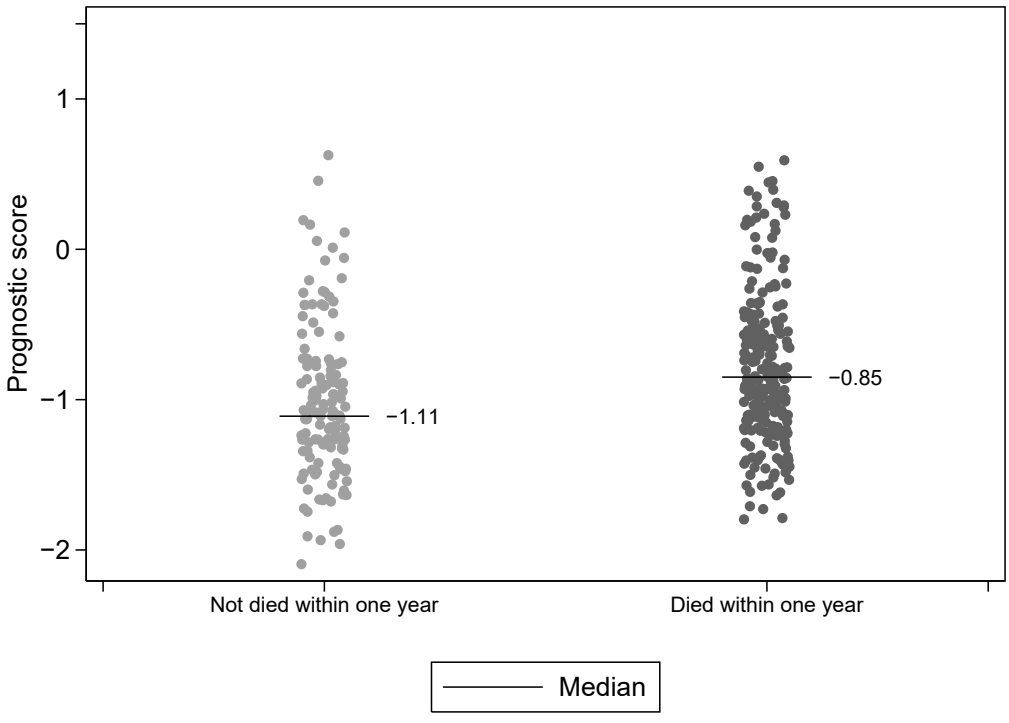
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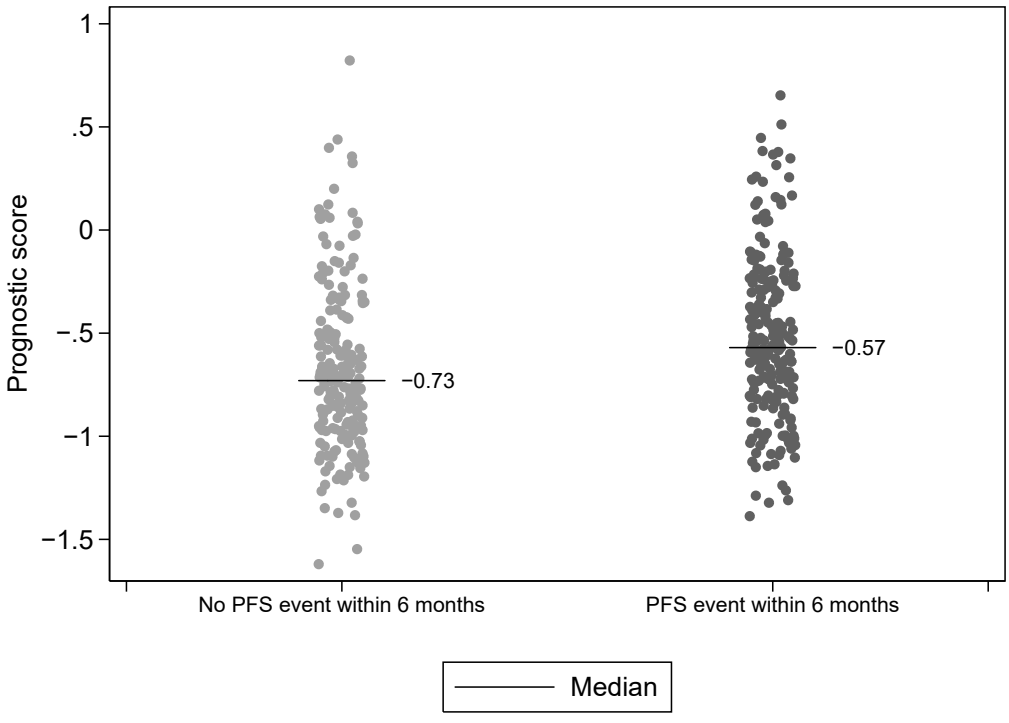
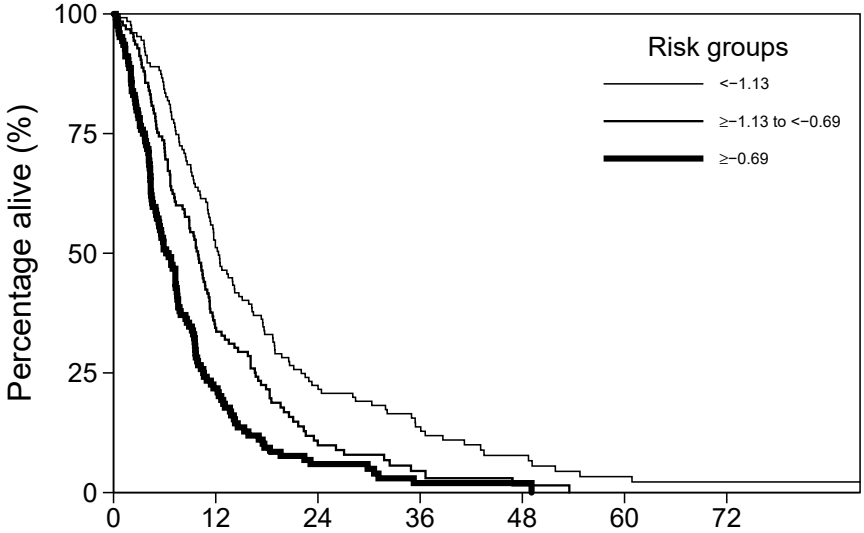
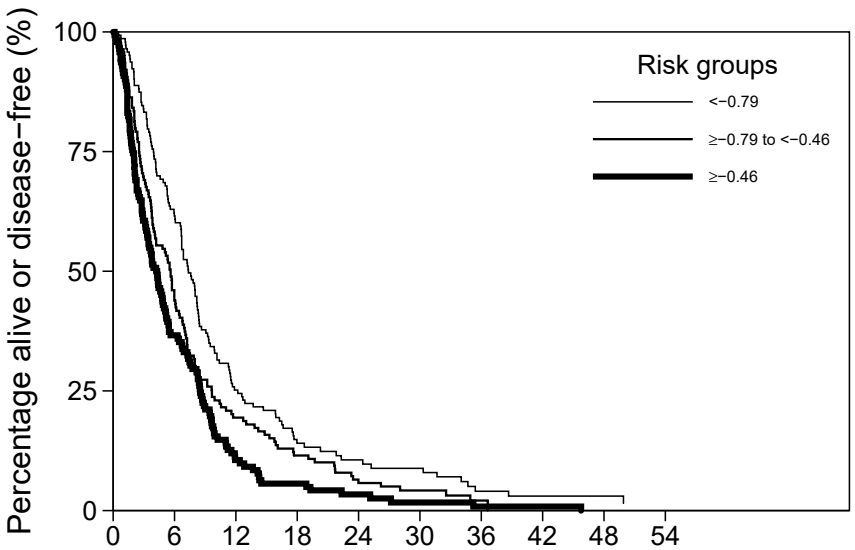
1
0
−1
−2
−1.11
−0.85
Not died within one year
Died within one year
Median

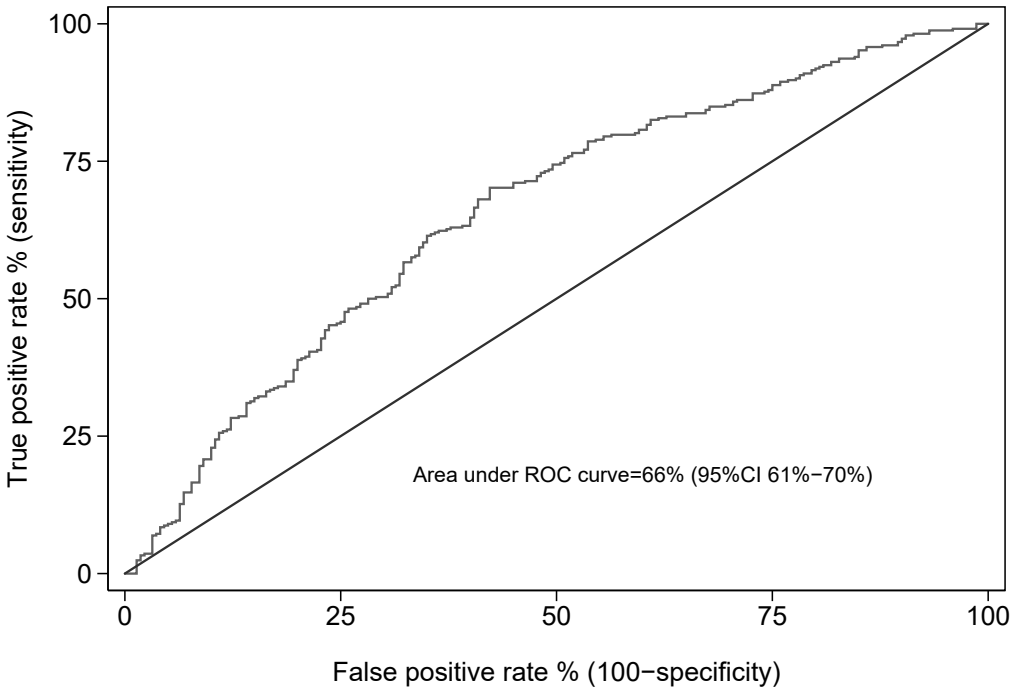

1
.5
0
−.5
−1
−1.5
Prognostic score
−0.73
−0.57
No PFS event within 6 months
PFS event within 6 months
Median

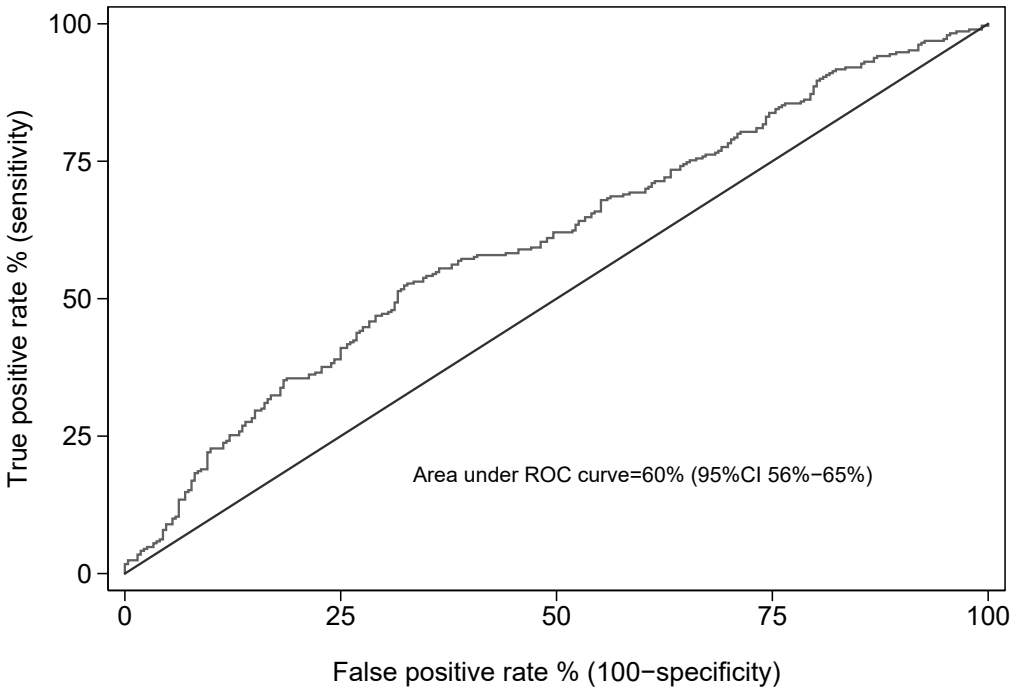


Number at risk							
<−1.13	127	65	27	15	7	3	2
≥−1.13 to <−0.69	125	43	10	3	1	0	0
≥−0.69	124	27	7	2	1	0	0



Number at risk							
<−0.79	143	36	12	4	2	1	1
≥−0.79 to <−0.46	139	27	8	1	0	0	0
≥−0.46	142	15	4	1	0	0	0


100
75
50
25
0
True positive rate % (sensitivity)
0
25
50
75
100
False positive rate % (100−specificity)
Area under ROC curve=66% (95%CI 61%−70%)


100
75
50
25
0
True positive rate % (sensitivity)
0
25
50
75
100
False positive rate % (100−specificity)
Area under ROC curve=60% (95%CI 56%−65%)

Appendix table 1: Description of validation datasets

Dataset characteristics	Knox {Knox, 2005 #691}	Jensen {Jensen, 2012 #2256}	Malka {Malka, 2014 #2293}	Rao {Rao, 2005 #674}	Wagner {Wagner, 2009 #1149}	Bekaii-Saab {Bekaii-Saab, 2011 #1767}	Moehler {Moehler, 2014 #2604}	Okusaka {Okusaka, 2010 #1391}	Goldstein {Goldstein, 2010 #1378}	Shannon {Shannon, 2014 #2669}
Number of patients	77	127	150	54	72	45	47	83	50	48
Relevant factors										
Haemoglobin (g/dL) Median (range) [N]	12.7 (9.2 to 15.8) [77]	12.6 (8.5 to 16.0) [120]	12.5 (8.0 to 16.8) [150]	12.0 (9.3 to 15.8) [53]	12.6 (8.3 to 15.3) [72]	12.5 (8.1 to 15.9) [41]	12.7 (8.8 to 16.6) [43]	12.3 (9.7 to 15.6) [83]	13.0 (9.0 to 16.0) [50]	13.1 (8.7 to 16.2) [48]
Neutrophils (x109/L) Median (range) [N]	4.6 (2.1 to 19.8) [77]	7.0 (2.6 to 23.7) [119]	6.2 (1.9 to 18.8) [127]	7.1 (4.1 to 9.1) [37]	5.9 (2.7 to 16.8) [55]	5.3 (2.2 to 12.7) [41]	6.2 (2.1 to 24.0) [34]	4.5 (1.8 to 10.9) [83]	6.1 (3.3 to 18.8) [50]	5.2 (2.6 to 14.9) [48]
Bilirubin (µmol/L) Median (range) [N]	12.0 (3.0 to 69.0) [77]	11.0 (3.0 to 97.0) [125]	13.0 (1.0 to 91.0) [140]	13.0 (4.0 to 38.0) [53]	12.4 (3.4 to 102.0) [68]	12.0 (5.1 to 29.1) [43]	10.3 (0.0 to 49.8) [47]	12.0 (3.4 to 46.2) [83]	12.0 (4.0 to 83.0) [50]	13.0 (3.0 to 55.0) [48]
White Blood Cell count (x109/L) Median (range) [N]	6.8 (3.9 to 23.9) [77]	9.9 (3.9 to 24.8) [120]	Not present	7.8 (4.3 to 14.5) [53]	8.9 (5.1 to 19.3) [72]	7.1 (3.1 to 15.7) [41]	Not present	6.8 (3.1 to 15.3) [83]	9.1 (5.1 to 24.4) [50]	7.8 (4.1 to 18.0) [48]
dNLR - Median (range) [N]	2.1 (0.8 to 20.0) [77]	2.3 (1.0 to 21.8) [119]	Not present	4.2 (1.0 to 26.2) [37]	2.4 (0.7 to 6.7) [55]	2.6 (1.0 to 9.4) [41]	Not present	2.1 (0.7 to 5.2) [83]	2.3 (1.1 to 16.6) [50]	2.4 (0.9 to 12.0) [48]
M stage - N (%)										
Locally advanced	36 (47%)	24 (19%)	32 (21%)	25 (46%)	8 (11%)	0 (0%)	20 (43%)	13 (16%)	17 (34%)	8 (17%)
Metastatic	41 (53%)	103 (81%)	118 (79%)	29 (54%)	58 (81%)	45 (100%)	27 (57%)	49 (59%)	31 (62%)	37 (77%)
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)	6 (8%)	0 (0%)	0 (0%)	21 (25%)	2 (4%)	3 (6%)
Gender- N (%)										
Female	37 (48%)	78 (61%)	65 (43%)	27 (50%)	45 (63%)	29 (64%)	20 (43%)	44 (53%)	27 (54%)	N/A

Male	40 (52%)	49 (39%)	85 (57%)	27 (50%)	27 (38%)	16 (36%)	27 (57%)	39 (47%)	23 (46%)	N/A
Unknown	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	N/A
Performance status- N (%)										
0	0 (0%)	47 (37%)	62 (41%)	6 (11%)	Not present	14 (31%)	Not present	62 (75%)	21 (42%)	18 (38%)
1	74 (96%)	65 (51%)	79 (53%)	37 (69%)	Not present	31 (69%)	Not present	21 (25%)	23 (46%)	30 (63%)
2	3 (4%)	13 (10%)	1 (1%)	10 (19%)	Not present	0 (0%)	Not present	0 (0%)	6 (12%)	0 (0%)
Unknown	0 (0%)	2 (2%)	8 (5%)	1 (2%)	Not present	0 (0%)	Not present	0 (0%)	0 (0%)	0 (0%)
Overall median survival time in months (IQR)	11.7 (6.7 to 28.4)	9.7 (4.4 to 15.8)	11.5 (6.5 to 23.3)	9.5 (5.6 to 14.9)	10.1 (6.3 to 16.8)	6.4 (3.0 to 16.3)	10.1 (5.0 to 17.2)	9.0 (6.0 to 16.1)	6.8 (3.7 to 13.5)	13.1 (5.7 to NR)
Total number of deaths (%)	70(91%)	118(93%)	124(83%)	49(91%)	67(93%)	43(96%)	41(87%)	75(90%)	48(96%)	29(60%)
Total number of PFS events (%)	76(99%)	123(97%)	140(93%)	52(96%)	72(100%)	45(100%)	46(98%)	77(93%)	50(100%)	41(85%)

Abbreviations: NR: not reached

Appendix table 2: Multivariate analysis of overall survival and progression-free survival among patients in the ABC-02 dataset who were treated with CisGem and were Performance Status 0 or 1 (Derivation dataset)*

	Adjusted HR (95% CI)	
Factor	Overall survival, N=141, N deaths=132	Progression-Free survival, N=141, N PFS events=134
Heamoglobin (g/dL)	0.84 (0.74 to 0.95)	0.84 (0.75 to 0.95)
P	0.006	0.007
Disease status		
Locally advanced	1.00	1.00
Metastatic	1.69 (1.15 to 2.49)	1.64 (1.12 to 2.42)
P	0.008	0.01
Bilirubin (µmol/L)	1.02 (1.00 to 1.05)	1.02 (1.00 to 1.05)
P	0.09	0.10
Neutrophils (x109/L)	1.10 (1.02 to 1.17)	1.09 (1.02 to 1.17)
P	0.01	0.01

Abbreviation: CI, confidence interval; HR, Hazard Ratio.

* Each HR was adjusted for all the other factors in the same model. The table lists the factors that were selected from backwards elimination Cox regression modelling

Appendix table 3 - ROC analysis by validation dataset

Validation datasets	**Models with all patients*** ROC Area (95%CI)		**Models with CisGem patients & PS 0-1**** ROC Area (95%CI)	
	OS model	*PFS model*	*OS model*	*PFS model*
{Knox, 2005 #691}	71% (59 to 83)	68% (56 to 80)	**73% (62 to 85)**	67% (55 to 79)
{Jensen, 2012 #2256}	54% (43 to 65)	63% (53 to 73)	51% (39 to 63)	61% (50 to 72)
{Malka, 2014 #2293}	N/A	N/A	67% (57 to 77)	62% (52 to 73)
{Rao, 2005 #674}	61% (41 to 80)	56% (37 to 76)	62% (41 to 82)	59% (40 to 79)
{Wagner, 2009 #1149}	67% (46 to 87)	N/A	70% (53 to 87)	62% (45 to 80)
{Bekaii-Saab,2011 #1767}	67% (46 to 87)	41 (14 to 68)	65% (44 to 86)	44% (17 to 72)
{Moehler, 2014 #2604}	N/A	N/A	**84% (69 to 99)**	70% (49 to 90)
{Okusaka, 2010 #1391}	70% (55 to 85)	64% (50 to 78)	66% (35 to 96)	57% (36 to 79)
{Goldstein,2010 #1378}	**73% (59 to 87)**	70% (54 to 85)	67% (50 to 83)	64% (46 to 82)
{Shannon,2014 #2669}	N/A	62% (45 to 80)	**73% (57 to 90)**	58% (41 to 76)

* Models presented in Table 2

** Models presented in Appendix Table 2

N/A: ROC area could not be calculated for these datasets because some of the key variables of the model were not present in those datasets

Appendix table 4 - Independent validation of scores derived from ABC-02, applied to a dataset composed of 10 independent international datasets [a]

FPR, % [b]	TPR, % [b]	LR	Prognostic score Cut-Off
1 year Overall Survival			
5	10	2	≥ -0.03
10	16	1.6	≥ -0.32
15	20	1.33	≥ -0.41
20	41`	2.05	≥ -0.70
25	46	1.84	≥ -0.77
50	74	1.48	≥ -1.12
6 months Progression-Free survival			
5	9	1.88	≥ 0.07
10	14	1.4	≥ -0.12
15	29	1.93	≥ -0.26
20	33	1.65	≥ -0.33
25	40	1.6	≥ -0.46
50	70	1.4	≥ -0.73

[a] Abbreviations: FPR, false-positive rate; LR, likelihood ratio; TPR, true-positive rate. The FPR indicates the proportion of patients who did not have the outcome of interest (eg, those who did not die within 1 year) whose prognostic score exceeded the specified cut-off; the TPR indicates the proportion of patients who did have the outcome of interest (eg, those who did not die within 1 year) whose prognostic score exceeded the specified cut-off; the LR is calculated as TPR/FPR.

[b] The prognostic score is based on the combination of selected factors measured at baseline. Prognostic score is derived from the linear predictor of the cox model (Table 2). Cut-offs are expressed as log(HR).

Appendix table 5 - 6 months and 12 months OS and PFS rates for the different risk score groups

Endpoint	Groups	6 months rate	12 months rate
Overall survival	< -1.13	84% (95%CI 77 to 90)	51% (95%CI 42 to 59)
	≥ -1.13 to <-0.69	72% (95%CI 63 to 79)	34%(95%CI 26 to 43)
	≥ -0.69	51% (95%CI 42 to 59)	22% (95%CI 15 to 29)
Progression Free survival	< -0.79	62% (95%CI 53 to 69)	25% (95%CI 18 to 33)
	≥ -0.79 to <-0.46	44% (95%CI 36 to 52)	19% (95%CI 13 to 26)
	≥ -0.46	37% (95%CI 29 to 44)	11% (95%CI 6 to 16)