Original Study

Validated Nomogram Predicting 6-Month Survival in Pancreatic Cancer Patients Receiving First-Line 5-Fluorouracil, Oxaliplatin, and Irinotecan

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Abstract

FOLFIRINOX (leucovorin, 5-fluorouracil, irinotecan, and oxaliplatin) is an accepted standard in metastatic and locally advanced pancreatic cancer (PC), but long-term prognosis is still poor. Indeed, no criteria reliably identify patients with limited, if any, chances of long-term benefit. We therefore developed and externally validated a prognostic nomogram predicting the risk of early death in PC patients treated with first-line triplet chemotherapy.

Background: FOLFIRINOX (leucovorin, 5-fluorouracil, irinotecan, and oxaliplatin) is an option for fit patients with metastatic (MPC) and locally advanced unresectable (LAPC) pancreatic cancer. However, no criteria reliably identify patients with better outcomes. **Patients and Methods:** We investigated putative prognostic factors among 137 MPC/LAPC patients treated with triplet chemotherapy. Association with 6-month survival status (primary endpoint) was assessed by multivariate logistic regression models. A nomogram predicting the risk of death at 6 months was built by assigning a numeric score to each identified variable, weighted on its level of association with survival. External validation was performed in an independent data set of 206 patients. The study was registered at ClinicalTrials.gov (NCT03590275). **Results:** Four variables (performance status, liver metastases, baseline carbohydrate antigen 19-9 level, and neutrophil-to-lymphocyte ratio) were found to be associated with 6-month survival by multivariate analysis or had sufficient clinical plausibility to be included in the nomogram. Accuracy was confirmed in the validation cohort

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(*C* index = 0.762; 95% confidence interval, 0.713-0.825). After grouping all cases, 4 subsets with different outcomes were identified by 0, 1, 2, or > 2 poor prognostic features ($P < .0001$). **Conclusion:** The nomogram we constructed accurately predicts the risk of death in the first 6 months after initiation of FOLFIRINOX in MPC/LAPC patients. This tool could be useful to guide communication about prognosis, and to inform the design and interpretation of clinical trials.

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Introduction

Pancreatic cancer (PC) represents a major challenge, as it is fourth among the leading causes of cancer death and is expected to rise to become the second most lethal malignancy by 2030.[1-3] Despite recent advances in systemic treatment, the prognosis of patients with metastatic (MPC) or locally advanced unresectable (LAPC) disease remains poor, with 5-year overall survival (OS) of less than 5%.[4] Phase 3 trials established FOLFIRINOX (leucovorin, 5-fluorouracil, irinotecan, and oxaliplatin) and gemcitabine plus nab-paclitaxel (Gem-Nab) as current standards in the first-line treatment of fit patients with MPC.[5,6] Both regimens also showed promising efficacy in patients with LAPC.[7-9] In particular, FOLFIRINOX is now regarded as a suitable option in LAPC cases[10,11] and has also been recently established as the new reference in the adjuvant setting.[12]

Nonetheless, triplet chemotherapy is burdened by potentially severe adverse events (mainly digestive and hematologic toxicities, with grade 3/4 neutropenia occurring in 46% of patients treated with FOLFIRINOX, including 5.4% febrile neutropenia), and median OS barely exceeds 11 months, even in selected patients enrolled onto randomized studies (ie, performance status [PS] 0-1, bilirubin level < 1.5 times the upper limit of normal, and age ≤ 75 years).[5] In routine clinical practice, only about 25% of patients with MPC would be eligible for FOLFIRINOX.[13] Different strategies (comprehensively known as modified FOLFIRINOX) aimed at improving tolerability have been tested, and are mostly based on removing 5-fluorouracil bolus and/or decreasing irinotecan dose, or are based on the up-front administration of growth factors.[14] This approach seems to reduce the rate of grade 3/4 gastrointestinal or hematologic events, with comparable results in terms of OS reported in the PRODIGE4-ACCORD11 trial.[14,15]

The Gem-Nab combination represents an accepted alternative option in the first line.[6] Despite being associated with an overall similar incidence of hematologic toxicities compared to FOLFIRINOX (grade 3/4 neutropenia, 38%; febrile neutropenia, 3%), Gem-Nab results in a higher rate of grade 3 or higher peripheral neuropathy (17% vs. 9%) and a lower rate of severe diarrhea (6% vs. 12.7%),[5,6] and is therefore generally regarded as a suitable option for a greater percentage of MPC patients in everyday practice.[13] With the intent to improve risk stratification and patient selection for routine clinical decision making and future trials, several authors have investigated clinical and laboratory factors putatively linked with patient outcome.[16,17] Goldstein et al[18] queried the MPACT study data set, identified several variables associated with OS, and developed a nomogram able to predict patient survival probability at different time points when treated with gemcitabine with or without nab-paclitaxel. Predictive algorithms have recently been gaining momentum in clinical practice. Among these, nomograms are the most frequently used tools thanks to their accuracy and ease of use.[19] Previous studies with modified FOLFIRINOX reported that liver metastases, PS, and neutrophil-to-lymphocyte ratio (NLR) are independently associated with OS.[14] However, no tool is available to predict single patient prognosis with the triplet regimen.

Because different treatment options are available and no head-to-head comparison has been conducted so far, discussing the relative benefits and risks of FOLFIRINOX and Gem-Nab with patients is challenging. We therefore aimed to develop and validate a simple nomogram able to predict 6-month survival probability in MPC and LAPC patients treated with first-line triplet chemotherapy (FOLFIRINOX, delivered on a classic or modified schedule).

Patients and Methods

Patient Selection and Data Collection

The developing set (DS) was constituted by consecutive MPC and LAPC patients treated at a single institution (Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy) from January 2008 to December 2014 and discussed by dedicated multidisciplinary team dealing with pancreatic malignancies. Eligible patients were identified as follows: age > 18 years; cytologically or histologically confirmed pancreatic carcinoma; nonresectable, stage III or IV disease according to the American Joint Committee on Cancer (AJCC) staging system; access to clinical data collected before beginning of first-line chemotherapy; availability of laboratory information before treatment initiation; objective tumor response evaluation; and survival data. The FOLFOXIRI (leucovorin, 5-fluorouracil, oxaliplatin, and irinotecan) schedule used in Pisa represents an alternative to standard FOLFIRINOX, derived from the experience in colorectal cancer[20] with apparently superimposable efficacy compared to FOLFIRINOX in MPC/LAPC. Details about the modified regimen have been described elsewhere.[14]

The putative predictors investigated were the following: age; gender; Eastern Cooperative Group (ECOG) PS (0 vs. 1); AJCC stage (III vs. IV); tumor location (head vs. body—tail); prior surgery of primary tumor (yes vs. no); previous adjuvant chemotherapy (yes vs. no); presence of biliary drainage (yes vs. no); number of disease sites; presence (yes vs. no) of metastases at specific sites, such as liver, lung, peritoneum, or bone; neutrophil, lymphocyte, and platelet counts; NLR and platelet-to-lymphocyte ratio before the first cycle of treatment; and pretreatment lactate dehydrogenase, carcinoembryonic antigen, and carbohydrate antigen 19-9 (CA19-9) serum

levels. Age, number of disease sites, and laboratory parameters were recorded and analyzed as continuous variables.

The external validation cohort involved MPC/LAPC patients treated at different Italian and French institutions from January 2011 to June 2017. Inclusion criteria for the validating set (VS) were the same used in the DS, as were the variables collected for analysis. All patients included in the VS received FOLFIRINOX as per the PRODIGE4-ACCORD11 schedule.[5]

The analyses included in this study were performed in accordance with the Declaration of Helsinki and were approved by the ethics committee of the coordinating center (Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy). Written informed consent from the patients for research use of data was obtained before the investigation. The protocol was registered at ClinicalTrials.gov (NCT03590275).

Statistical Analyses

An early death binary variable indicating 6-month survival status was calculated from survival times, with a value of 1 assigned if an event of death occurred in the first 180 days and 0 assigned otherwise. Association of different covariates with 6-month survival status was evaluated by building univariate unconditional logistic regressions, modeling each variable with 6-month survival status. The Wald test was used to assess statistical significance, defined as 2-tailed $P < .05$. Considering the high variability of CA19-9, this covariate was logarithmically transformed before the analyses were conducted. Statistically significant covariates were used to develop different multivariate logistic regression models. Forward and backward methods were used. The Wald test was used to assess the significance of each covariate in the multivariate model. Global fit was evaluated with the Nagelkerke R^2, Somer D, and model log-likelihood ratio chi-square. Collinearity was addressed by t test, Mann-Whitney test, Fisher exact test, ANOVA, linear regressions, and variance inflation factors, depending on the nature of the covariates and their characteristics (binary, categorical, or continuous). The same tests were also used to assess differences in clinical characteristics between patients included in the VS and DS cohorts. Decision regarding inclusion of a specific variable into the final model was addressed taking into consideration their statistical significance, the percentage of models in which it remained significant, the global fit of the model, and the clinical plausibility of covariates. Predicted probabilities were tested against the observed probabilities in the VS. Somer D, C index, Spiegelhalter Z test, and Brier score were used to evaluate the discrimination of the model. The 95% confidence intervals (CIs) of the C index were calculated with bootstrap. The calibration plot was assessed visually. Survival analyses were performed by the Kaplan-Meier method with log-rank test and by building Cox regression models. Median follow-up times were calculated by the reverse Kaplan-Meier method.

The response rate was evaluated according to Response Evaluation Criteria in Solid Tumors 1.1. Progression-free survival (PFS) was defined as time from start of FOLFIRINOX to clinical or radiologic progression or death from any cause, whichever occurred first, or until the date of the last follow-up, at which point data were censored. OS was defined as time from start of FOLFIRINOX to death from any cause. Survival data were censored at the last follow-up. Receiver operating characteristic curves were used to assess the best cutoff values for categorization of continuous variables. Packages "Survival" and "rms" of R software were used for all the analyses.

Results

Patient Characteristics and Treatment Outcome

The characteristics of patients in the DS and VS are presented in Table 1. Data from 343 patients were analyzed, with 137 and 206 cases included in the DS and the VS, respectively. More patients in the VS had an ECOG PS of 1 compared to the DS (54.9% vs. 32.8%; $P < .001$). NLR was also significantly higher among the patients in the VS (median, 3.2 vs. 2.3; $P < .001$). No significant differences in number and location of metastases, basal CA19-9 serum level, or other known prognostic factors were observed (all $P > .1$).

Median follow-up was 30 months for the DS and 35 months for the VS. Outcomes achieved in the 2 cohorts were similar. Response rate was 38.6% and 31.4%, while median PFS was 8.0 months (95% CI, 6.7-9.2) and 7.2 months (95% CI, 5.6-8.2) in the DS and VS, respectively. Median OS was 11.6 months (95% CI, 10.5-13.9) in the DS and 10.5 months (95% CI, 9.2-12.1) in the VS. Death events were observed in the majority of patients, with only 8.8% and 9.7% of patients censored for OS in the DS and VS, respectively. Notably, there were no censored observations in the first 180 days.

Prognostic Nomogram Development

All the collected variables were analyzed for association with 6-month survival (Table 2). Four of the considered variables were selected for the final multivariable model: ECOG PS, pretreatment NLR, liver metastases, and basal serum CA19-9 (Table 3). Collinearity analyses revealed a slight correlation between CA19-9 and presence of liver metastases, and between ECOG PS and NLR. However, variance inflation factor was always < 2, so we decided to keep the model without further modifications. Pretreatment platelet-to-lymphocyte ratio, number of sites involved, and disease stage, although significant or borderline significant by univariate analysis, were not retained because of an excessive amount of collinearity with NLR and liver metastases. Global fit was evaluated by Nagelkerke R^2, Somer D, and area under the curve (AUC). The model showed a good global fit with Nagelkerke R^2 of 0.283, Somer D of 0.592, C index of 0.796, and a highly significant log-likelihood ($P < .0001$). The resulting nomogram is shown in Figure 1.

Prognostic Nomogram Validation

Probabilities predicted by the nomogram were tested against those observed in the VS. The nomogram discriminative ability was satisfied with a Somer D of 0.524, corresponding to a C index of 0.762 (95% CI, 0.713-0.825). The Brier score resulted in 0.16, and the Spiegelhalter Z test was not significant ($P = .087$). Visual inspection of the calibration plot showed a good overlap between predicted and observed probabilities, even if there was a slight underestimation for patients at very high risk of early death (Figure 2).

Survival Analysis Based on Prognostic Factors

As an ancillary analysis, we performed a categorization of the variables included in the model to assess if they could be used to

Table 1 Patient Characteristics

Characteristic	Developing Set (N = 137)	Validating Set (N = 206)	P
Gender			.152
Male	66 (48.2)	116 (56.3)	
Female	71 (51.8)	90 (43.7)	
Age (Y)			.564
Median	60	62	
Range	33-75	41-78	
ECOG PS			<.001
0	92 (67.2)	93 (45.1)	
1	45 (32.8)	113 (54.9)	
Tumor Site			.579
Head	74 (54)	119 (57.5)	
Body-tail	63 (46)	88 (42.5)	
TNM Stage			.428
III	56 (40.9)	75 (36.4)	
IV	81 (59.1)	131 (63.6)	
Previous Surgery			.160
Yes	15 (10.9)	34 (16.5)	
No	122 (89.1)	172 (83.5)	
Adjuvant CT			.363
Yes	11 (8)	24 (11.7)	
No	126 (92)	182 (88.3)	
No. of Involved Sites			.356
1	60 (43.8)	75 (36.2)	
2	62 (45.3)	104 (50.2)	
≥3	15 (10.9)	28 (13.6)	
Liver Metastases			.322
Yes	64 (46.7)	108 (52.4)	
No	73 (53.3)	98 (47.6)	
Lung Metastases			.608
Yes	14 (10.2)	25 (12.1)	
No	123 (89.8)	181 (87.9)	
Peritoneal Metastases			.667
Yes	26 (19)	35 (17)	
No	111 (81)	171 (83)	
Bone Metastases			.718
Yes	4 (2.9)	4 (1.5)	
No	133 (97.1)	203 (98.5)	
CA19-9 (U/mL)			.183
Median	470	570	
Range	1-75,000	.1-181300	
IQR	91-2001.5	77-3713	
NLR			<.001
Median	2.3	3.2	
Range	0.6-9.1	.3-9.3	
PLR			.276
Median	48	52	
Range	17-261	15-302	

Abbreviations: CT = computed tomography; ECOG PS = Eastern Cooperative Oncology Group performance status; IQR = interquartile range; NLR = neutrophil-to-lymphocyte ratio; PLR = platelet-to-lymphocyte ratio; TNM = tumor, node, metastasis classification system.

stratify patients into different risk groups. In order to do that, we combined the patients in the DS and VS, and designed 4 different risk categories based on the number of poor prognostic features present: ECOG PS 1, presence of liver metastases, $\log_{CA19\text{-}9}$, and NLR above a threshold value. Receiver operating characteristic curves were developed for the continuous variables $\log_{CA19\text{-}9}$ and NLR, and returned AUC values of 0.641 and 0.676, respectively. We therefore set a threshold of 6.75 for $\log_{CA19\text{-}9}$ (which corresponds to a basal value of 845 U/mL), obtaining a sensitivity of 0.64 and a specificity of 0.62. For NLR, the threshold was set at 2.46, with a sensitivity of 0.78 and a specificity of 0.52. Median OS significantly differed between the 4 subgroups identified, ranging from 7.2 months (95% CI, 5.6-8.7), through 10.8 months (95% CI, 9.4-12.9) and 13.9 months (95% CI, 12.5-16.6), and up to 18.3 months (95% CI, 14.5-23.5) for patients with > 2, 2, 1, and 0 risk factors, respectively ($P < .0001$ for overall comparison) (Figure 3).

Discussion

Life expectancy of patients with unresectable PC treated with first-line chemotherapy remains poor despite the recent

Table 2 Results of Univariate Models

Characteristic	OR	95% CI	P
Age	0.64	0.36-1.13	.124
Gender (male vs. female)	1.79	0.74-4.34	.197
ECOG PS (1 vs. 0)	2.21	1.01-5.35	.046
Disease stage (IV vs. III)	2.55	0.95-6.88	.067
Site of disease in pancreas (head vs. body-tail)	0.29	0.03-2.33	.240
Previous surgery (yes vs. no)	0.66	0.14-3.14	.603
Previous adjuvant chemotherapy (yes vs. no)	0.43	0.05-3.48	.425
Presence of biliary drainage (no vs. yes)	0.44	0.14-1.37	.155
No. of sites involved	1.85	1.09-3.16	.022
Liver metastases (yes vs. no)	3.69	1.43-9.55	.007
Lung metastases (yes vs. no)	1.94	0.56-6.79	.298
Peritoneal metastases (yes vs. no)	1.08	0.36-3.22	.884
Bone metastases (yes vs. no)	1.52	0.15-15.10	.724
Pretreatment NLR	2.99	1.62-5.05	<.001
Pretreatment PLR	1.64	1.04-2.58	.031
Pretreatment $\log_{CA19\text{-}9}$ level	1.93	1.00-3.91	.049
Pretreatment CEA level	1.02	0.99-1.04	.097
Pretreatment LDH level	1.65	0.87-3.01	.121

Abbreviations: CEA = carcinoembryonic antigen; CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; LDH = lactate dehydrogenase; NLR = neutrophil-to-lymphocyte ratio; OR = odds ratio; PLR = platelet-to-lymphocyte ratio.

Table 3 Results of Multivariable Model

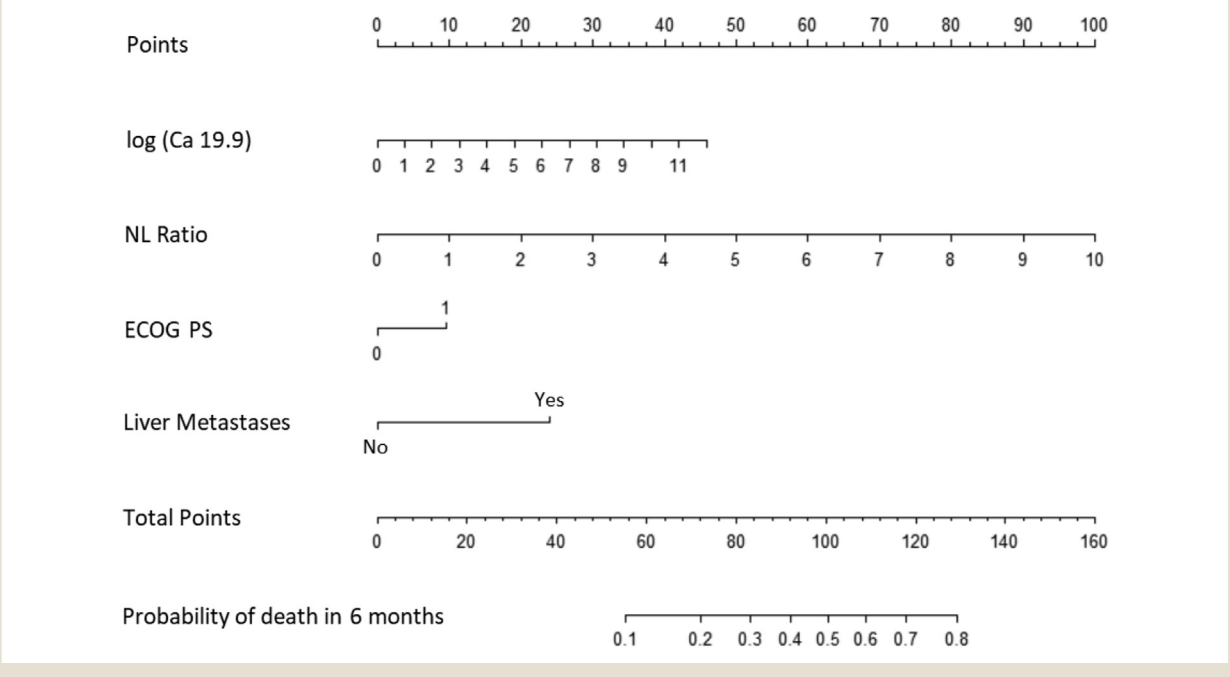
Characteristic	No. of Patients	No. of Events	OR	95% CI	*P*
ECOG PS					
0	92	13	1		
1	45	12	1.59	0.75-4.65	.156
Pretreatment NLR	137	25	2.66	1.33-5.35	.006
Liver Metastases					
No	73	7	1		
Yes	64	18	3.21	1.07-9.61	.037
Baseline $\log_{CA19-9}$	137	25	1.81	1.01-4.22	.048

Abbreviations: CI = confidence interval.; ECOG PS = Eastern Cooperative Oncology Group performance status; NLR = neutrophil-to-lymphocyte ratio; OR = odds ratio.

introduction of more active chemotherapy regimens.[4-6] In light of the toxicity profile of an intensive triplet schedule such as classic or modified FOLFIRINOX, the ability to anticipate single-patient prognosis is valuable. It allows discussion of the benefit-to-risk ratio of this regimen and permits a more informed decision to be made about different first-line therapeutic options. Authoritative experts have advocated the need for alternative measures to understand and communicate the impact of treatment on OS.[21] Evidence in the literature demonstrates that discussion about prognosis during clinical encounters strengthens the patient—oncologist relationship,[22] thus prompting the need for validated and easy-to-use instruments to clearly communicate risks at defined time points during the course of the disease. Similar instruments have been proposed for second-line therapy in MPC,[23] but they lack the triplet chemotherapy regimen used in the first-line setting. In addition, in case of clinical trials, prognostic nomograms could be useful tools for a better stratification of the enrolled patients and interpretation of the results in different subgroups.[24]

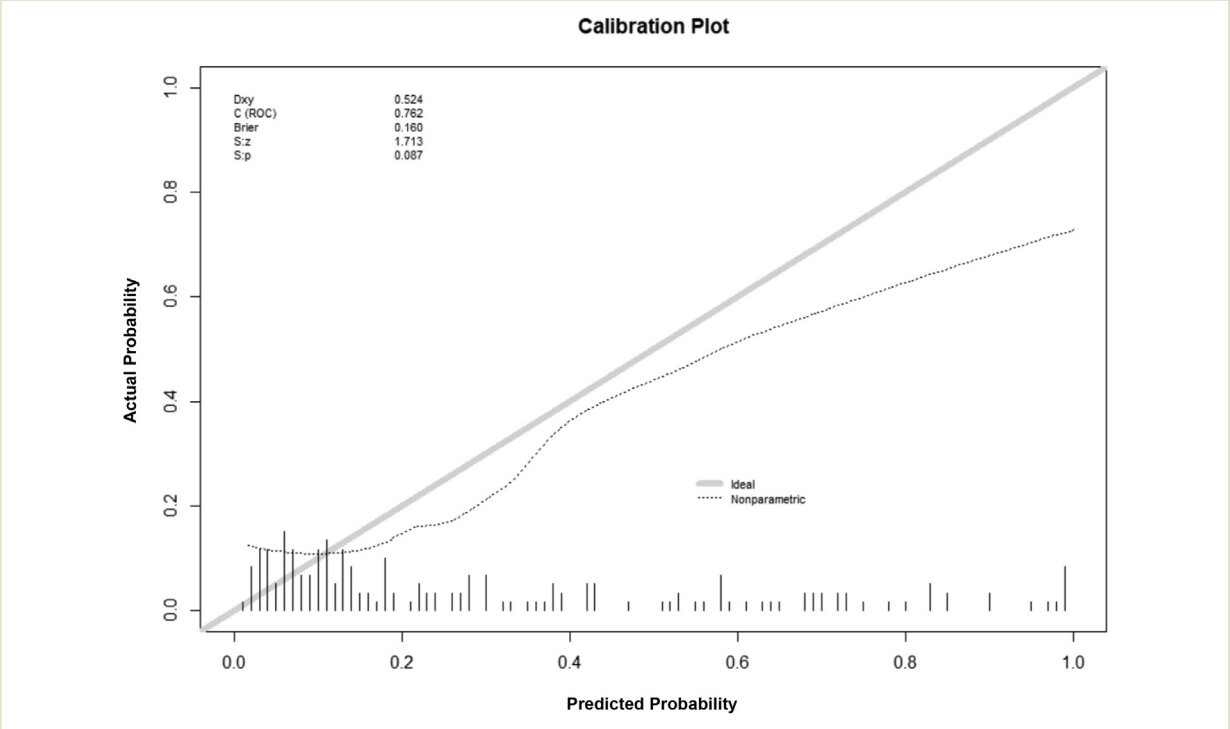
Our study identified easily available and measurable parameters to be major determinants of prognosis in this population, such as ECOG PS, NLR, liver metastases, and CA19-9 levels, thus making the nomogram accessible in the routine clinical setting. A large body of literature supports the prognostic importance of these variables in PC patients treated with gemcitabine-based

Figure 1 Nomogram Predicting Risk of Death at 6 Months After Initiation of FOLFIRINOX. To Calculate Score for Single Variable, Locate Appropriate Point in Each Axis and Draw a Line Up to "Points" Axis. Then Sum Scores for Each Variable, Locate Total Score on "Total Points," and Draw Line Downward to "Probability of Death in 6 Months" Axis. Identified Value Represents Probability of Death at 6 Months After Starting Treatment



Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; NL ratio = neutrophil-to-lymphocyte ratio.

Figure 2 Calibration Plot for External Validation of Nomogram. Calibration Plot of Observed Versus Predicted Probabilities. Gray Line Represents Ideal Perfect Model; Dotted Line, Results of Model



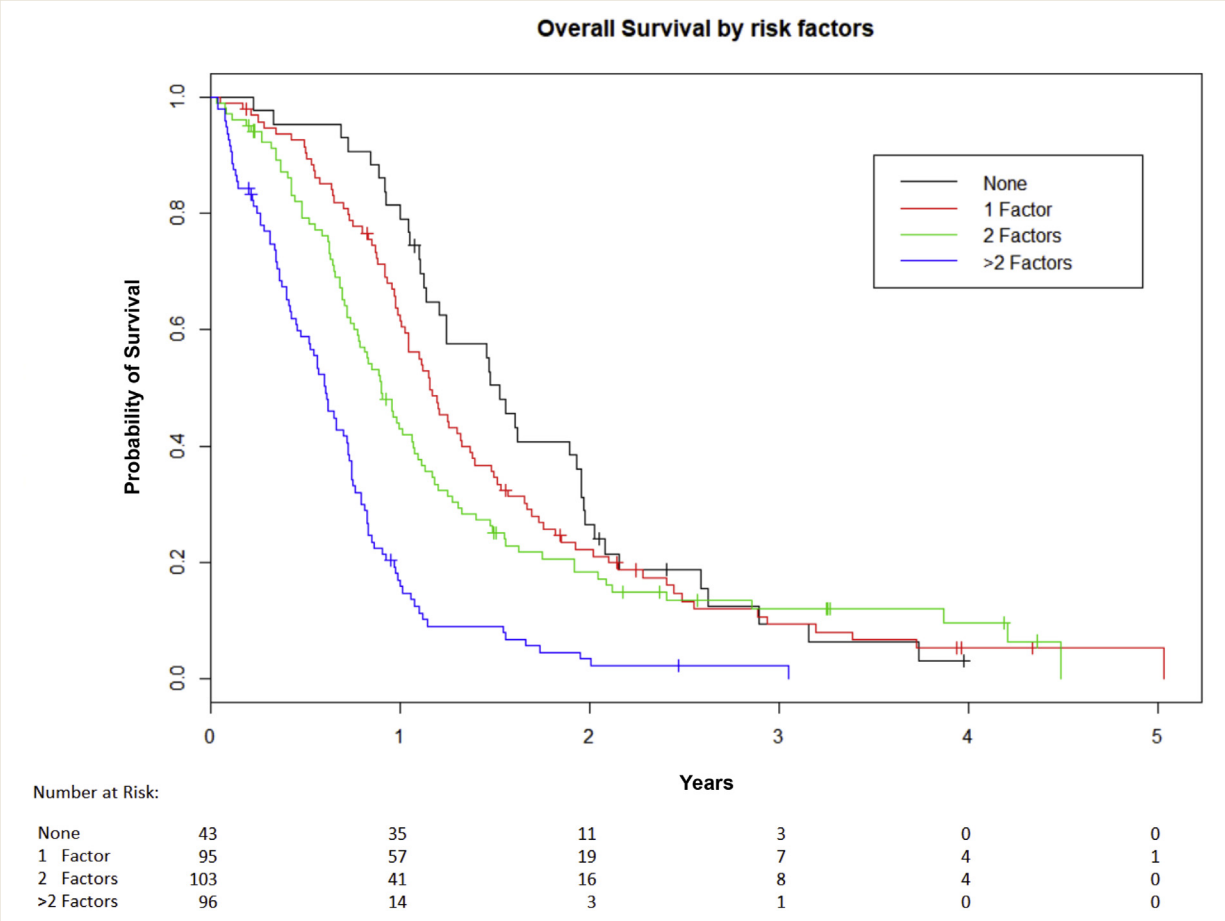
Abbreviations: Brier = Brier score; C (AUC) = *C* index; Dxy = Somer *D*; S:p = *P* value of Spiegelhalter *Z* test; S:z = *z* value of Spiegelhalter *Z* test.

chemotherapy, particularly for PS and CA19-9 values.[25,26] Nonetheless, to our knowledge, this is the first attempt to include them in a validated model able to predict the early deaths of MPC/LAPC patients treated with a more modern regimen such as FOLFIRINOX. Of interest, stratifying patients for the presence of each single determinant identified different populations with distinct survival outcomes. In particular, in the most favorable risk subgroup (ie, no poor prognostic features present), median OS was almost 3 times longer than that observed for the worst risk category (ie, > 2 poor prognostic features present), making the information retrieved by the nomogram useful for both practice and research. Currently, validated predictive biomarkers are lacking in this setting,[27] and prognostic stratification is thus essential to discuss alternative treatment options in single cases. Therefore, our nomogram could represent a suitable tool for the identification of different patient subgroups, and could prompt research on the biological bases of the influence of these clinical variables on survival outcomes.

Variables included in the nomogram were either confirmed as independent prognostic determinants at multivariate analysis or were retained because of the robust evidence of their prognostic value from the available literature. Notably, previous studies have shown tumor stage to be a prognostic determinant.[4,7] However, its significance was not formally demonstrated in our data sets (P = .067 at univariate analysis). This could possibly be due to the relatively low number of LAPC cases in our study, as well as the potential presence of other poor prognostic features in the LAPC cohort. We therefore decided not to retain it in the final nomogram. This decision was also supported by the evidence of high collinearity between disease stage and the presence of liver metastases.

Three of 4 factors included in our nomogram were also included in the nomogram developed from the MPACT database (comprising PS, NLR, liver metastases, serum albumin, sum of the largest lesions, receipt of analgesics, and treatment arm),[18] further underlining the external validity of our work. Notably, the relative contribution of CA19-9 to the performance of the MPACT nomogram, when added to PS, NLR, liver lesions, and serum albumin, was limited. Indeed, in our study, CA19-9 was the strongest predictor of OS among the analyzed variables. This is in line with the previous literature, which convincingly established this serum tumor marker as a main confirmed determinant of patient outcome in this population.[17,25,26] Moreover, some limitations of the MPACT nomogram make it of relatively low immediate utility in routine practice. The lack of external validation, the few points assigned to several variables (such as receipt of analgesics and treatment arm), and the inclusion of highly selected patients from a registering phase 3 trial might prevent the applicability of these results to other populations and/or other treatment regimens. However, in light of the partly overlapping factors included in the 2 nomograms and the ease of use of our prognostic variables, it could be of interest to test the performance of

Figure 3 Survival Curves for Different Risk Categories. Risk Factors Were as Follows: (i) Presence Of Liver Metastases; (ii) Eastern Cooperative Oncology Group Performance Status of 1; (iii) Baseline Neutrophil-To-lymphocyte Ratio > 6.75; (iv) Baseline CA19-9 > 845 U/mL



this FOLFIRINOX nomogram in patients treated with other regimens, namely Gem-Nab. In this regard, one study confirmed the role of PS, NLR, and CA19-9 in a prognostic nomogram developed from a retrospective series of 210 patients treated with first-line Gem-Nab.[28]

When planning the study design, we decided to build an instrument specifically addressing the risk of early death instead of general OS. This decision was taken in light of the risks of toxicity associated with FOLFIRINOX and other potential issues affecting patient daily life, such as the need to implant a central venous catheter for prolonged infusions. Indeed, there is little doubt that FOLFIRINOX (whatever schedule is provided) remains a challenging treatment option; ideally, it should be provided to patients who can experience the greatest benefit in terms of OS while sparing those who are likely to get little or no advantage because of the very short OS probability. The choice of the 6-month period as primary outcome measure was based on the results of the PRODIGE4-ACCORD11 trial, which reported a median PFS of 6.4 months and a median OS of 11.1 months in the experimental arm.[5] In our opinion, the probability of experiencing early death in the first 6 months after treatment initiation (ie, less than the median PFS expected with FOLFIRINOX) can be considered an acceptable criterion to discuss with the patient when evaluating treatment alternatives to triplet chemotherapy.

The main limitation of our study is its retrospective design and the nonexhaustive nature of data collection about other potentially prognostic parameters. However, patient characteristics were generally well balanced in the DS and VS. Furthermore, when treatment activity and efficacy were investigated, no difference was reported in terms of response rate, PFS, and OS between the 2 cohorts (and therefore between FOLFIRINOX and FOLFOXIRI), and results were comparable with that described in the literature. As discussed, we did not evaluate the outcome of the different risk categories with other treatment options. Therefore, it should be kept in mind that our study was not designed to validate the developed nomogram as a predictive tool to anticipate the benefit from a specific regimen (ie, FOLFIRINOX) compared to other options (such as Gem-Nab, single-agent chemotherapy, or supportive care only). The information gleaned from the nomogram is a more detailed prognostic assessment of single cases, and

FOLFIRINOX (or modified treatment schedules) remains a valid option for fit MPC/LAPC patients.

Conclusion

It is possible to accurately predict the risk of death in the first 6 months after initiating therapy with FOLFIRINOX for MPC/LAPC by a few easily available, reproducible, and cheap clinical and laboratory parameters. Our nomogram and different risk categories allow immediate prognostic stratification and provide easy-to-interpret data for both clinicians and patients. This instrument could facilitate patient−physician communication in clinical practice and improve prognostic stratification in clinical research. Validation of this tool for other treatment regimens such as Gem-Nab is warranted.

Clinical Practice Points

- Despite recent advances, prognosis of patients with metastatic and locally advanced PC remains poor.
- FOLFIRINOX and Gem-Nab are both standards in the first-line treatment of fit patients, but no head-to-head comparison has been conducted so far.
- Toxicities of triplet chemotherapy may be relevant, and many patients derive limited benefit from intensive treatment; indeed, no tool is currently available to individualize the therapeutic approach in single cases.
- We therefore developed (from a single-institution experience) and validated (by external collection of cases from Italian and French referral centers) a simple nomogram able to predict 6-month survival probability in PC patients receiving first-line FOLFIRINOX (provided according to a classic or modified schedule).
- Easily available, reproducible, and cheap clinical and laboratory parameters confirmed their prognostic value in this population and were finally included in the model: PS, NLR, liver metastases, and CA19-9 levels before treatment.
- The presence of these variables also stratified our series into 4 risk categories with significantly different survival outcomes.
- Our nomogram can be immediately implemented in clinical practice in order to improve communication about prognosis with PC patients.
- This tool could also be of help in clinical research, as it demonstrated ways to improve patient stratification.
- Validation of the nomogram in patients treated with other regimens, such as Gem-Nab, is warranted.

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Disclosure

The authors have stated that they have no conflict of interest.

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