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RESEARCH ARTICLE

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Predicting overall survival and resection in patients with locally advanced pancreatic cancer treated with FOLFIRINOX: Development and internal validation of two nomograms

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Abbreviations: CA 19.9, carbohydrate antigen 19.9; CCI score, Charlson Comorbidity Index; CHA, common hepatic artery; CI, confidence interval; CT, Computed tomography; c-index, concordance statistics; DPCG, Dutch Pancreatic Cancer Group; FOLFIRINOX, combination of leucovorin, 5-fluorouracil, plus irinotecan, and oxaliplatin; IQR, interquartile range; LAPC, locally advanced pancreatic cancer; NCCN, National Comprehensive Cancer Network; OS, overall survival; RECIST, Response Evaluation Criteria In Solid Tumors; ROC-curve, receiver operating characteristic curve; SMA, superior mesenteric artery; SMV, superior mesenteric vein; WHO performance score, World Health Organization performance score.

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Abstract

Background and Objectives: Patients with locally advanced pancreatic cancer (LAPC) are increasingly treated with FOLFIRINOX, resulting in improved survival and resection of tumors that were initially unresectable. It remains unclear, however, which specific patients benefit from FOLFIRINOX. Two nomograms were developed predicting overall survival (OS) and resection at the start of FOLFIRINOX for LAPC.

Methods: From our multicenter, prospective LAPC registry in 14 Dutch hospitals, LAPC patients starting first-line FOLFIRINOX (April 2015–December 2017) were included. Stepwise backward selection according to the Akaike Information Criterion was used to identify independent baseline predictors for OS and resection. Two prognostic nomograms were generated.

Results: A total of 252 patients were included, with a median OS of 14 months. Thirty-two patients (13%) underwent resection, with a median OS of 23 months. Older age, female sex, Charlson Comorbidity Index ≤1, and CA 19.9 < 274 were independent factors predicting a better OS (c-index: 0.61). WHO ps >1, involvement of the superior mesenteric artery, celiac trunk, and superior mesenteric vein ≥ 270° were independent factors decreasing the probability of resection (c-index: 0.79).

Conclusions: Two nomograms were developed to predict OS and resection in patients with LAPC before starting treatment with FOLFIRINOX. These nomograms could be beneficial in the shared decision-making process and counseling of these patients.

KEYWORDS
chemotherapy, FOLFIRINOX, locally advanced pancreatic cancer, resection, survival

1. INTRODUCTION

It is estimated, that 30%–35% of patients who are diagnosed with pancreatic cancer have locally advanced disease (LAPC).[1,2] LAPC is characterized by extensive vascular involvement, which precludes surgical resection of the tumor.[3] Over the last few decades, the median overall survival (OS) in these patients remained only around 11 months.[4] With the introduction of newer chemotherapeutic regimens, such as FOLFIRINOX (a combination of leucovorin, 5-fluorouracil, plus irinotecan, and oxaliplatin), the OS of patients with LAPC improved, resulting in an OS of 15–24 months.[5–7] Nowadays, the majority of patients with LAPC are treated with first-line FOLFIRINOX.[8] Optional modified dose-regimens of FOLFIRINOX are associated with acceptable toxicity.[9,10]

After induction chemotherapy, some patients in whom the tumor was initially determined unresectable can actually undergo tumor resection. In patients with LAPC treated with FOLFIRINOX, resection rates ranging from 20% to 60% have been described.[5,6,11,12] Median OS in these patients is up to 35 months.[12,13]

It is not yet established, however, in which specific patients FOLFIRINOX chemotherapy increases survival and which patients will become eligible for tumor resection. Studies reporting these outcomes were mostly single-center studies with a highly selected patient population, including many tertiary referrals. Prospective data from a large cohort reflecting a real-world setting are therefore needed. These data can be used to design nomograms for OS and the probability of tumor resection. This could be of value during the individual shared decision-making process and guide treatment decisions on whether to start FOLFIRINOX treatment or not. Nomograms are commonly used in oncologic clinical practice for clinical decision-making and patient counseling.[14]

We, therefore, sought to identify prognostic baseline factors from a nationwide prospective multicenter cohort of patients with LAPC who were treated with FOLFIRINOX. Two nomograms to predict OS and tumor resection were developed.

2. MATERIALS AND METHODS

2.1. Patient selection

This study was conducted as part of a prospective observational registry study, which included consecutive patients diagnosed with LAPC between April 2015 and December 2017 in 14 centers in the Netherlands, affiliated with the Dutch Pancreatic Cancer Group (DPCG).[15] LAPC was defined according to the DPCG criteria[16] and established on radiologic imaging or during upfront explorative laparotomy. For the current study, we selected all patients who started first line treatment with FOLFIRINOX. Patients treated with other first line therapies, and patients treated with best supportive care were excluded. All patients gave informed consent for registration and the Institutional Review Boards approved the registry within all participating centers.

2.2. Data collection

We performed a literature search to identify potential prognostics baseline factors for OS and tumor resection in patients with ductal pancreatic adenocarcinoma. Based on this literature search, the following variables were chosen: age, gender, World Health Organization performance score (WHO performance score), Charlson Comorbidity Index (CCI score), pain, jaundice, weight loss, tumor size, tumor location, TNM stage (8th AJCC edition[17]), baseline serum CA 19.9, and vascular involvement (based on radiologic imaging) of the superior mesenteric artery (SMA), common hepatic artery (CHA), celiac trunk, portal vein (PV), and superior mesenteric vein (SMV). Treatment variables collected were: the number of chemotherapy cycles given, surgical exploration with or without resection. Baseline CT-scans and evaluation CT-scans after induction chemotherapy (i.e., 4 cycles FOLFIRINOX) were prospectively evaluated by a national expert panel including experienced abdominal radiologists and pancreatic surgeons. The radiologists scored the vascular involvement and response according to RECIST version 1.1.[18] Pancreatic surgeons reviewed all tumors according to the National Comprehensive Cancer Network (NCCN) criteria,[3] to assess whether resection after induction chemotherapy was possible. Based on this multidisciplinary expert panel, the decision to proceed to surgery was made, taking the tumor response and relation to the venous and arterial vasculature as evaluated on imaging into account. Data from baseline CT scans were used for the development of the models. OS was measured from the date of LAPC diagnosis until the date of death. Patients were censored if they were still alive at the final follow-up.

2.3. Statistical analysis and model development

Continuous data were presented as median with interquartile range (IQR) and categorical data as counts with percentage. OS was estimated using the Kaplan Meier method and the log-rank test was used to analyze differences between groups. Missing data were handled by multiple imputations, to which 10 data sets were created. Each analysis was performed in 10 imputed datasets. Pooled estimates and statistics were reported.

The prognostic models were developed according to the PROBAST criteria and were reported according to the TRIPOD statement.[19,20] Multivariable regression analyses were performed to investigate independent prognostic factors for overall survival (Cox regression) and probability of resection (logistic regression). For both models, backward selection (LR) according to the Akaike Information Criterion was used for model development. The predictive accuracy of the models was assessed using the concordance statistics (c-index) or receiver operating characteristic curve (ROC-curve). Calibration plots were developed for each model to compare the predicted outcomes with the actual outcomes. Bootstrapping with 500 resamples was used for internal validation of the models. After internal validation, two nomograms were developed.

Analyses were performed using IBM SPSS Statistics for Windows version 25.0 (IBM Corp.) and R version 3.6.1 (The R Project for Statistical Computing; cran.r-project.org). A two-sided p value of less than 0.05 was considered statistically significant

3. RESULTS

3.1. Patient cohort

Figure 1 shows the flowchart of patient selection and treatment. Within the study period, a total of 252 patients underwent first line treatment with FOLFIRINOX. Baseline characteristics are presented in Table 1. The mean age was 65 years (IQR, 57–70 years) and approximately half of the patients were men (52%, 130/252). Most tumors were located in the pancreatic head (67%, 168/252), with a median tumor size of 40 mm. Patients undergoing resection seem to have a better WHO ps (WHO 0–1 in 100%, 30/30 vs. 92%, 187/203), and smaller tumor size (35 vs. 40 mm).

After 4 cycles of induction FOLFIRINOX, 221 patients (88%, 221/252) underwent response evaluation via cross-section imaging according to RECIST 1.1.[18] Progressive disease was seen in 28 patients (13%, 28/221), stable disease in 160 patients (72%, 160/221), and 33 patients (15%, 33/221) had a partial response. A total of 79 patients (31%, 79/252) underwent explorative laparotomy, of whom 32 patients (13%, 32/252) subsequently underwent tumor resection. Patients that could not undergo tumor resection continued their chemotherapeutic regimen. Of the resected patients, 20 patients (63%, 20/32) received adjuvant chemotherapy, of whom 17 continued FOLFIRINOX. Postoperative outcomes of resected patients are presented in Supplemental Table1.

Median OS in all 252 patients was 14.1 months (95% confidence interval [CI], 12.9–15.7 months). One- and two-year survival was 59% and 22%, respectively. Patients undergoing tumor resection had a median OS of 23.4 months (95% CI 13.9–32.9 months), as compared to 13.3 months (95% CI 12.1–14.6 months) in patients who did

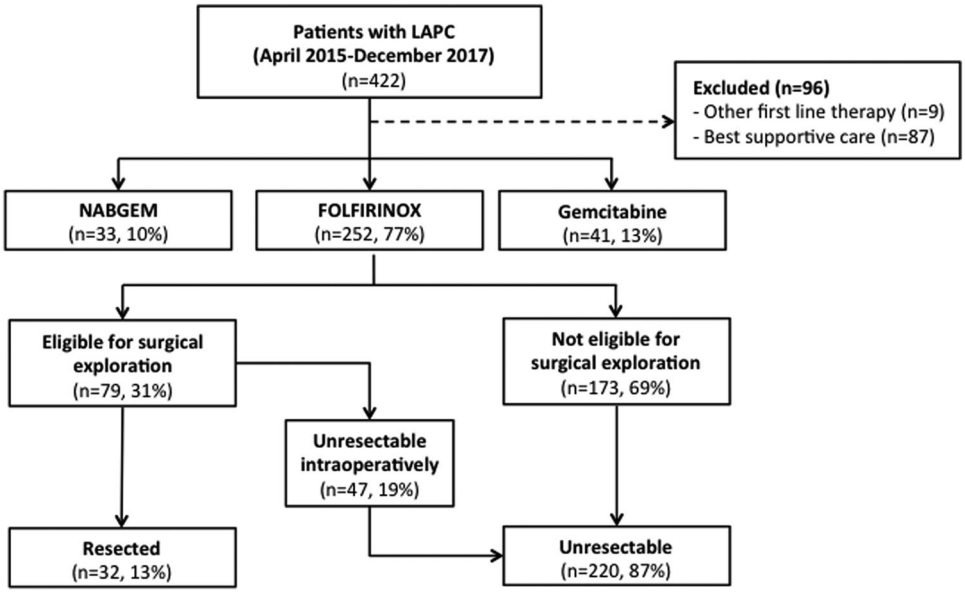

FIGURE 1 Flowchart of patient selection. LAPC, locally advanced pancreatic cancer; NABGEM, Nab-paclitaxel plus gemcitabine

not undergo tumor resection ($p < .01$). One- and two-year survival in resected patients was 87% and 49%, respectively. Survival curves are shown in Figure 2.

3.2. Prognostic factors

The results for both prognostic models are given in Table 2a. The model for OS included age, gender, CCI score, and serum CA 19.9. The c-index of this model was 0.61, with a calibration slope of 0.98 for 1-year survival, and a calibration slope of 0.58 for 2-year survival (Figure S1). Bootstrapping, with 500 resamples, yielded a c-index of 0.60 (Table 2b).

The model for resection included WHO performance score, and vascular involvement of the SMA, celiac trunk, and SMV. The c-index was 0.79, with a calibration slope of 1.02 (Supplemental Figure 2). The c-index after bootstrapping was 0.79.

3.3. Nomograms

The nomograms for both models are shown in Figure 3. With the first model (Figure 3A), the probability of 1-year survival between 20% and 80% can be predicted. The probability of 2-year survival can be predicted between 1% and 60%. The second model (Figure 3B) predicts the probability of a resection between 1% and 35%.

Both nomograms can be used for an individual patient according to the following steps: (1) determine the total points for each prognostic or predictive variable by drawing a straight line upwards from the variable point to the top point reference line, (2) sum the points for each variable, and (3) draw a straight line from the sum of the total points on the reference line to the bottom probability lines to determine the patient's likelihood of 1- or 2-year survival or the likelihood of resection. Both prediction models are also available online via www.pancreascalculator.com.

4. DISCUSSION

This multicenter study developed and internally validated two nomograms to predict survival and tumor resection after first-line treatment with FOLFIRINOX in a multicenter cohort of patients with LAPC. The model for 1- and 2-year OS included older age, female sex, CCI score ≤1, and serum CA 19.9 < 274 U/ml as positive prognostic factors with a good calibration and reasonable discrimination. The model to predict resection included WHO performance score ≤1, and vascular involvement of the SMA, celiac trunk, and SMV, with a good calibration and good discrimination. Both nomograms include data that are readily available in daily practice and are easy to use.

Only two other studies have developed nomograms to predict outcomes in patients with LAPC. One presented a nomogram in patients with LAPC (combined with borderline resectable tumors), who were mostly treated with gemcitabine-based chemoradiation. In this model, a radiotherapeutic dose ≥61 Gy, surgical resection, pretreatment maximum standardized uptake value (SUV_{max}) <3.5 (on PET-CT), and pretreatment serum CA 19.9 ≤ 400 U/ml predicted an improved overall survival.[21] Another nomogram, based on baseline variables, in patients treated with gemcitabine-based chemotherapy or chemoradiation suggested age, tumor size, albumin, pain, and elevated serum CA 19.9 as predictors for overall survival.[22] None of these nomograms, however, were developed for treatment with FOLFIRINOX, whereas this is nowadays the preferred chemotherapy in patients with LAPC.

Surprisingly, higher age was associated with better survival in our model. Most other studies have suggested that age has no influence on overall survival, or that a younger age predicts better

TABLE 1 Baseline patient and tumor characteristics

	All patients *n = 252 (%)*	Non-resected patients *n = 220 (%)*	Resected patients *n = 32 (%)*
Age, median [IQR]	65 [57–70]	65 [57–70]	65 [60–71]
Sex			
Male	130 (52)	112 (51)	18 (56)
Female	122 (48)	108 (49)	14 (44)
Weight loss[a]			
Yes	200 (82)	177 (83)	23 (72)
No	44 (18)	35 (17)	9 (28)
Jaundice[b]			
Yes	93 (37)	82 (37)	11 (35)
No	157 (63)	137 (63)	20 (65)
Pain[c]			
Yes	195 (80)	171 (81)	24 (75)
No	48 (20)	40 (19)	8 (25)
Charlson Comorbidity Index			
0–1	202 (80)	176 (80)	26 (81)
≥2	50 (20)	44 (20)	6 (19)
WHO ps[d]			
0–1	217 (93)	187 (92)	30 (100)
≥2	16 (7)	16 (8)	0 (0)
Tumor location			
Pancreatic head	168 (67)	143 (65)	25 (78)
Pancreatic body/tail	84 (33)	77 (35)	7 (22)
Tumor size, mm, median [IQR][e]	40 [30–47]	40 [30–49]	35 [27–44]
T stage			
≤T3	73 (29)	55 (25)	18 (56)
T4	179 (71)	165 (75)	14 (44)
N stage			
N0	182 (72)	161 (73)	21 (66)
N1	70 (28)	59 (27)	11 (34)
CA 19.9, median [IQR][f]	274 [37–1200]	274 [37–1243]	268 [33–790]
Cycles FOLFIRINOX, median [IQR][g]	6 [4–10]	7 [4–10]	4 [4–8]

Abbreviations: CA 19.9, carbohydrate antigen 19.9; IQR, interquartile range; WHO ps, World Health Organization performance score.

[a]8 missing.

[b]2 missing.

[c]9 missing.

[d]19 missing.

[e]4 missing.

[f]47 missing.

[g]2 missing.

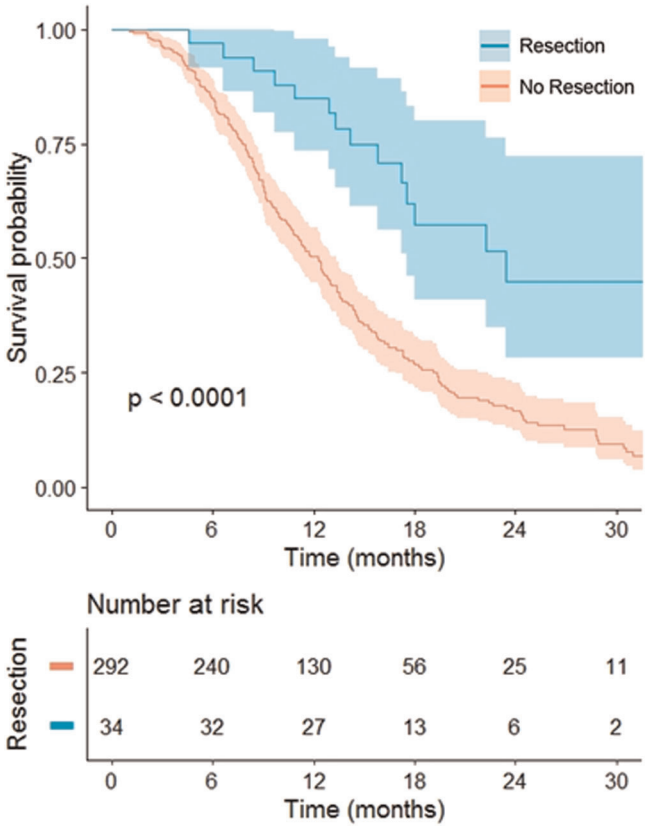

FIGURE 2 Comparison of overall survival (with corresponding 95% confidence intervals) between resected and unresected patients with locally advanced pancreatic cancer, all started treatment with FOLFIRINOX [Color figure can be viewed at wileyonlinelibrary.com]

outcomes.[22–24] An explanation for this unexpected finding is the inclusion of only very fit elderly patients with a favorable prognosis who are deemed eligible for treatment with FOLFIRINOX. Some studies regarding other types of cancer suggest younger patients have a worse prognosis, due to more aggressive subtypes.[25,26] Our finding that female sex was associated with improved survival has been previously suggested by others, especially in patients treated with FOLFIRINOX.[27–29] The other factors that were found to be associated with longer survival, the CCI and serum CA 19.9 are known prognostic factors in pancreatic cancer.[30–33] High serum CA 19.9 levels might suggest micro-metastatic disease or a high disease load.[34] It has been shown that a decrease in serum CA 19.9 following induction therapy might be a predictor for prolonged survival.[35,36] As the intention of this study was to develop nomograms that can be used before the start of first-line treatment with FOLFIRINOX, we only included baseline CA 19.9 levels.

The probability of undergoing tumor resection is predicted by a patient's WHO performance score and vascular involvement of the tumor. In line with our findings, the influence of the performance status on the probability of resection has been previously reported, with a lower performance score leading to an increased possibility of resection.[12,37] Currently, the decision to perform resection in patients with LAPC is mostly based on anatomic criteria, such as vascular involvement

TABLE 2a Multivariable Cox regression analysis to predict overall survival in patients with locally advanced pancreatic cancer, who started first line treatment with FOLFIRINOX

	HR	95% CI	*p* value
Age	0.97	[0.95–0.99]	<0.01
Sex (male vs. female)	0.71	[0.53–0.97]	0.03
Charlson Comorbidity Index (≤1 vs. >1)	2.01	[1.38–2.94]	<0.01
CA 19.9 (<274 vs. >274)	1.33	[0.97–1.82]	0.08

Abbreviations: CA 19.9, carbohydrate antigen 19.9; CI, confidence interval; HR, hazard ratio.

TABLE 2b Multivariable logistic regression analysis to predict the probability for resection in patients with locally advanced pancreatic cancer, who started treatment with first line FOLFIRINOX

	OR	95% CI	*p* value
WHO ps (≤1 vs. >1)	0.26	[0.03–1.11]	0.12
SMA			
<90°	Ref	-	-
90°–180°	0.23	[0.06–0.67]	0.01
>180°	0.27	[0.06–0.85]	0.05
Celiac trunk			
<90°	Ref	-	-
90°–180°	0.38	[0.09–1.19]	0.13
>180°	0.11	[0.01–0.52]	0.03
SMV (≤270° vs. >270°)	0.18	[0.04–0.57]	<0.01

Abbreviations: CI, confidence interval; OR, odds ratio; SMA, superior mesenteric artery; SMV, superior mesenteric vein; WHO ps, World Health Organization performance score.

according to the NCCN criteria determined on radiographic imaging.[3,12] This factor was therefore not surprisingly associated with resection in our model. The model shows that arterial involvement >90° already substantially decreases the probability of resection, as compared to <90° contact, which can be relevant information when consulting a patient at diagnosis. After induction chemotherapy with FOLFIRINOX, it may be difficult to evaluate vascular involvement on imaging, as fibrosis can be confused with residual tumor.[38,39] In line with our findings, previous studies described tumor involvement of the SMA as a worse predictor for the probability of resection.[7,40] The unexpected finding that 90°–180° involvement of the SMA is a slightly worse predictor than >180° involvement might be explained by the relatively small patient group who underwent tumor resection with SMA involvement. Involvement of the celiac trunk is not always a contraindication for resection. Pancreatic neck or body tumors can be resected by performing an Appleby procedure (i.e., distal pancreatectomy with celiac artery resection).[41] This, however, is not possible for pancreatic head tumors. Extensive and proximal involvement of the SMV might decrease the probability of resection because of involvement of the proximal jejunal veins, hampering venous reconstruction.[3,42] The decision to proceed to surgery after induction chemotherapy is often a difficult decision in clinical practice.[1] The use of the baseline imaging in the developed nomogram might support the decision-making process after neoadjuvant therapy and manage patients' expectations regarding the probability of resection.

Nowadays, newer chemotherapeutic regimens, especially FOLFIRINOX, are recommended as first line treatment for patients with LAPC, with a promising increase in OS.[5,37,43] In our cohort, 13% of patients underwent resection after FOLFIRINOX treatment, with a median OS of 23 months. We included all consecutive patients diagnosed with LAPC and starting treatment with FOLFIRINOX, in a multicenter setting. This might explain the lower, but the perhaps more realistic outcome with respect to resection rate, similar to the 9% resection rate described in another unselected cohort of patients treated with four different chemotherapeutic regimens.[8] Even though these more realistic outcomes show improved survival in resected patients, it is important to take into consideration that patients with LAPC undergoing resection represent a highly selected population. The higher resection rates and improved survival in previous studies are mostly based on the patient population from single centers. Furthermore, it is not known if these patients would have had the same survival benefit when treated with FOLFIRINOX only.[44] No randomized trial has been performed to investigate the benefit of resection after FOLFIRINOX treatment in terms of survival. It should therefore be noted that the main goal of FOLFIRINOX treatment in patients with LAPC is to increase survival and quality of life, rather than achieving surgical resection.

Our study has several limitations. First, the number of patients undergoing resection was relatively small, which might have caused the overfitting of the model. We still developed the nomogram for resection because our cohort is one of the largest cohorts including consecutive patients diagnosed with LAPC who started first-line treatment with FOLFIRINOX. Thereby, this study reflects the current clinical practice as much as possible and minimizes the possibility of bias. Although the number of events was small, the model demonstrated a good predictive accuracy after internal validation. Subsequent external validation of the model is, however, needed. A second limitation of our study refers to the performance of the nomogram predicting OS. Patients with LAPC demonstrate a small survival distribution since the majority of these patients have a poor prognosis. This might explain the relatively low c-index and reasonable discrimination for 2-year survival. This is, however, the first nomogram reported to predict OS in patients with LAPC, who are eligible and willing to start treatment with FOLFIRINOX. As nomograms are increasingly used in daily clinical practice, especially in the treatment of oncologic patients,[14] we believe this information can be useful in the discussion between the patient and their physician whether to start treatment with FOLFIRINOX or not. And third, in the Netherlands, the DPCG criteria[16] are used to diagnose patients with LAPC. All patients, however, are evaluated according to the

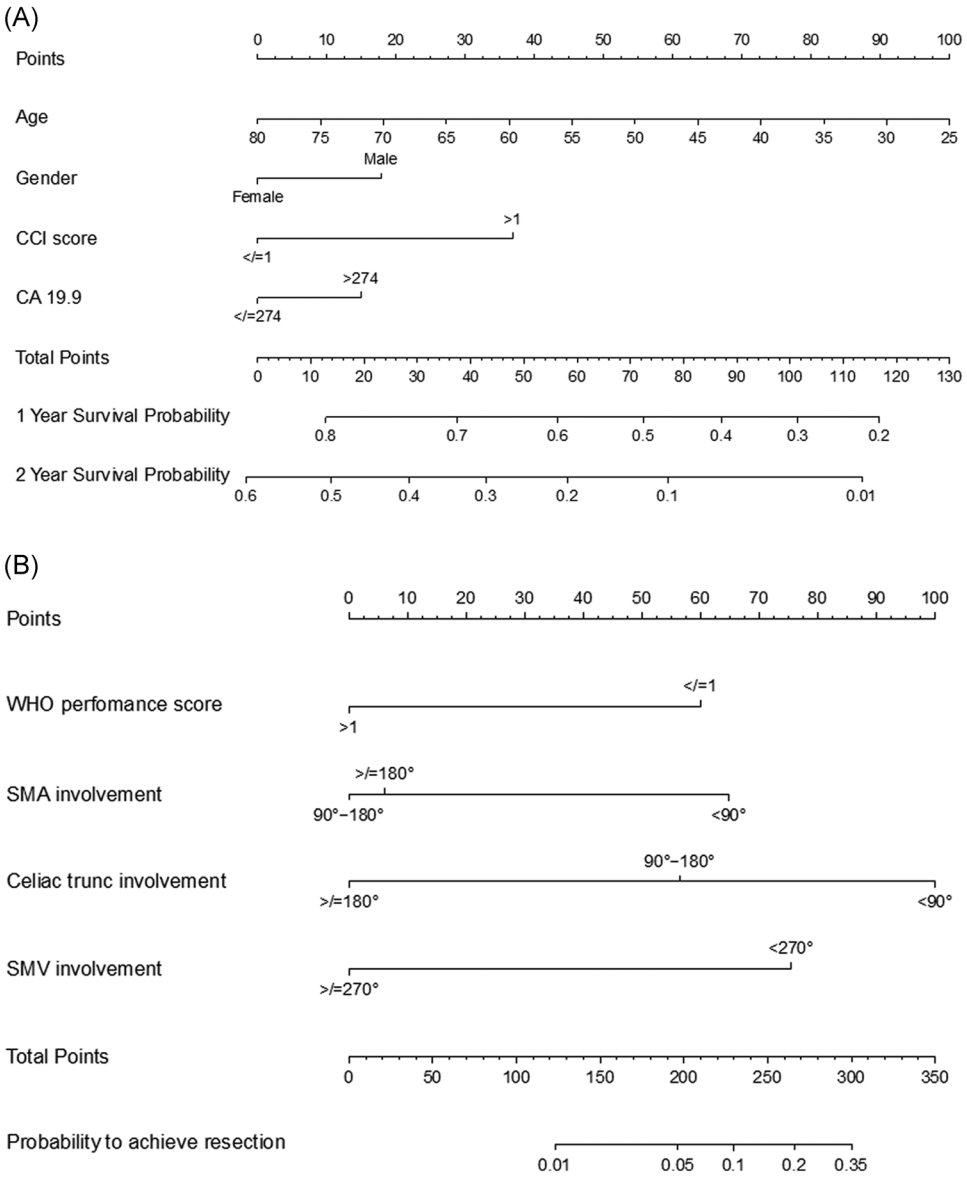

FIGURE 3 (A) Nomogram predicting 1- and 2-year survival in patients with locally advanced pancreatic cancer starting treatment with FOLFIRINOX. CA 19.9, carbohydrate antigen 19.9; CCI, Charlson Comorbidity Index. (B) Nomogram for the probability of resection in patients with locally advanced pancreatic cancer starting treatment with FOLFIRINOX. WHO performance score indicates World Health Organization performance score. SMA, superior mesenteric artery; SMV, superior mesenteric vein

NCCN criteria[3] after induction chemotherapy. This will lead to more patients receiving induction chemotherapy, but will not deprive patients from their possibility for a resection.

5. CONCLUSIONS

In conclusion, the proposed nomograms for the prediction of OS and tumor resection may support the shared decision-making process and manage expectations in patients with LAPC undergoing treatment with FOLFIRINOX. Both nomograms will be freely available on www.pancreascalculator.com after publication.

AUTHOR CONTRIBUTIONS

Lilly J. H. Brada, Marieke S. Walma, I. Quintus Molenaar, and Hjalmar C. van Santvoort contributed to the conception and design of the work. All authors contributed to patient recruitment and data acquisition. Lilly J. H. Brada, Marieke S. Walma, Lois A. Daamen, Stijn van Roessel, and Hjalmar C. van Santvoort performed the statistical analysis and data analysis. Lilly J. H. Brada drafted the manuscript. All authors made substantial contributions to the interpretation of the data, added important intellectual content to the work, and approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work and agree that no questions remain related to the accuracy or integrity of any part of the study.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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