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External validation of three lymph node ratio-based nomograms predicting survival using an international cohort of patients with resected pancreatic head ductal adenocarcinoma

Michael Schneider [a], Ismail Labgaa [a], Dionisios Vrochides [b], Alessandro Zerbi [c, d], Gennaro Nappo [c], Julie Perinel [a, e], Mustapha Adham [e], Stijn van Roessel [f], Marc Besselink [f], J. Sven D. Mieog [g], Jesse V. Groen [g], Nicolas Demartines [a, *], Markus Schäfer [a], Gaëtan-Romain Joliat [a, h]

[a] Department of Visceral Surgery, Lausanne University Hospital CHUV, Lausanne, Switzerland
[b] Division of Hepatobiliary and Pancreatic Surgery, Carolinas Medical Center, Charlotte, USA
[c] Humanitas Clinical and Research Center - IRCCS, Milan, Italy
[d] Department of Biomedical Sciences, Humanitas University, Milan, Italy
[e] Department of Digestive Surgery, Edouard Herriot Hospital, Lyon, France
[f] Department of Surgery, Cancer Center Amsterdam, Amsterdam UMC, University of Amsterdam, the Netherlands
[g] Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands
[h] Graduate School for Health Sciences, University of Bern, Switzerland

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ABSTRACT

Introduction: Lymph node ratio (LNR) is an important prognostic factor of survival in patients with pancreatic ductal adenocarcinoma (PDAC). This study aimed to validate three LNR-based nomograms using an international cohort.

Materials and methods: Consecutive PDAC patients who underwent upfront pancreatoduodenectomy from six centers (Europe/USA) were collected (2000–2017). Patients with metastases, R2 resection, missing LNR data, and who died within 90 postoperative days were excluded. The updated Amsterdam nomogram, the nomogram by Pu et al., and the nomogram by Li et al. were selected. For the validation, calibration, discrimination capacity, and clinical utility were assessed.

Results: After exclusion of 176 patients, 1′113 patients were included. Median overall survival (OS) of the cohort was 23 months (95% CI: 21–25).

For the three nomograms, Kaplan-Meier curves showed significant OS diminution with increasing scores ($p < 0.01$). All nomograms showed good calibration (non-significant Hosmer-Lemeshow tests). For the Amsterdam nomogram, area under the ROC curve (AUROC) for 3-year OS was 0.64 and 0.67 for 5-year OS. Sensitivity and specificity for 3-year OS prediction were 65% and 59%. Regarding the nomogram by Pu et al., AUROC for 3- and 5-year OS were 0.66 and 0.70. Sensitivity and specificity for 3-year OS prediction were 68% and 53%. For the Li nomogram, AUROC for 3- and 5-year OS were 0.67 and 0.71, while sensitivity and specificity for 3-year OS prediction were 63% and 60%.

Conclusion: The three nomograms were validated using an international cohort. Those nomograms can be used in clinical practice to evaluate survival after pancreatoduodenectomy for PDAC.

1. Introduction

Pancreatic cancer is the fourth leading cause of cancer deaths in the United States of America (USA) with an overall 5-year survival of 8–10% [1,2]. Less than 20% of patients with adenocarcinoma of the pancreatic head have a localized and resectable disease at

* Corresponding author. Department of Visceral Surgery, Lausanne University Hospital CHUV, Rue du Bugnon 46, 1011, Lausanne, Switzerland.
E-mail address: demartines@chuv.ch (N. Demartines).

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diagnosis [3]. Even if oncological pancreatoduodenectomy is performed in this patient group, 5-year survival is only 20% [1,2].

Various scores and nomograms using prognostic factors have been developed to facilitate decision-making and to tailor the management, as well as to estimate long-term survival and recurrence rate during the follow-up. Lymph node ratio (LNR), which represents the number of positive lymph nodes divided by the overall number of all lymph nodes resected during surgery, has now been identified as a strong prognostic factor of survival in patients with pancreatic ductal adenocarcinoma (PDAC) [4–7]. Other known prognostic factors are tumor size, tumor differentiation, lymph node involvement, metastasis, and resection status [8–10]. As LNR appears as a major prognostic factor, the present study focused on nomograms including LNR and predicting overall survival (OS) in patients with resected PDAC. Considering those elements, three recently published nomograms (van Roessel et al., Pu et al., and Li et al.) were selected [11–13].

The aim of the present study was to perform an external validation of the 3 above-mentioned nomograms with an international cohort of patients who underwent upfront pancreatoduodenectomy for ductal adenocarcinoma.

2. Materials and Methods

2.1. Patients and eligibility criteria

Data were collected from consecutive patients who underwent pancreatoduodenectomy for PDAC in six international institutions (Lausanne University Hospital, Lausanne, Switzerland; Carolinas Medical Center, Charlotte, USA; Humanitas Hospital - IRCCS, Milan, Italy; Edouard Herriot Hospital, Lyon, France; Amsterdam University Medical Center, Amsterdam, The Netherlands; and Leiden University Medical Center, Leiden, The Netherlands). The inclusion period was from January 1, 2000 to December 31, 2017. Inclusion criteria were age >18 years old, upfront surgery (i.e., no neoadjuvant treatment), and acceptance of data collection. Patients with distant metastasis, R2 resection, missing data regarding LNR, and with 90-day mortality were excluded. Preoperative characteristics, pathology analyses (TNM, tumor size, differentiation, resection margin status, LNR), operative details (operative time, blood loss, pylorus preservation), postoperative complications (Clavien classification [14]), and follow-up details (survival, postoperative chemotherapy or radiotherapy) were collected.

2.2. Nomograms

Nomograms were selected if they predicted survival of patients with PDAC of the pancreatic head and if they included LNR in their predictive factors. Scores without nomograms were not considered.

The first selected nomogram was established by the Amsterdam group [15] in 2015. There were 760 patients who underwent pancreatoduodenectomy for PDAC, distal common bile duct cancer, ampullary, or duodenal cancer. The nomogram was based on four factors: resection margin (1 mm definition), tumor differentiation, LNR, and adjuvant treatment. This nomogram was validated and updated using an international cohort by van Roessel et al. in 2020 [11]. We used the updated version of the nomogram by van Roessel et al. for this study. The updated version of the nomogram did not change the included variables of the nomogram but adapted the beta coefficients to improve the discrimination capacity (area under curve for the prediction of 3-year OS increased from 0.69 for the original nomogram to 0.71 for the updated nomogram). Three categories of risk were defined: low risk group (0–107 points), intermediate risk group (108–167 points), and high risk group (>167 points).

The second nomogram was elaborated by the Shanghai group of Pu et al. [12] in 2018 on 3458 patients with resected PDAC of the pancreatic head. The nomogram was based on age, LNR, tumor grade (differentiation), and pT stage classification. It was not specified if patients with neoadjuvant treatment were included. Probabilities of OS were subdivided into four groups according to nomogram values: group 1 $\leq$ 88 points, group 2: 89–114 points, group 3: 115–169 points, and group 4 > 169 points.

The third nomogram was published in 2019 by Li et al. [13] and included 6341 PDAC patients >40 years old who underwent surgical resection. This nomogram was based on age, tumor location, tumor grade, TNM stage (stage I or II), and LNR. It predicted 1-year, 2-year and 3-year OS based on the mentioned variables. Three risk categories were defined based on the nomogram scores: low risk group (0–9 points), middle risk group (10–19 points), and high risk group ($\geq$20 points).

2.3. Statistical analyses

The software package SPSS® version 26 (IBM, Armonk, New York, USA) was used for statistical analyses. Continuous data were presented as median with interquartile range (IQR) and categorical data as proportion with percentage. Median overall OS was calculated using Kaplan-Meier method and presented with 95% confidence interval (CI). Median follow-up was calculated using the inverse Kaplan-Meier method. Uni- and multivariable analyses using proportional hazards model (Cox regression) were performed to find predictive factors of OS. Each nomogram was applied to every patient of the present cohort, which provided three scores per patient. Survival curves were compared using log-rank test. Calibration was assessed with calibration plots and Hosmer-Lemeshow goodness-of-fit test. For each score, OS at 3 years was estimated using the nomograms (predicted survival). Kaplan-Meier curves using patient data were performed to calculate observed survival. Predicted and observed survivals were then plotted in a calibration graph with measures of intercept and slope. Receiver operating characteristic (ROC) curves were performed to assess discrimination capacity of the nomograms. To assess clinical usefulness, sensitivity and specificity were calculated at the maximum Youden index for each nomogram. The Youden index (Youden J statistic) was defined as sensitivity + specificity − 1.

This study was granted approval by the local ethics committee (#2017-1169).

3. Results

A total of 1′289 patients were operated during the inclusion period. Forty-one patients had missing data (3%) regarding LNR and the 90-day mortality rate was 81/1289 (6%). Thirty-two patients had metastases (2%) and 22 were R2 resections (2%). Hence, the final analyzed cohort included 1113 patients. Patients' pre-, intra-, and postoperative characteristics are summarized in Table 1. Median age was 68 years (IQR: 61–75) and 48% of the cohort were women. Median OS was 23 months (95% CI: 21–25) and median follow-up time was 48 months (95% CI: 44–52). Median LNR was 0.133 (IQR: 0.038–0.294) for the entire cohort and 0.192 (IQR: 0.100–0.333) for patients with lymph node involvement (pN+). Median number of collected lymph nodes was 18 (IQR: 18–19) for the whole cohort. Median number of collected lymph nodes per center was as follows: Lausanne: 20 (IQR: 13–27), Charlotte: 16 (IQR: 11–22), Milan: 23 (IQR: 18–28), Lyon: 21 (IQR:16–29), Amsterdam: 15 (IQR:11–19), and Leiden: 15 (IQR: 11–20). Median number of collected lymph nodes gradually increased over the years: 10 (IQR: 7–19) in 2000–2005, 11 (IQR: 8–16) in 2006–2010, 15 (IQR: 11–21) in 2011–2015, and 21 (IQR: 16–27) in 2016–2017

Table 1
Demographical, clinicopathological characteristics, and postoperative results of included patients (n = 1113).

	Medians or Numbers
Age (years, IQR)	68 (61–75)
Sex	
Male (%)	577 (52)
Female (%)	536 (48)
ASA	
I-II (%)	655 (56)
BMI (IQR)	24 (22–27)
Pre-existing diabetes (%)	167 (15)
Jaundice (%)	775 (70)
Preoperative biliary stenting (%)	651 (58)
Preoperative CA 19-9 (U/ml, IQR)	148 (35–512)
Tumor size (mm, IQR)	30 (22–38)
Portal vein resection (%)	216 (19)
Operation time (min, IQR)	350 (275–447)
pT stage	
pT1-pT2 (%)	198 (18)
pT3-pT4 (%)	915 (82)
Lymph node involvement	
N0 (%)	246 (22)
N1 (%)	460 (41)
N2 (%)	407 (37)
Vascular invasion (%)	544 (49)
Lymphatic vessel invasion (%)	490 (44)
Perineural invasion (%)	805 (72)
Grade[a]	
G1 (%)	105 (10)
G2 (%)	515 (46)
G3 (%)	436 (39)
G4 (%)	19 (2)
AJCC TNM Stage	
I (%)	78 (7)
II (%)	613 (55)
III (%)	422 (38)
Resection[b]	
R0 (%)	655 (59)
R1 (%)	458 (41)
LNR total cohort (IQR)	0.133 (0.038–0.294)
LNR pN + patients (IQR)	0.192 (0.100–0.333)
Adjuvant chemotherapy (%)[c]	790 (71)
Survival (months, 95% CI)	23 (21–25)

IQR: interquartile range, ASA: American Society of Anesthesiologists; BMI: Body-Mass Index (kg/m^2); AJCC: American Joint Committee on Cancer (8th Edition); LNR: Lymph Node Ratio, CI: confidence interval.

[a] 38 patients had missing data regarding grading (3%).

[b] R0 resection was defined as absence of microscopic tumor within 1 mm of the resection margin (1 mm rule).

[c] The types of chemotherapy regimens were only available for 479 patients (61%). Among these patients, most of them had a gemcitabine-based regimen (380 patients, 79%).

(Supplementary Table 1). Supplementary Table 1 also shows the evolution of LNR over the years. Independent predictive factors of OS were in this cohort: LNR, tumor differentiation, and adjuvant chemotherapy (Supplementary Table 2).

3.1. Updated Amsterdam nomogram by van Roessel et al.

Patients from the cohorts of Amsterdam (n = 111) and Leiden (n = 236) were excluded because they were already involved for the nomogram establishment and update. Patients were separated into three groups following the scale established by van Roessel et al. to assess Kaplan-Meier curves: low risk group (0–107 points, n = 162), intermediate risk group (108–167 points, n = 177), and high risk group (>167 points, n = 405). Twenty-two patients had missing data regarding items of the nomogram. Fig. 1 shows the Kaplan-Meier curves of the three groups (median OS: low risk group, 21 months, 95% CI 17–25 *vs.* intermediate risk group, 17 months, 95% CI 15–19 *vs.* high risk group, 16 months, 95% CI 15–18, p < 0.01). The calibration graph is shown in Fig. 2a (slope 0.6, intercept 1.7). The Hosmer-Lemeshow goodness of fit test was non-significant, showing that observed and predicted values were not different (p = 0.411). The AUC for prediction of 3-year OS was 0.644 (95% CI 0.602–0.683, Fig. 3). For 3-year OS prediction, sensitivity was 65% and specificity 59% for a cut-off at 139 points (maximum Youden index). The AUC for prediction of the 5-year OS was 0.670 (95% CI 0.609–0.730, Supplementary Fig. 1). In patients with adjuvant chemotherapy, the AUC for prediction of 3-year OS was 0.629 (95% CI 0.577–0.681, Supplementary Fig. 2). In patients without adjuvant chemotherapy, the AUC for prediction of 3-year OS was 0.739 (95% CI 0.674–0.805, Supplementary Fig. 3).

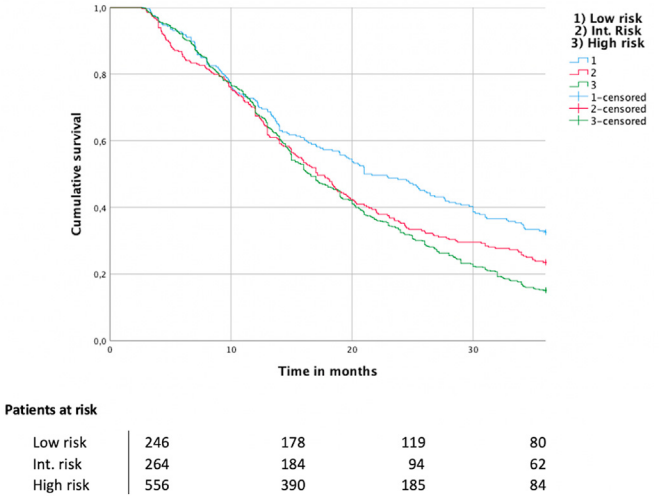

Fig. 1. Kaplan-Meier curves of overall survival (OS) stratified by risk groups derived from the Amsterdam nomogram (median OS: low risk group, 21 months, 95% CI 17–25 *vs.* intermediate risk group, 17 months, 95% CI 15–19 *vs.* high-risk group, 16 months 95% CI 15–18, p < 0.01).

3.2. Nomogram by Pu et al.

Patients were categorized as in the study by Pu et *al.* [12]: group 1: ≤88 points (n = 195), group 2: 89–114 points (n = 213), group 3: 115–169 points (n = 555), and group 4: >169 points (n = 103). They were 47 missing data concerning nomogram items. Fig. 4 shows the Kaplan-Meier curves (median OS: group 1, 25 months, 95% CI 22–29 *vs.* group 2, 21 months, 95% CI 18–24 *vs.* group 3, 16 months, 95% CI 15–17 *vs.* group 4, 13 months, 95% CI 10–16, p < 0.01). The calibration graph is shown in Fig. 2b (slope 0.8, intercept 2.7). The Hosmer-Lemeshow test showed that predicted and observed values were similar (p = 0.080). On ROC curve analysis for prediction of 3-year OS, AUC was 0.655 (95% CI 0.615–0.695, Fig. 3). Sensitivity for 3-year OS prediction was 68% and specificity 53% for a cut-off at 111 points (maximum Youden index). On ROC curve analysis for prediction of 5-year OS, AUC was 0.696 (95% CI 0.642–0.751, Supplementary Fig. 1). In patients with adjuvant chemotherapy, the AUC for prediction of 3-year OS was 0.611 (95% CI 0.558–0.664, Supplementary Fig. 2). The AUC for prediction of 3-year OS for patients without adjuvant chemotherapy was 0.722 (95% CI 0.650–0.793, Supplementary Fig. 3). The AUC of the nomogram for predicting who received adjuvant chemotherapy was 0.495 (95% CI 0.456–0.533).

3.3. Nomogram by Li et al.

Patients were separated into 3 groups as in the original article. Patients were categorized into low risk group (n = 89), middle risk

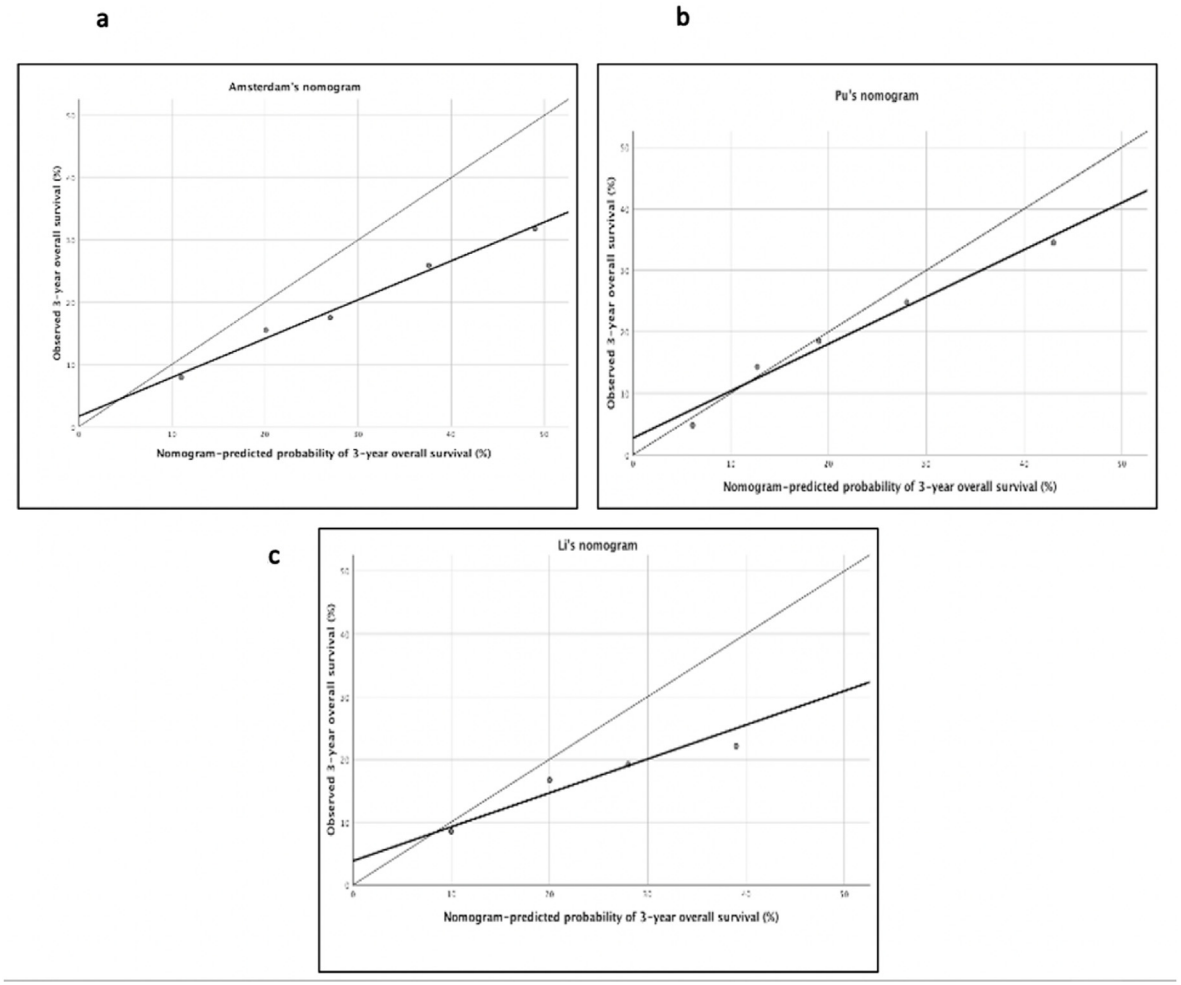

Fig. 2. Calibration plots. Fig. 2a Calibration plot for the nomogram by van Roessel et al. (intercept: 1.7, slope: 0.6). Fig. 2b Calibration plot for the nomogram by Pu et al. (intercept: 2.7, slope: 0.8). Fig. 2c Calibration plot for the nomogram by Li et al. (intercept: 3.8, slope: 0.5).

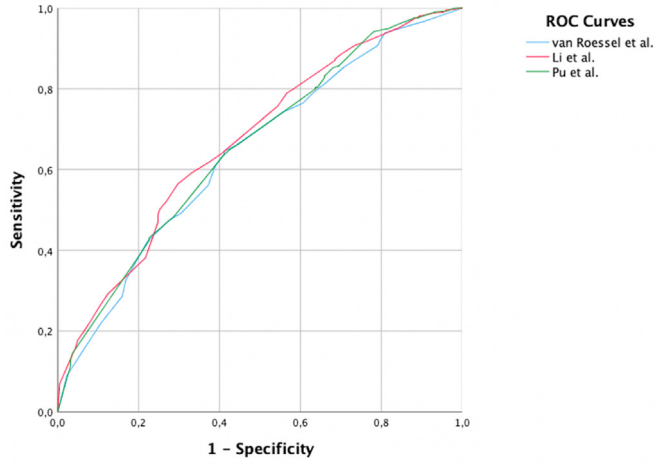

Fig. 3. ROC curves for 3-year OS for the 3 nomograms (areas under curve: 0.644 for the nomogram by van Roessel et al., 0.655 for the nomogram by Pu et al., and 0.665 for the nomogram by Li et al.).

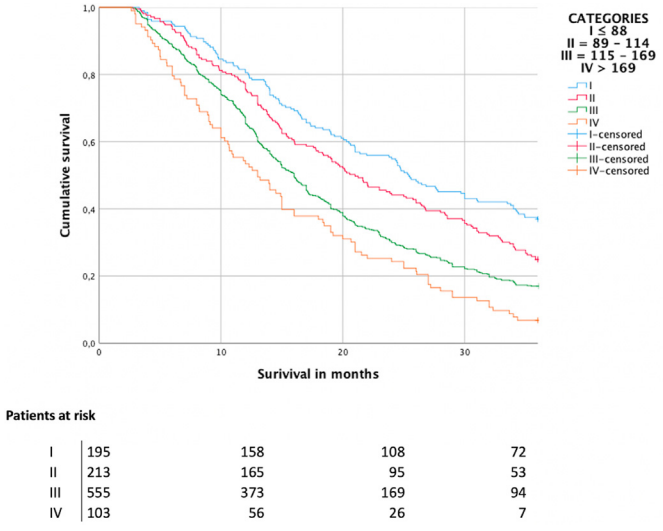

Fig. 4. Kaplan-Meier curves of overall survival (OS) stratified by risk groups derived from the nomogram by Pu et al. (median OS: group 1, 25 months, 95% CI 22–29 *vs.* group 2, 21 months, 95% CI 18–24 *vs.* group 3, 16 months, 95% CI 15–17 *vs.* group 4, 13 months, 95% CI 10–16, $p < 0.01$).

group (n = 856), and high risk group (n = 159). Nine patients had missing data for nomogram items. Fig. 5 shows the Kaplan-Meier curves (median OS: low risk group, 31 months, 95% CI 23–39 *vs.*

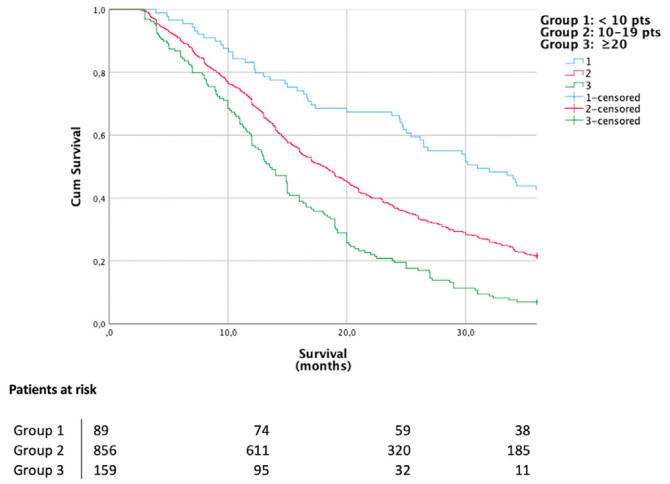

Fig. 5. Kaplan-Meier curves of overall survival (OS) stratified by risk groups derived from the nomogram by Li et al. (median OS: low risk group, 31 months, 95% CI 23–39 *vs.* middle risk group, 18 months, 95% CI 17–19 *vs.* high-risk group 14 months, 95% CI 12–15, $p < 0.01$).

middle risk group, 18 months, 95% CI 17–19 *vs.* high-risk group 14 months, 95% CI 12–15, $p < 0.01$). The calibration graph is shown in Fig. 2c (slope 0.5, intercept 3.8). No significant difference was found between observed and predicted survivals ($p = 0.170$, Hosmer-Lemeshow test). For prediction of 3-year survival, AUC was 0.665 (95% CI 0.631–0.710) (Fig. 3). At the threshold of the maximal Youden index (14.5 points), sensitivity for 3-year OS prediction was 63% and specificity 60%. For 5-year survival prediction, AUC was 0.714 (95% CI 0.657–0.771, Supplementary Fig. 1). In patients with adjuvant chemotherapy, the AUC for prediction of 3-year OS was 0.633 (95% CI 0.581–0.685, Supplementary Fig. 2). The AUC for prediction of 3-year OS for patients without adjuvant chemotherapy was 0.731 (95% IC 0.662–0.801, Supplementary Fig. 3). The AUC of the nomogram for predicting who received adjuvant chemotherapy was 0.494 (95% CI 0.453–0.535).

4. Discussion

In this international multicentric retrospective cohort of 1113 patients who underwent upfront pancreatoduodenectomy for PDAC, the three evaluated LNR-based nomograms showed good results in terms of calibration, discrimination, and clinical utility to predict 3-year survival after surgery. Moreover, all three nomograms were able to stratify survival based on the categories of risks (subgroups).

Calibration tests of the three nomograms showed satisfying results as all Hosmer-Lemeshow goodness-of-fit tests were not significant. Regarding calibration plots, the nomogram by Pu et al. had the best calibration line with a slope of 0.8 (close to 1 which represents the slope when predicted and observed values are similar) compared to a slope of 0.6 for the Amsterdam nomogram and of 0.5 for the nomogram by Li et al. As all 3 lines of the calibration plots had a slope <1, the 3 nomograms had a tendency to overestimate the predicted 3-year survivals compared to the observed 3-year survivals of the cohort patients. This difference might be explained by the characteristics of the patients and the various regimens of adjuvant chemotherapy or radiotherapy used in the various cohorts. Discrimination capacities were similar between the 3 nomograms with AUC comprised between 0.64 and 0.67 for the 3-year OS. These AUC for survival can be considered as satisfactory (0.6 <AUC <0.7) in terms of discriminative power. Discrimination for 5-year OS was better than for 3-year OS as the AUC for each nomogram were higher (from 0.67 to 0.71). To further assess the AUC taking into account the time dependency of the survival (time-to-event variable), time-dependent ROC curves could be calculated but this necessitates more complex statistical analyses [16]. Regarding clinical utility of these 3 nomograms, sensitivity for 3-year OS prediction at maximum Youden index values varied between 63% and 68% and specificity at maximum Youden index values varied between 53% and 60%.

Regarding OS in the different subgroups, median OS in the present cohort was, for example, 16 months in the high-risk group as defined by van Roessel et al. compared to 15 months in the original study [11]. Regarding Pu's nomogram, median OS in this cohort were 25, 21, 16, and 13 months in the different subgroups (I to IV) compared to 32, 21, 15, and 10 months in the original cohort by Pu et al. [12]. Finally, using the nomogram by Li et al. [13], median OS in the present cohort was 14 months in the high-risk group and was approximately 12 months in the original article (estimated from the Kaplan-Meier curves). In addition, the Asian nomograms seemed to have a better capacity to discriminate patients in the low/intermediate risk groups compared to the Amsterdam nomogram. That can be potentially explained by the fact that factors included in the Asian nomograms were almost similar and that age was not considered in the updated Amsterdam nomogram (only tumor related factors). The updated Amsterdam nomogram also included adjuvant chemotherapy as an item. As the Asian nomograms performed equally well without taking into account this item, considering adjuvant chemotherapy might not be necessary to increase OS prediction. The different survivals stratified according to the nomograms' scores were similar between the present cohort and the original cohorts used for the nomogram creation, which supports potential generalization of these nomograms.

LNR and tumor differentiation (grading) were the prognostic factors common between all 3 nomograms and the present cohort, underlining the importance of including these factors in predictive scores or nomograms. The other factors included in the nomograms were varied. Pu et al. and *Li* et al. included the same prognostic factors except for tumor location, which was taken into account only by Li et al. In the present cohort, all patients had their tumors in the pancreatic head which gave 2.75 patients to all patients according to Li's nomogram. That can explain why the group 2 (10–19 points) of Li's nomogram was overrepresented with 856 patients. The Amsterdam nomogram used only factors linked to the tumor, the surgery and the adjuvant treatment but not patient characteristics such as age that had a significant impact in the cohort by Li et al. (age >60 years) [13]. Age was also a prognostic factor in the multivariate analysis by Pu et al. [12]. Tumor resection status that is also a known prognostic factor [17–20] and a criterion of the Amsterdam nomogram was not identified as predictor of OS in the present cohort (Supplementary Table 2) [21].

To put into perspective the importance of including LNR in predictive nomograms, the 3 presented nomograms were compared to the staging system by Chen et al. published in 2016 [22]. The authors developed a staging system incorporating tumor grade, in addition to T stage and N stage (based on the 8th AJCC staging). This staging system was applied to the present cohort and found an AUC for the prediction of 5-year OS of 0.657. If we compare the AUC of this 3-item staging score with the 3 scores included in the manuscript, all nomograms with LNR had better AUC (Amsterdam: 0.67, Pu: 0.696, and Li: 0.714).

Nomograms have been developed to have a graphical prediction tool based on predictive factors. Advantages of nomograms in PDAC are that they permit to have an individual risk prediction and are easy to use. A disadvantage of the nomograms is that they might

not take into account all predictive and important prognostic factors and might be sometimes oversimplified. In addition, a limitation of nomograms predicting OS is that they predict deaths from all origins using risk factors only associated with PDAC. Nevertheless, they remain an interesting help to assist decision-making and to estimate survival and are of clinical relevance. The question of the time points of survival-predicting nomogram calculation (preoperatively or postoperatively) depends on the goal that is searched. Having a preoperative nomogram can help in the decision-making, while a postoperative nomogram can estimate more precisely survival and might guide the follow-up or adjuvant treatment (if not included in the nomogram).

Some study limitations should be acknowledged. This cross-sectional study has a retrospective design, which can include missing data and mistakes during data collection. Another limitation is the heterogeneity between the centers. Also, the post-operative care (diverse regimens of adjuvant treatments) can impact the survival. Finally, this cohort included only patients who underwent surgery without neoadjuvant treatment. The nomograms should also be assessed in patients with resectable or borderline resectable tumor who had neoadjuvant chemotherapy.

In conclusion, the three included nomograms are validated tools that can be used in clinical practice after PDAC resection to obtain a survival estimate.

Declaration of competing interests and financial disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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CRediT authorship contribution statement

Michael Schneider: Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Writing – original draft, Writing – review & editing. **Ismail Labgaa:** Data curation, Formal analysis, Supervision, Validation, Writing – review & editing. **Dionisios Vrochides:** Data curation, Supervision, Validation, Writing – review & editing. **Alessandro Zerbi:** Data curation, Supervision, Validation, Writing – review & editing. **Gennaro Nappo:** Data curation, Supervision, Validation, Writing – review & editing. **Julie Perinel:** Data curation, Supervision, Validation, Writing – review & editing. **Mustapha Adham:** Data curation, Supervision, Validation, Writing – review & editing. **Stijn van Roessel:** Data curation, Supervision, Validation, Writing – review & editing. **Marc Besselink:** Data curation, Supervision, Validation, Writing – review & editing. **J. Sven D. Mieog:** Data curation, Supervision, Validation, Writing – review & editing. **Jesse V. Groen:** Data curation, Supervision, Validation, Writing – review & editing. **Nicolas Demartines:** Formal analysis, Project administration, Supervision, Validation, Writing – review & editing. **Markus Schäfer:** Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Validation, Writing – review & editing. **Gaëtan-Romain Joliat:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2022.05.002.

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