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Surgical Risk Scores as Morbidity and Mortality Predictors in Periampullary Cancer

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Abstract: Background: Surgery in periampullary cancers (PAC) is associated with high morbimortality rates. There are multiple scores used to predict surgical risk. This study aims to identify a possible correlation between POSSUM, P-POSSUM, E-PASS, and mE-PASS scores and morbimortality in patients operated on for PAC. **Methods:** POSSUM, P-POSSUM, E-PASS, and mE-PASS were calculated for patients operated for PAC in Hospital de Braga between 1 January 2011 and 31 August 2021. The calibration and discrimination of scores were analyzed by comparing the predicted mortality and morbidity with the observed one and by evaluating the Receiver Operating Characteristic (ROC) curve, respectively. **Results:** The study included 58 patients. The most frequent location was the ampulla of Vater (AVC) (43.10%), and the most frequent stage was IIb (48.28%). The postoperative mortality and morbidity observed at 30 days were 3.45% and 37.93%, respectively. P-POSSUM (O:E 0.45), POSSUM (O:E 0.16), and E-PASS (O:E 0.03) overestimated mortality, and mE-PASS underestimated it (O:E 1.89). In most subgroups, both POSSUM scores showed the best calibration. CRS and E-PASS showed the highest discriminative ability for mortality (AUC 0.982). In the pancreatic head carcinoma subgroup, the SSS showed better calibration for morbidity. The operative score had the best discrimination for the CAV subgroup (AUC 0.767) and for stage IIb (AUC 0.900). No scale showed discriminative ability in overall morbidity. **Conclusions:** POSSUM and P-POSSUM obtained the best calibration regarding subgroup mortality. E-PASS and CRS showed the highest discrimination for mortality, and the operative score showed the greatest discrimination for morbidity in the subgroups.

Keywords: E-PASS; mE-PASS; periampullary cancer; POSSUM; P-POSSUM

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1. Introduction

Cancer is an important cause of death worldwide. It is expected that the mortality rate from cancer increases as the population increases, ages, and adopts lifestyles that increase the risk of cancer [1].

Periampullary carcinoma (PAC) comprises less than two centimeters of the major duodenal papilla and consists of head of the pancreas carcinoma (HPC), distal common bile duct carcinoma (DCBDC), ampullary cancer (AC), and duodenum carcinoma (DC). PAC accounts for 5% of gastrointestinal tract cancer, and HPC is the most frequent subtype

(3%) [2]. The clinical features are variable. The biggest variation is the onset of jaundice and its relation to constitutional symptoms.

Most patients have locally advanced or metastatic disease, which excludes them from a curative surgical option. The most frequent curative option is a pancreatoduodenectomy (PD), which can include the preservation of the pylorus, although this does not entail any meaningful change in the outcome [3,4].

PD is associated with high morbidity and mortality rates [5]. The two most common complications are gastric emptying delay and pancreatic fistulas, leading to an extended hospital stay and worse quality of life [6].

The use of scores or scales to estimate patients' mortality and morbidity before surgery has been proven to be useful in the preoperative optimization of patients.

The POSSUM score is built using two other scores, the physiologic and surgical scores. They are derived from 48 physiological variables and 12 surgical variables. POSSUM is applicable to different types of surgery and is a good predicter of morbidity and mortality. It is calculated using exponential regression [7,8].

Some authors verified that POSSUM overestimated the mortality rate [7,9–11] and, in some high-risk cases, overestimated morbidity, while in low-risk cases, it underestimated morbidity [12]. Whitley suggested a modification to the POSSUM, creating the P-POSSUM score [13], which is apparently closer to the observed mortality rates [7,9].

The E-PASS score's goal is to predict a patient's risk after surgery by quantifying the patient's fitness for surgery. This score is built using three other scores: the Preoperative Risk Score (PRS), the Surgical Stress Score (SSS), and the Comprehensive Risk Score (CRS). It was later modified by its authors (mE-PASS), allowing for the estimation of patients' mortality and morbidity along with surgical planning [14,15].

2. Results

2.1. Sample Characterization

The sample was composed of 58 patients who underwent surgery for periampullary cancer in Hospital de Braga between 1 January 2011 and 31 August 2021, after all inclusion and exclusion criteria were applied. The sample was submitted to Kolmogorov–Smirnov test and histogram symmetry analysis.

Age follows a normal distribution ($p > 0.05$). The mean age at the surgery date was 67.29 years, with a standard deviation of 8.48 years. The minimum age was 41 years, and the maximum age was 82 years. Only 8.62% ($n = 5$) were at or under 52 years old, and 8.62% ($n = 5$) of patients were at least 78 years old, as can be observed in Table 1.

This trial showed a predominance of male patients: 68.97% ($n = 40$) versus 31.03% ($n = 11$) female patients. The most common tumor location was ampulla of Vater cancer (AVC), 43.10% ($n = 25$). About 37.93% ($n = 22$) had head of pancreas carcinoma (HCP), and the rest, 18.97% ($n = 11$), had common bile duct carcinoma (DCBDC). There were no duodenum carcinoma cases, as can be observed in Table 1.

Considering tumor staging, there is a greater prevalence of stage IIb, with 48.28% of cases (28 patients), followed by stage Ib 20.69% ($n = 12$). A total of 12.07% ($n = 7$) of patients were in stage IIa, and 8.26% (5 patients) were in stage Ia. In stage III, there were 10.34% ($n = 6$), as can be observed in Table 1.

The mean survival was 46.4 months (CI 95%: 37.4–55.4), and the median was 43.4 months (CI 95%: 26.5–60.2). The mean time of disease-free survival was 45.4 months (CI 95%: 33.7–57.1), and the median was 26.2 months (CI 95%: 12.2–40.2). The survival rate was 96.55% at 30 days, 75.86% at one year, 39.66% at three years, and 17.64% at five years (Figures 1 and 2).

Table 1. Sample characterization.

	N (%)
Age (years)	
<41	1 (1.72)
42–50	1 (1.72)
51–59	5 (8.62)
60–67	19 (32.76)
68–76	25 (43.10)
>77	7 (12.07)
Sex	
Female	18 (31.03)
Male	40 (68.97)
Localization	
Pancreas	22 (37.93)
Ampulla of Vater	25 (43.10)
Duodenum	0
Gallbladder/Common bile duct	11 (18.97)
Tumor Staging	
Stage Ia	5 (8.62)
Stage Ib	12 (20.69)
Stage IIa	7 (12.07)
Stage IIb	28 (48.28)
Stage III	6 (10.34)

N—absolute value; %—relative frequency.

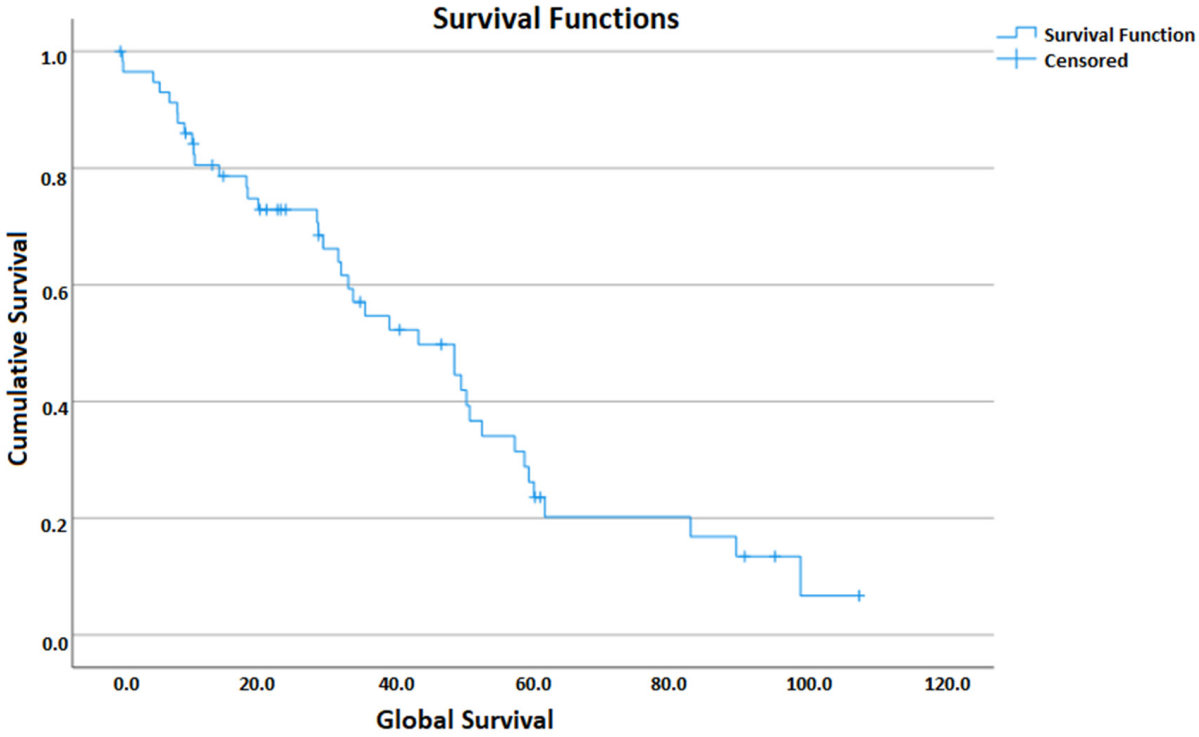


Figure 1. Kaplan–Meier curve relating to global survival (in months).

The overall mortality during the trial was 67.24% (n = 39), and the 30-day mortality was 3.45% (n = 2).

During follow-up time (115 months), 50% of patients had tumoral recurrence. A total of 7 patients had locoregional disease recurrence, 15 had hepatic recurrence, 5 had

peritoneal recurrence, 4 had pulmonary recurrence, 1 had nodal recurrence, and 1 had pleural recurrence. In some cases, recurrence happened in more than one location.

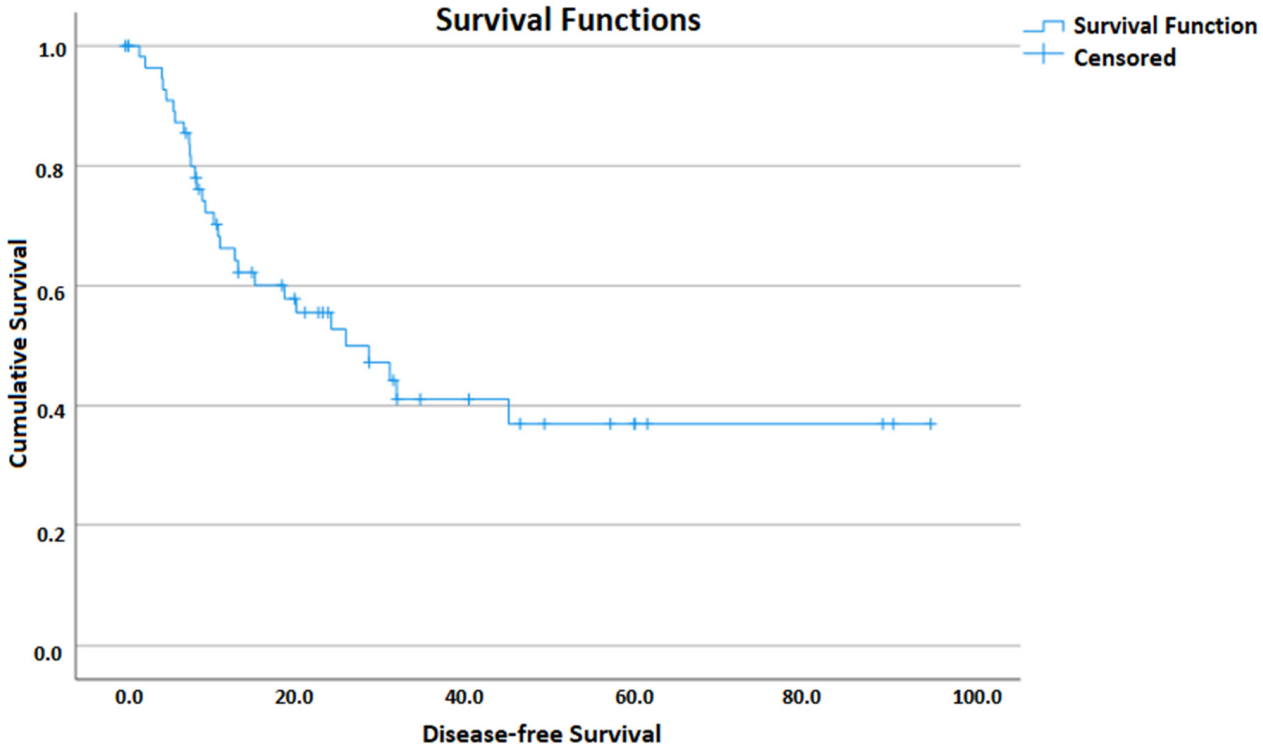


Figure 2. Kaplan–Meier curve relating to disease-free survival (in months).

Global morbidity was 82.76% (n = 48), of which 62.07% was mild morbidity (grades I and II), and 37.93% was moderate to severe morbidity (grades III to V). It was more common to have both local and systemic complications (41.38%, n = 24) than only systemic complications (31.03%, n = 18) or local complications (10.34%, n = 6). The most common morbidities were intraabdominal infection and abscess, at 37.93% (n = 22); hypertension, at 34.48% (n = 20); pleural effusion, at 31.03% (n = 18); pancreatic fistula, at 29.31% (n = 17); and delay of gastric emptying, at 24.14% (n = 14), as can be observed in Table 2.

Table 2. The 30-day mortality postoperative and total mortality (until 31 August 2021), morbidity, cause of morbidity (local and systemic complications), and morbidity severity in the sample.

	N (%)	No Complication N (%)	Presence of Complication N (%)
Complications (Claven–Dindo)			
No complications/mild complications	36 (62.07)		
Moderate/severe complications	22 (37.93)		
Systemic or local complications			
No complications	10 (17.24)		
Local complications	6 (10.34)		
Systemic complications	18 (31.03)		
Systemic and local complications	24 (41.38)		
Complications evaluated			
Pancreatic fistula		41 (70.69)	17 (29.31)
Pleural effusion		40 (68.97)	18 (31.03)
Infection of operative site		50 (86.21)	8 (13.79)

Table 2. *Cont.*

	N (%)	No Complication N (%)	Presence of Complication N (%)
Postoperative fever		47 (81.03)	11 (18.97)
Hypertension		38 (65.52)	20 (34.48)
Anastomosis dehiscence		54 (93.10)	4 (6.90)
Gastrointestinal fistulas		52 (89.66)	6 (10.34)
Sepsis		56 (96.55)	2 (3.45)
Delirium		53 (91.38)	5 (8.62)
Heart failure		55 (94.83)	3 (5.17)
Aspiration pneumonia		56 (96.55)	2 (3.45)
Atelectasis		52 (89.66)	6 (10.34)
Hematoma		57 (98.28)	1 (1.72)
Stroke		57 (98.28)	1 (1.72)
Seroma		57 (98.28)	1 (1.72)
Stress ulcer		57 (98.28)	1 (1.72)
Delay of gastric emptying		44 (75.86)	14 (24.14)
Acute renal failure		55 (94.83)	3 (5.17)
Hemorrhagic		56 (96.55)	2 (3.45)
Pneumonia		56 (96.55)	2 (3.45)
Intraabdominal infection and abscess		36 (62.07)	22 (37.93)
Gastrointestinal hemorrhagic		54 (93.10)	4 (6.90)
30-day mortality		56 (96.55)	2 (3.45)
Global mortality		19 (32.76)	39 (67.24)

N—absolute value; %—relative frequency.

2.2. Physiological and Operative Parameters

The result of each physiological parameter used in the calculation of the POSSUM and P-POSSUM score is present in Table 3, and operative data used in the calculation of the operative score are also indicated in Table 4.

Regarding the physiological score, 65.52% of patients had a diuretic, digoxin, antianginal, or hypertension therapy as everyday medication (38 patients). In the respiratory signs category, only 3.45% of patients had dyspnea on exertion or mild COAD (two patients). In the EKG category, 3.45% had atrial fibrillation (60–90 bpm) (2 patients), and 46.55% had other alterations (27 patients). In terms of blood systolic pressure, 55.17% were between 110 and 130 mmHg (32 patients), 41.38% were between 131 and 170 or 100 and 109 (24 patients), and 1.72% were above 170 or between 90 and 99 (1 patient). In the cardiac frequency category, 1.72% had a heart rate <90 or between 101 and 120 (one patient each), 67.24% had a heart rate between 50 and 80 (39 patients), and 31.03% were between 81 and 100 or 40 and 49 (18 patients). All the patients were rated above 15 on the Glasgow Coma Scale. Regarding hemoglobin values, 34.48% had 13–16 g/dL (20 patients), 32.76% had 10–11.4 or 17.1–18 g/dL (19 patients), 20.69% had 11.5–12.9 or 16.1–17 g/dL, and 12.07% had a value <10 or >18g/dL (7 patients). In relation to the white blood cell count, 79.31% had a value between 4 and 10 $\times$ 10^{12}/L (46 patients), and 20.69% had a value between 10.1 and 20 $\times$ 10^{12}/L (12 patients). Regarding the urea, 50% had a value inferior to 7.5 mmol/L (29 patients), 20.69% had a value between 7.6 and 10 mmol/L (12 patients), 15.52% had a value between 10.1 and 15 mmol/L (9 patients), and 13.79% had a value >15 mmol/L (8 patients). The sodium value was >136 mEq/L in 86.21% of the cases (50 patients), between 131 and 135 mEq/L in 12.07% of the cases (7 patients), and between 126 and 130 mEq/L in 1.72% of the cases (1 patient). The potassium value was between 3.5 and 5 mEq/L in 94.83% of the cases (55 patients), but 5.17% of cases had a value between 3.2 and 3.4 mEq/L or between 5.1 and 5.3 (3 patients).

Table 3. Physiological score of POSSUM and P-POSSUM in the sample.

		N (%)
Age (years)	<41	1 (1.72)
	42–50	1 (1.72)
	51–59	5 (8.62)
	60–67	19 (32.76)
	68–76	25 (43.10)
	>77	7 (12.07)
Cardiac signs	Normal	20 (34.48)
	Diuretic, digoxin, antianginal, or hypertension therapy	38 (65.52)
	Oedema, warfarin, borderline cardiomegaly	0 (0)
	Raised jugular venous pressure, cardiomegaly	0 (0)
Respiratory signs	Normal	56 (96.55)
	Shortness of breath on exertion, mild chronic obstructive pulmonary disease	2 (3.45)
	Short of breath on stairs, moderate chronic obstructive pulmonary disease	0 (0)
	Dyspnea at rest (rate > 30/min), fibrosis or consolidation in the X-ray	0 (0)
EKG	Normal	29 (50.00)
	Atrial fibrilation 60–90 bpm	2 (3.45)
	Other alterations	27 (46.55)
Systolic blood pressure (mmHg)	110–130	32 (55.17)
	131–170 or 100–109	24 (41.38)
	>170 or 90–99	1 (1.72)
	<90	1 (1.72)
Pulse rate (bpm)	50–80	39 (67.24)
	81–100 or 40–49	18 (31.03)
	101–120	1 (1.72)
	>120 or <40	0 (0)
Glasgow Coma Scale	15	58 (100)
	12–14	0 (0)
	9–11	0 (0)
	<9	0 (0)
Hemoglobin (g/dL)	13–16	20 (34.48)
	11.5–12.9 or 16.1–17	12 (20.69)
	10–11.4 or 17.1–18	19 (32.76)
	<10 or >18	7 (12.07)
White cell count	$4–10 \times 10^{12}$/L	46 (79.31)
	$10.1–20 \times 10^{12}$/L or $3.1–3.9 \times 10^{12}$/L	12 (20.69)
	$>20 \times 10^{12}$/L or $<3 \times 10^{12}$/L	0 (0)
Serum urea (mmol/L)	<7.5	29 (50.00)
	7.6–10	12 (20.69)
	10.1–15	9 (15.52)
	>15	8 (13.79)
Serum sodium (mEq/L)	>136	50 (86.21)
	131–135	7 (12.07)
	126–130	1 (1.72)
	<126	0 (0)
Serum potassium (mEq/L)	3.5–5	55 (94.83)
	3.2–3.4 or 5.1–5.3	3 (5.17)
	2.9–3.1 or 5.4–5.9	0 (0)
	<2.9 or >5.9	0 (0)

N—absolute value; %—relative frequency.

Table 4. Operative score of POSSUM and P-POSSUM in the sample.

		N (%)
Operation severity	Minor	0 (0)
	Moderate	0 (0)
	Major	0 (0)
	Major+	58 (100)
No. of procedures in the last 30 days	1	52 (89.66)
	2	4 (6.90)
	>2	2 (3.45)
Peritoneal soiling	None	1 (1.72)
	Minor (serous fluid)	31 (53.45)
	Local pus	14 (24.14)
	Free bowel content, pus or blood	12 (20.69)
Total blood loss (mL)	<100	33 (56.90)
	101–500	20 (34.48)
	501–999	3 (5.17)
	≥1000	2 (3.45)
Presence of malignacy	None	0 (0)
	Primary only	27 (46.55)
	Nodal metastases	30 (51.72)
	Distant metastases	1 (1.72)
Mode of surgery	Elective	58 (100)
	Emergency ressuscitation of >2 h possible or operation < 24 h after admission	0 (0)
	Emergency (immediate surgery < 2 h needed)	0 (0)

N—absolute value; %—relative frequency.

In the operative score, all of the patients had "Major + Surgery" in terms of severity. Most of the patients had no other procedure in the following 30 days (89.66%—52 patients); however, 6.9% (4 patients) had two procedures, and 3.45% (2 patients) had more than two procedures performed. Peritoneal contamination was absent in 1.72% of cases (1 patient) and was mild or serious in 53.45% of cases (31 patients). In 24.14% (14 patients), there was localized purulent content in the peritoneum, and 20.69% (12 patients) had fecal or purulent peritonitis or a hemoperitoneum. Most patients' blood loss was below 100 mL (56.90%—33 patients), but 3.45% (2 patients) lost 1000 mL or more. In 34.48% (20 patients) of cases, losses were between 101 and 500 mL, and 5.17% (3 patients) of the patients had losses between 501 and 999 mL. Regarding malignancy, 46.55% (27 patients) were primary only, 51.72% (30 patients) had nodal metastases, and 1.72% (1 patient) had distant metastases. All the cases were subjected to surgery in elective conditions.

2.3. Pre-Operative Risk Score and Surgical Stress Score Used in E-PASS and mE-PASS Score

The results of each category included in the calculation of pre-operative risk score (PRS) in E-PASS and mE-PASS are present in the attached tables. Surgical data included in the calculation of surgical stress score belonging to E-PASS score are shown in Tables 5 and 6.

Table 5. Preoperative risk score (E-PASS and mE-PASS) in the sample.

		N (%)
Age (years)	<41	1 (1.72)
	42–50	1 (1.72)
	51–59	5 (8.62)
	60–67	19 (32.76)
	68–76	25 (43.10)
	>77	7 (12.07)
Severe heart disease	Absence	57 (98.28)
	Presence	1 (1.72)
Severe pulmonary disease	Absence	58 (100)
	Presence	0 (0)
Diabetes mellitus	Absence	40 (68.97)
	Presence	18 (31.03)
Performance status index	Asymptomatic (fully active, able to carry on all pre-disease activities without restriction)	14 (24.14)
	Symptomatic but completely ambulatory (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; for example, light housework, office work)	32 (55.17)
	Symptomatic, <50% in bed during the day (ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours)	7 (12.07)
	Symptomatic, >50% in bed, but not bedbound (capable of only limited self-care, confined to bed or chair 50% or more of waking hours)	5 (8.62)
	Bedbound (completely disabled, cannot carry on any self-care, totally confined to bed or chair)	0 (0)
American Society of Anesthesiologists physiological status classification	Healthy person	33 (56.90)
	Mild systemic disease	6 (10.34)
	Severe systemic disease	18 (31.03)
	Severe systemic disease that is a constant threat to life	1 (1.72)
	A moribund person who is not expected to survive without the operation	0 (0)
	A declared brain-dead person whose organs are being removed for donor purposes	0 (0)

N—absolute value; %—relative frequency.

In the process of calculating the pre-operative risk score, only 1.72% (one patient) of patients had severe heart disease, and none had severe respiratory disease. A total of 31.03% (18 patients) of patients had diabetes mellitus. Regarding the performance status index, 24.14% (14 patients) did not have symptoms that limited social activity, 55.17% (32 patients) had mild symptomatology that limited muscular laboratorial activity, 12.07% (7 patients) had a disease that required assistance in daily activities, and 8.62% (5 patients) had a disease that required frequent assistance with everyday activities. According to the ASA score, 10.34% (14 patients) of patients were healthy, 56.90% (33 patients) had mild

systemic disease, 31.03% (18 patients) had a non-incapacitant severe systemic disease, and 1.72% (1 patient) had life-threatening systemic disease.

Table 6. Surgical stress score (E-PASS) applied to this sample.

	Mean	Standard Deviation	Maximium	Minimum	Median	N (%)
Blood loss/body weight (g/kg)	2.95173	3.29269	1.449275	0.54945	0.91751	
Operation time (hours)	7.2	2.1	12	1	7	
Extent of skin incision						
Minor incisions for laparoscopic or thoracoscopic surgery (including scope-assisted surgery)						0 (0.0)
Laparotomy or thoracotomy alone						58 (100.0)
Both laparotomy and thoracotomy						0 (0.0)

N—absolute value; %—relative frequency.

The mean surgical time was 7.2 h, with a standard deviation of 2.1 h, in which the maximum was 12 h and the minimum was 1 h. The median time of surgery was 7 h. The mean relation between blood losses (in grams) and patient weight (in kilograms) was 2.95173 g/kg, with a standard deviation of 3.29269, with a maximum of 14.49275 g/kg and a minimum of 0.54945 g/kg. The median, in this case, was 0.91751. All patients were submitted to a laparotomy.

2.4. Patient Score Results

The mortality risk predicted by the POSSUM score varied between 5.63% and 78.41%, with a median of 21.93%. According to P-POSSUM, the mortality risk was between 1.25% and 64.69%, with a median of 7.72%. The morbidity risk predicted by the POSSUM score varied between 30.58% and 98.51%. The most common values were between 73.81% and 91.86% (36.21%—n = 21). The physiological score applied to the sample had a minimum score of 12 and a maximum of 37, but most of them scored between 24 and 30 (36.21%—n = 21). The operative score had values between 15 and 26, but 55.17% (n = 32) had a score inferior to 18.

The mortality risk, as predicted by E-PASS, was between 0% and 382.41%. Most patients were between 27.09 and 98.63% (33.93%—n = 22). The mE-PASS predicted mortality risk ranged between 0.44% and 7.09%, with 48.28% (n = 28) of patients having values between 0.65 and 1.83%. The Comprehensive Risk Score (CRS) presented a minimum value of 0.145 and a maximum value of 1.296. Most patients (51.72%—n = 30) scored between 0.172 and 0.432. The Preoperative Risk Score (PRS) showed values between 0.206 and 1.127, and 37.93% (n = 22) had a score between 0.330 and 0.522. The Surgical Stress Score (SSS) presented 0.136 as a minimum value and 0.617 as a maximum value, and 39.66% (n = 23) of patients had values between 0.288 and 0.334. The mE-PASS' Comprehensive Risk Score (CRSf)'s values varied between 0.456 and 1.296, but most patients' scores were between 0.554 and 0.736 (43.10%—n = 25). The mE-PASS's Surgical Stress Score (SSSf) was between 0.191 and 1.028, and 86.21% (n = 50) of patients scored 0.496.

2.5. Evaluation of Surgical Risk Scores

2.5.1. Mortality

After applying the Mann–Whitney U Test to compare the different scores, significant differences were found between patients who died 30 days after surgery and those who did not in the following scores: E-PASS [Mortality (Md = 313.48%; n = 2); no mortality (Md = 95.75%; n = 56); U = 2.000; z = −1.793; p = 0.021; r = −0.342], PRS [Mortality (Md = 0.895; n = 2); no mortality (Md = 0.474; n = 56); U = 10.000; z = −1.961; p = 0.050;

r = −0.257], SSS [Mortality (Md = 0.559; *n* = 2); no mortality (Md = 0.297; *n* = 56); U = 3.000; z = −2.259; *p* = 0.024; r = −0.297] and CRS [Mortality (Md = 1.055; *n* = 2); no mortality (Md = 0.421; *n* = 56); U = 2.000; z = −2.301; *p* = 0.021; r = −0.302]. After applying Cohen's criteria (1988), E-PASS had a small effect size, and PRS, SSS, and CRS scores had a medium effect size. Due to the small number of patients that died, it was not possible to apply logistic regression with the aim of understanding if these scores would be independent mortality predictors.

2.5.2. Morbidity

There were no statistically significant differences in any score between patients who developed morbidity and patients who did not.

Logistic regression was performed to evaluate the impact of the scores (POSSUM, PS, OS, PRS, SSS, CRS, SSSf, and CRSf) as independent predictors of morbidity. The model was not able to differentiate patients who had morbidity from those who did not, X2 (6, N = 58) = 7574, *p* = 0.271. The model explains between 12.1% (Cox & Snell R2) and 16.7% (Nagelkerke R2) of the variance in severity of complications, and 69% of cases were correctly classified. Statistic significant independent predictors were not identified.

2.6. Scores' Calibration

Score calibration was checked using the O:E ratio and Hosmer–Lemeshow test. The O:E ratio was only used for POSSUM and E-PASS scores and their variations.

2.6.1. Mortality

The 30-day mortality estimated by the scores POSSUM, P-POSSUM, E-PASS, and mE-PASS were 21.93%, 7.72%, 98.63%, and 1.83%, respectively. The 30-day observed mortality was 3.45% (*n* = 2), which shows an O:E ratio of 0.16, 0.45, 0.03, and 1.89, respectively. The POSSUM score was better calibrated in stage III (O:E = 0.93) and the DCBDC localization (O:E = 0.54) subgroups. The P-POSSUM score was more precise in stage Ib (O:E = 1.49) and HPC localization (O:E = 0.53). All scores showed good calibration [16] ($p > 0.05$ in the Hosmer–Lemeshow test).

2.6.2. Morbidity

The observed postoperative morbidity was 37.98% (*n* = 22), and POSSUM's predicted morbidity was 73.80%, with a ratio of 0.51. The score was more precise in the Ib and III Stages (O:E = 1.01; O:E = 0.93) and HPC and AC localizations subgroups.

Physiological and operative scores showed bad calibration ($p < 0.05$ in the Hosmer–Lemeshow test) [16]. The remaining scores showed good calibration.

2.7. Scores' Discrimination Capacity

The scores' discrimination capacity to mortality and morbidity was tested using the area under the curve ROC (AUC).

2.7.1. Mortality

The AUC was analyzed: E-PASS and CRS showed AUC = 0.982 (IC 95% = 0.943–1.000; *p* = 0.021), and SSS showed AUC = 0.973 (IC 95% = 0.973–0.921; *p* = 0.024) (Figure 3).

In stage Ib and III subgroups and HPC and DCBDC subgroups, none of the scores had significant results. In stage Ia, IIa, and IIb subgroups and CA subgroups, the scores did not verify mortality.

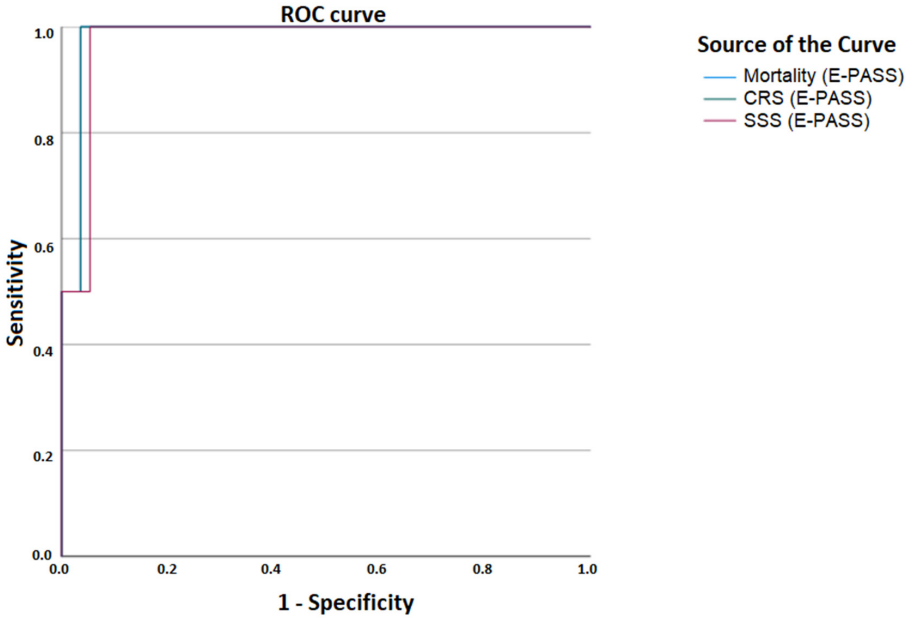


Figure 3. ROC curve for mortality.

2.7.2. Morbidity

None of the scores showed significant results. The AC subgroup had the biggest AUC in the operative score (AUC = 0.767; IC 95% = 0.529–1.000; p = 0.027) (Figure 4). The HPC subgroup had significant AUC in the SSS (AUC = 0.846; IC 95% = 0.676–1.000; p = 0.007) and in the CRS (AUC = 0.769; IC 95% = 0.572–0.967; p = 0.035) (Figure 5). In the DCBDC subgroup, none of the scores showed statistically significant results. In the stage IIb subgroup, the AUC was bigger in the operative score (OS) (AUC = 0.900; IC 95% = 0.788–1.000; p = 0.001), POSSUM (AUC = 0.812; IC 95% = 0.593–1.000; p = 0.011), and physiological score (PS) (AUC = 0.747; IC 95% = 0.788–1.000; p = 0.045) (Figure 6). In stages Ib, IIa, III, and IV, none of the scores had statistically significant results. In stage Ia, morbidity was not verified. Regarding local complications, systemic complications, and local and systemic complications subgroups, the operative score showed statistically significant results, with an AUC value of 0.829 (IC 95% = 0.651–1.000; p-value = 0.007) for the systemic and local complication subgroup (Figure 7). There was no other score or subgroup with statistically significant results.

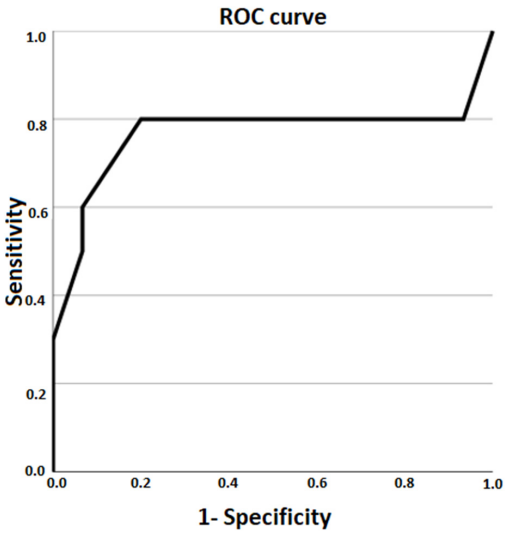


Figure 4. ROC curve for morbidity in the ampullary cancer subgroup.

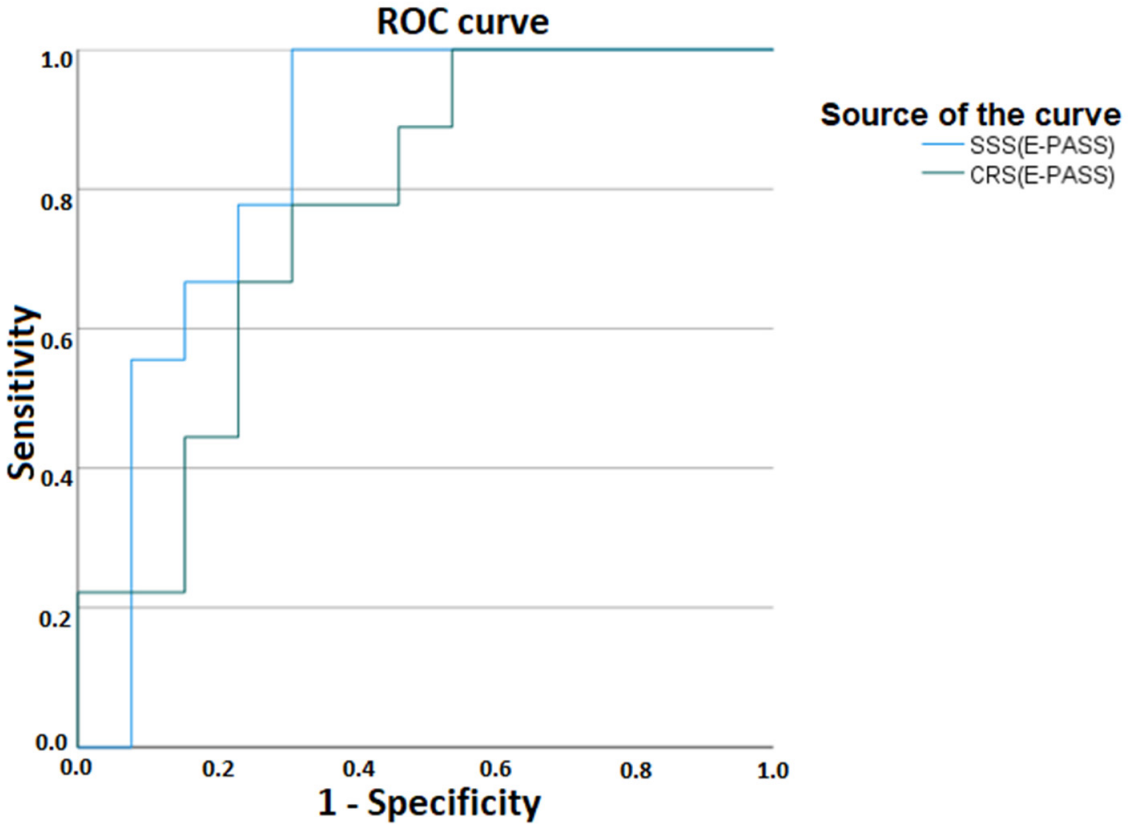


Figure 5. ROC curve for morbidity in the head of pancreas cancer subgroup.

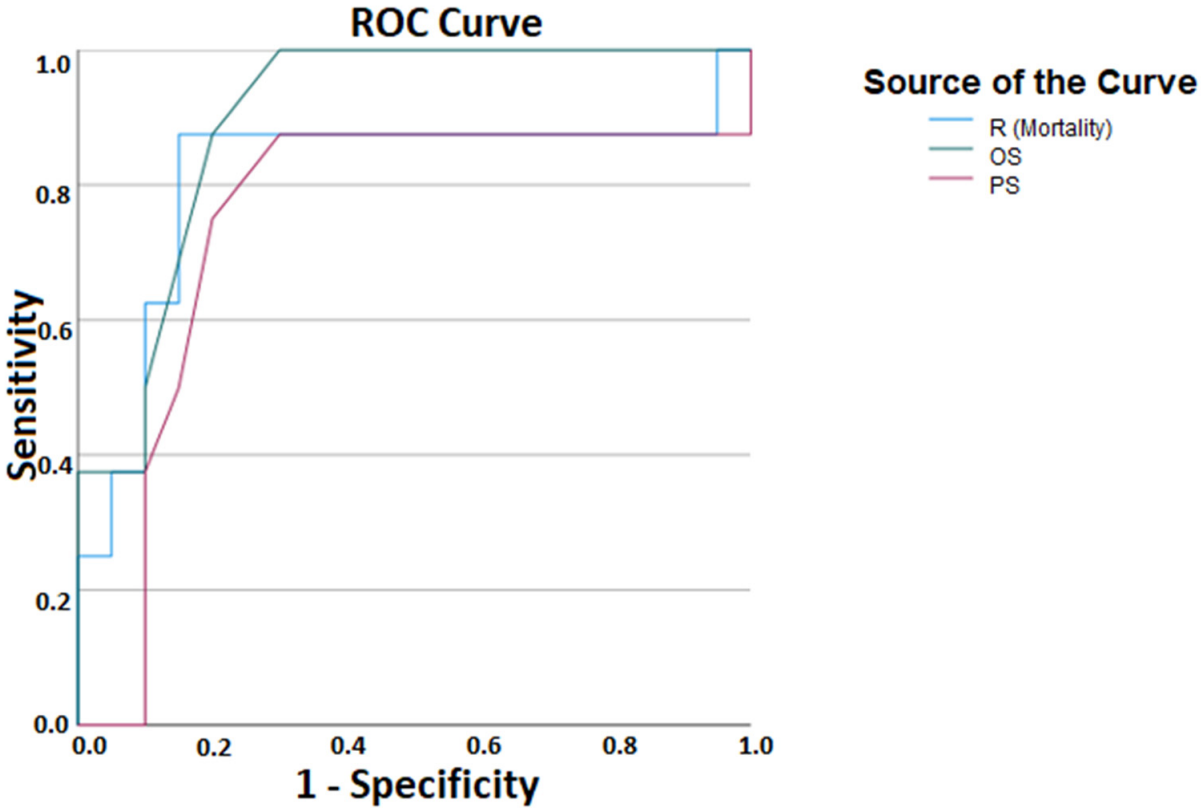


Figure 6. ROC curve for stage IIb.

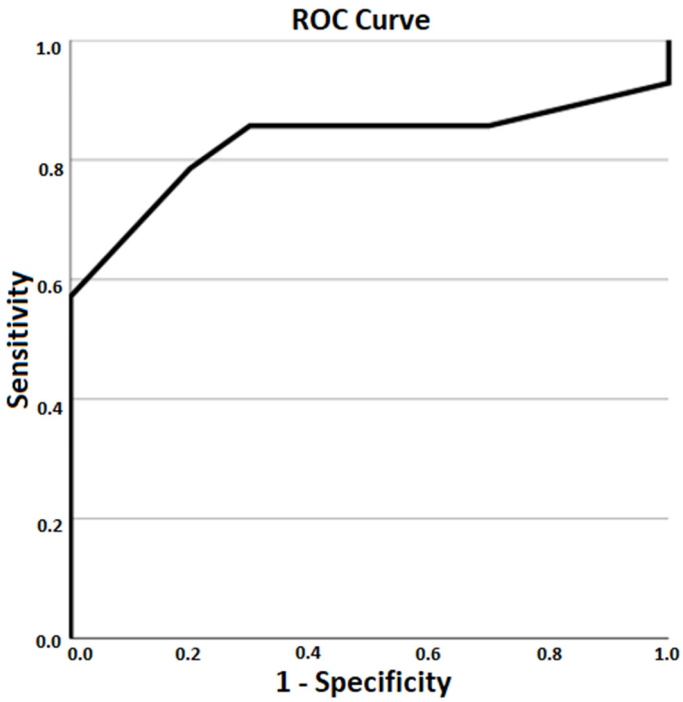


Figure 7. ROC curve for local and systemic complications.

2.8. Survival Predictive Factors Analyses

Patients were split between two groups for every score using the median of each score. The mean was used to split patients into two groups regarding morbidity POSSUM's score. This rearrangement was used to compare the survival between groups, and Cox Regression was used to identify survival predictors. SSSf was the only score that showed statistically significant results as a survival predictor (p = 0.001; hazard ratio = 0.084; IC 95% 0.020–0.358). Patients with a bigger value in the SSSf had a reduced survival time. The subgroup of patients that had an operative score lower than or equal to 0.496 had a mean survival of 48.904 months and a median of 48.600 months. Patients who had higher values than 0.496 had a mean survival of 16.275 months and a median of 11.000 months (p = 0.002) (Figure 8).

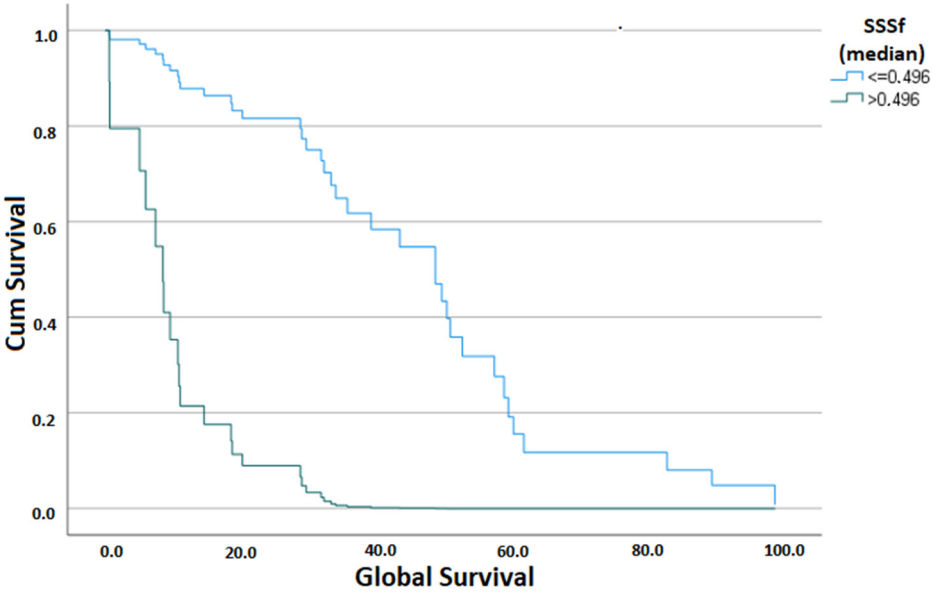


Figure 8. Cumulative survival of patients with SSSf lower than or equal to 0.496 and patients with SSSf greater than 0.496.

3. Materials and Methods

This is an observational, descriptive, and analytic study. The population of this study was patients with histologic diagnosis of periampullary cancer submitted for surgery at General Surgery ward of Hospital de Braga between 1 January 2011 and 31 May 2021. The sample was composed of patients who had all the inclusion criteria and none of the exclusion criteria. The inclusion criteria were patients with histologic diagnosis of periampullary cancer who were submitted to surgical treatment with curative goal with blood work before surgery. The exclusion criteria include patients with a different histologic diagnosis, patients submitted to surgical treatment with palliative goal, patients who were not submitted to surgery, and patients whose score could not be obtained.

The clinical and anatomopathological data obtained were the following: age; gender; daily medication; prior medical illness like severe cardiac disease, severe pulmonary disease, peripheral edema, cardiomegaly or borderline, raised jugular venous pressure (JVP), and diabetes mellitus; the Eastern Cooperative Oncology Group performance status index; the American Society of Anesthesiologists physiologic status classification; blood pressure; pulse; Glasgow coma scale; ECG; blood loss; body weight; operative time in hours; size of skin incision; operative severity; number of procedures made in one operative period; peritoneal soiling; presence of malignancy; laboratory investigations such as hemoglobin, white blood cell count, urea, sodium, and potassium; tumoral localization and stage; tumoral recurrence and date; mortality date; complications; 30-day mortality and global mortality; and mode of surgery.

Tumor localization was classified as head of pancreas carcinoma (HPC), distal common bile duct carcinoma (DCBDC), ampullary cancer (AC), and duodenum carcinoma (DC). Post-operative mortality was defined as deaths attributed to surgery up to 30 days after. Based on the date of surgery and death, it was possible to calculate the overall survival. Post-operative morbidity [17] was evaluated with Clavien–Dindo classification and later divided into two groups: patients without morbidity or with mild morbidity (grade I and II) and patients with moderate to severe morbidity (grade III to V).

Data collection was performed by the first author, and data were informatized in an Excel database. To ensure anonymity and confidentiality, the identification number of patients was different from the clinical file number. The right association between identification number and clinical file number was kept in the database, with the first author being responsible for its confidentiality.

The study protocol was authorized by Ethics Committee of Hospital de Braga and Ethics Subcommittee of Life and Health Sciences Ethics Committee of Universidade do Minho. The data collected were processed in Statistical Package for Social Science® (SPSS®), 27th version for Windows.

The sample was initially characterized descriptively regarding gender, tumor location, and staging, and their frequencies and percentages were obtained. The normality of continuous variables was assessed by Smirnov normality test, histogram symmetry analysis, and kurtosis value. If normality was verified, mean and standard deviation were used as central measures of tendency. If normality was not verified, median and interquartile range were used.

The physiologic and surgical scores, the mortality, and morbidity risk predicted by POSSUM and P-POSSUM were calculated with the use of Excel®. They each use two equations to calculate the mortality risk from different POSSUM scores and one to calculate the morbidity risk. E-PASS and mE-PASS score use two equations to calculate mortality risk but do not have an equation to calculate the morbidity risk. A relation between morbidity rate and the value of CRS score was established. The two POSSUM and P-POSSUMs score components [9,11,13] and the three EPASS score components [14,15,18,19] were analyzed.

According to score results, quantitative variables were compared using Mann–Whitney if they were not normal. *t*-tests were applied when quantitative variables were normal. Logistic regression was directed to identify morbidity and mortality predictors.

Scores were also evaluated regarding global calibration and discrimination. *p*-values lower than 0.05 were considered significant. Calibration was defined as the score's capacity to predict the outcome's correct probability to occur in the population [20]. It was tested by comparing the number of observed events with the number of events expected through O:E ratio and Hosmer–Lemeshow test. p-value < 0.05 indicates that the score has a bad calibration in Hosmer–Lemeshow test [16]. Discrimination was defined as the capability of the score to distinguish patients who will survive from patients who will decease [20], which is measured by area under ROC's curve (AUC). An AUC value inferior to 0.70 indicates low discrimination, a value between 0.7 and 0.8 indicates medium discrimination, and a value above 0.8 indicates good discrimination [20]. Kaplan–Meier curves were applied to analyze the survival. The survival between groups was compared through Log-rank test, and Cox regression was used to identify survival predictors.

4. Discussion

Cancer is an important cause of death worldwide [1]. The only curative therapeutic option in patients with periampullary cancer is surgery [5,21]. Patients need to be carefully selected because of the high mortality and morbidity rates.

Most of our patients were male, with a mean age of 67 years. The most common localization was ampullary cancer. The most common stage was IIb. The results regarding sex, gender, and age were very similar to the literature. In the literature, the most common localization of cancer was HPC. There was no data regarding cancer staging [7,9,11–15,18,19,21].

A pancreatoduodenectomy is the most used surgical procedure and is the surgical gold standard to treat periampullary cancers [3]. However, it is associated with high morbidity and mortality rates [4,5]. In this study, the mortality rate was 3.45%, and the morbidity rate was 37.93%, which was slightly lower than what is described in the literature [7,9–13,21,22] (5.23% and 44.23%, respectively). The most common morbidity in the sample was intraabdominal infection, which differs from the literature (generally, pancreatic fistula is the most common complication).

Even though treatment and staging keep evolving, PAC is still associated with low 5-year survival rates of 20% to 24% after surgery and adjuvant treatment [4]. Our survival rate was 96.55% at 30 days, 75.86% at one year, and 39.66% and 17.64% at 5 years. According to the literature, the survival rate observed was 94.77% at 30 days, 80% at one year, and 44% and 23% at 5 years [7,9–13,21–26].

Risk surgical scores were meant for the preoperative identification of patients with major risk for developing morbidity and mortality after surgery. There are multiple applicable scores, but no one has satisfactorily fulfilled that need [7,9–11,21].

This study evaluated the precision of the POSSUM, P-POSSUM, E-PASS, and mE-PASS scores in patients submitted for surgery for PAC via general surgery in Hospital de Braga. Medical files were consulted to obtain the value for each score.

In terms of the E-PASS ($p = 0.021$), CRS ($p = 0.021$), SSS ($p = 0.024$), and PRS ($p = 0.050$) scores, patients who deceased showed different results than those who did not decease. Patients who developed morbidity did not have different results than those who did not develop morbidity, which is different from what is described in the literature regarding the POSSUM score [7,9]. Unlike what is presented in the literature, a correlation between CRS, SSS, PRS, and morbidity was not found [15,16,18,24,27].

In the evaluation of the scores' calibration, POSSUM and P-POSSUM overestimated mortality 6.36 times (O:E = 0.16) and 2.24 times (O:E = 0.45), respectively. In the literature, the results were similar in relation to POSSUM (O:E = 0.15) but were different regarding P-POSSUM score (O:E = 0.67–5.4) [7,10,13]. In the case of the E-PASS score, it overestimated mortality 28.59 times (O:E = 0.03), while the mE-PASS score underestimated it 1.89 times (O:E = 1.89). POSSUM overestimated morbidity 2.24 times (O:E = 0.51), differently from what is reported in the literature (a ratio of O:E between 0.62 and 1.4). In this sample, P-POSSUM gives a better estimate of mortality and morbidity.

The discriminative capability of the scores was analyzed using the ROC curve [28]. E-PASS and CRS had excellent discrimination regarding mortality (AUC = 0.982; $p = 0.021$), followed by SSS (AUC = 0.973; $p = 0.024$).

Regarding morbidity, no score had statistically significant results. In the AC and stage IIb subgroups, the operative score had an acceptable (AUC = 0.767; $p = 0.27$) and excellent discrimination (AUC = 0.900; $p = 0.001$), respectively. In the stage IIb subgroup, besides the operative score results, POSSUM and physiological score presented good (AUC = 0.812; $p = 0.011$) and acceptable (AUC = 0.747; $p = 0.045$) discrimination, respectively. In the HPC subgroup, SSS had excellent discrimination (AUC = 0.846; $p = 0.007$), and CRS had good discrimination (AUC = 0.769; $p = 0.035$). In this study, E-PASS and CRS had the best discriminative value for mortality, and SS had the best discrimination in the subgroup HPC. In the operative scores case, it had the best discrimination regarding morbidity in the Stage IIB and CA subgroups despite having bad calibration. However, none of the scores had significant discrimination capabilities. In the literature [19,21], it is described that EPASS (AUC = 0.75), mE-PASS (AUC = 0.69), and P-POSSUM (AUC = 0.69) scores had acceptable discrimination, and CRSf (AUC = 0.79) and CRS (AUC = 0.78) had acceptable discrimination in the DCBDC subgroup relative to mortality. Regarding morbidity, the literature presents SSS with an acceptable discrimination (AUC = 0.71) and PRS (AUC = 0.87) and CRS (AUC = 0.88) scores with good discrimination [23]. In some studies, POSSUM did not have statistically significant results in morbidity cases [29], similar to our results. In another study [12], only the operative score was discriminative (AUC = 0.526), while other scores, like SSS (AUC = 0.421), CRS (AUC = 0.436), physiological score (AUC = 0.441), and PRS (AUC = 0.479), did not have discrimination value.

The published bibliography did not yield unanimous results in identifying the best surgical risk score [7,9–13,21,23]. In this sample, P-POSSUM showed the best calibration in the overall estimation of the mortality risk, while POSSUM and P-POSSUM showed the best calibration in the subgroups despite not presenting discriminative capacity in global analysis regarding mortality. CRS and E-PASS scores had a better discriminative value for mortality.

In relation to morbidity, P-POSSUM gives the best estimation and has good calibration, but it did not present discriminative capability globally or in the subgroups. The operative score had better discrimination in stage IIb and CA subgroups, although they did not have discriminative value in global analyses.

This trial had some limitations. It was a retrospective study, making it hard to ensure the right data collection. Its small number of cases could limit the precision of results. Moreover, it is hard to anticipate mortality and apply this score in PAC in small samples [7,9,21]. Morbidity was easier to predict. The POSSUM score was conceived to calculate the mortality and morbidity rate. In the EPASS and mE-PASS scores, there is no equation to calculate morbidity rate, although a strong association between morbidity, CRS, and CRSf in the literature has been described. It would be more useful in this case to develop one equation to more adequality define the morbidity rate.

5. Conclusions

Multiple models were created to estimate the surgical risk of patients submitted to pancreatoduodenectomy (PD), but none of them achieved this in a satisfactory manner. Regarding mortality, POSSUM and P-POSSUM scores yielded better calibration in this study's subgroups. CRS and E-PASS scores showed better discrimination in this topic. In the case of morbidity, the operative score had the greatest discrimination in the subgroups.

The ideal setting to analyze the surgical risk of the sample would be to associate POSSUM, P-POSSUM, and E-PASS; however, this would be difficult to accomplish. Given this, the best score to evaluate the surgical risk is the P-POSSUM score in this sample.

The surgical risk scores should be tested in different populations to evaluate their predictive power. In the future, it will be important to develop a surgical risk score adequate for Portuguese hospitals.

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Institutional Review Board Statement: This study was conducted under compliance with the Declaration of Helsinki and was approved by the Ethics Committee of Hospital de Braga, HB 32_2013, and the Ethics Committee of Life and Health Science Research Institute SECVS_064/2013.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to ethical restrictions imposed by the Institutional Review Board and the data contain sensitive personal information and cannot be shared publicly to protect participant confidentiality.

Conflicts of Interest: The authors declare no conflicts of interest.

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