Original Article

Postoperative procalcitonin is a biomarker for excluding the onset of clinically relevant pancreatic fistula after pancreaticoduodenectomy

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Background: Early detection and therapy of pancreatic fistula after pancreaticoduodenectomy is crucial to improve outcomes of this surgery. Since it is not clear if procalcitonin (PCT), can predict the onset of clinically relevant post-operative pancreatic fistula (CR-POPF), we aimed to investigate this ability.

Methods: One-hundred-thirty pancreaticoduodenectomies (PD) were analyzed. Receiver Operating Characteristic curves analysis defined the optimal cut-offs for PCT and drains amylase levels (DAL). Complications were compared using chi-square for proportions test.

Results: DAL ≥2,000 U/L in postoperative day (POD) 2 had 71% positive predictive value (PPV) and 91% negative predictive value (NPV) for CR-POPF (P<0.001). In POD2, PCT ≥0.5 ng/mL showed NPV 91% (P<0.045) and increased DAL PPV for CR-POPF to 81%. In POD3, POD4 and POD5, DAL (cut-offs 780, 157 and 330 U/L, respectively) showed NPV for CR-POPF >90% (P<0.0001). PCT ≥0.5 ng/mL showed NPV for CR-POPF of about 90%. In POD5, combining DAL (cut-off 330 U/L) and PCT (cut-off 0.5 ng/mL), a PPV for CR-POPF of 81% was detected. A progressive increased risk of CR-POPF from POD2 [odds ratio (OR) =3.05; P=0.0348] to POD5 (OR =4.589; P=0.0082) was observed. In POD2 and 5, PCT ≥0.5 ng/mL, alone and in combination with DAL, may be a reliable marker for identifying patients at highest risk of CR-POPF after PD.

Conclusions: This association could be proposed to select high risk patients that could benefit of "intensive" postoperative management.

Keywords: Pancreatoduodenectomy; postoperative pancreatic fistula; procalcitonin; drains amylase levels; biomarkers

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Introduction

Pancreaticoduodenectomy (PD) is still burdened by high complication rates and not-negligible mortality (up to 5%), even in high-volume centers (1). Undoubtedly, the main complication is represented by the postoperative pancreatic fistula (POPF), which often leads to other complications, as hemorrhage and sepsis that can be lethal (2).

The "International Study Group on Pancreatic Surgery (ISGPS)" defined POPF as the presence of amylase content three times higher than the Upper Limit of Normal (ULN) of serum amylase, in any measurable volume of fluid collected from abdominal drains starting from postoperative day 3 (POD3). Furthermore, based on its clinical impact, POPF is usually classified in grade A, B and C (3). Due to the lack of clinical impact, Grade A pancreatic fistula is also called "Biochemical Leak" (BL). Grade B and C POPFs are both defined "Clinically Relevant POPF" (CR-POPF) (4), due to the impact on patients' clinical condition (5).

Even if some Authors questioned the reliability of drains amylase levels (DAL) and the utility of surgical drains, since they may not function properly, or even be the cause of POPF and infectious complications themselves (6), in other words, according to the ISGPS classification (4), DAL remain the main tool for detecting a pancreatic fistula, but its severity can properly be defined only in the aftermath on the basis of postoperative outcomes observed in weeks after the PD.

Therefore, in recent years, a radical change in management of POPF has been proposed. A transition from a reactive strategy, based on the treatment of complications when they become evident, to a proactive strategy, which aims to early detect CR-POPF and prevent further complications has been advocated (7). Hence, novel tools for early detection and prediction of CR-POPF, that recently has been reported to affect 17% (8) and up to 29% of PDs (9), are urgently needed.

Advantages of timely diagnosis and prediction of postoperative anastomotic leaks have been widely reported in different types of abdominal surgery. Recently, procalcitonin (PCT) has been suggested to be a reliable biomarker of postoperative infection (10) and anastomotic dehiscence after colorectal surgery (11), as well as a useful marker of postoperative bacterial infections associated with complications after gastrointestinal surgery (12).

The role of this biomarker in POPF assessment and prediction is still unclear. Few, and nonetheless with different and controversial conclusions, are the studies focused on this topic (13-15). To date, it has been reported that when compared to other inflammatory markers as white blood cells (WBCs) and C-reactive protein (PCR), PCT is a valid tool to predict the development of CR-POPF after PD. Unfortunately, there is no agreement on the optimal cut-off that has to be used and in which postoperative day (POD). Furthermore, in the very first postoperative days, inflammation due to the surgical trauma influences PCT values (16). Therefore, in order to improve its performance, some authors proposed the use of PCT in combination with other markers (15).

On this basis, the aim of this study was to investigate the ability of postoperative PCT, alone and in association with drains amylase levels, to predict the onset CR-POPF after pancreaticoduodenectomy. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-803/rc).

Highlight box

Key findings

- Procalcitonin ≥0.5 ng/mL in post-operative day 2 and 5, alone and in combination with drain amylase levels, may be an easy and reliable tool for identifying patients at highest risk of clinically relevant pancreatic fistula after pancreatoduodenectomy

What is known and what is new?

- Procalcitonin has been demonstrated to be useful in predict postoperative infection and anastomotic dehiscence after colorectal surgery, as well as a marker of postoperative bacterial infections associated with complications after gastrointestinal surgery.
- The persistence of procalcitonin levels higher than 0.5 ng/mL from postoperative day 2 to postoperative day 5 is associated with a progressive and significant increased risk of developing clinically relevant pancreatic fistula. Furthermore, PCT at the optimal cut-off significantly increases the predictive capacity for CR-POPF of drains amylase levels in post operative day 2 and 5.

What is the implication, and what should change now?

- Patients with higher risk could benefit of more "intensive" postoperative management (e.g., late drains removal, targeted antimicrobial therapy), early abdominal CT-scan, etc.).

Methods

From a prospective maintained database, data of consecutive patients who underwent PDs between January 2012 and January 2020 at the Department of General Surgery of the Campus Bio-Medico University of Rome, Italy, have been retrospectively analyzed.

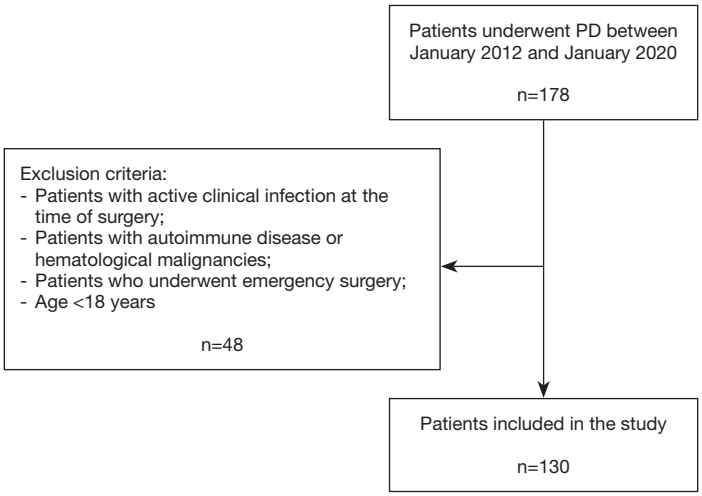

Figure 1 Flow chart showing patients selection process. PD, pancreaticoduodenectomy.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The local Ethical Committee approved the study (28/19 OSS ComEt CBM). Patient consent was waived due to the retrospective design of the study and considering that data are de-identified.

Demographic characteristics (age, sex, etc.), site and histological type of all tumors were collected. All patients underwent Whipple or Traverso-Longmire PD based on tumor location and received a single layer duct-to-mucosa pancreato-jejunal reconstruction. At the end of the procedure, two Jackson-Pratt abdominal drains were placed. Details of surgical procedures have been previously described (17).

Postoperative PCT and drains amylase levels concentration were measured on Alinity C and Alinity I Autoanalyzers (Abbott Park, Illinois, USA) with commercially available chemilumescence kit and immunoassays (Abbott Park, Illinois, USA). POPF was defined according to the criteria of the International Study Group of Pancreatic Surgery (3,4). The exclusion criteria are described in *Figure 1*.

Statistical analysis

Analysis was performed using Med-Calc 18.11.3 statistical package (MedCalc software, Mariakerke, Belgium). The "receiver operating characteristic" (ROC) curves and "Area under the curve" (AUC) defined the optimal cut-offs of PCT and DAL to identify the development of CR-POPF in different postoperative days.

Using the identified cut-offs in different postoperative days, positive predictive values (PPV) and negative predictive values (NPV) of PCT and DAL, alone and in combination with each other, were calculated to assess the probability of developing CR-POPF.

The odds ratios of the two biomarkers at their optimal cut-offs in different postoperative days were calculated to assess the risk of developing any grade of POPF (A, B and C), a CR-POPF (B and C) and grade C POPF.

All P values <0.05 were considered statistically significant.

Results

Patient's characteristics

Demographic and clinical patients' characteristics

Based on the criteria described in *Figure 1*, 130 out of 178 patients were considered eligible for the analysis. As reported in *Table 1*, 72 (55.4%) patients were men and 58 (44.6%) female. The median age was 71 years (range, 38–85 years), and the median BMI was 23.53 kg/m^2 (range, 17.2–38.5 years). *Table 1* also shows comorbidities and operative data of all the series.

Five (3.8%) patients were affected by benign neoplasm and 125 (96.1%) by malignant tumors. In patients with benign neoplasm, a surgical approach was needed due to the compressive symptoms on the adjacent structures caused by the tumor.

Among patients suffering from malignant disease, 105 (80.7%) had adenocarcinoma, which turned out to be the

Table 1 Demographic and clinical characteristics of the study population

Demographic and clinical characteristics	Study population (n=130)
Age, years [range]	71 [38–85]
Gender, n (%)	
Male	72 (55.4%)
Female	58 (44.6%)
BMI, kg/m^2 [range]	23.53 [17.2–38.5]
Comorbidity, n (%)	
Cardiovascular disease	54 (41.5%)
Diabetes	19 (14.6%)
Chronic respiratory disease	14 (10.8%)
Chronic kidney disease	2 (1.5%)
Type of PD, n (%)	
Traverso procedure	90 (69.2%)
Whipple procedure	40 (30.8%)
Surgical approach, n (%)	
Open	117 (90.0%)
Laparoscopic	8 (6.2%)
Conversion	5 (3.8%)
Histology, n (%)	
Benign neoplasm	
IPMN	3 (60.0%)
Tubulo-villous adenoma	2 (40.0%)
Malignant pathology	
Adenocarcinoma	105 (84.0%)
Cholangiocarcinoma	12 (9.6%)
Neuroendocrine tumor	7 (5.6%)
Pseudopapillary tumor	1 (0.8%)
Tumor location, n (%)	
Pancreas	90 (69.2%)
Vater's ampulla	22 (16.9%)
Distal common bile duct	14 (10.8%)
Duodenum	3 (2.3%)
Pylorus	1 (0.8%)

PD, pancreatoduodenectomy; IPMN, intraductal papillary mucinous neoplasm.

most frequent histology in the population under study. The most frequent pathological localization was the pancreatic head, found in 90 (69.2%) patients. All others histological type and tumor sites are reported in *Table 1*.

CR-POPF characteristics

CR-POPF developed in 20 out of 130 patients (15.4%). More in detail, 11 (8.5%) patients developed a grade B pancreatic fistula and 9 (6.9%) a grade C pancreatic fistula.

ROC curve analysis for CR-POPF

Table 2 shows the results of ROC curves analysis and the best cut-off values for each of the biomarkers, the corresponding PPV and NPV, and the value of the AUC and the significant P values.

More in detail, we found that drains amylase levels in post-operative day 2, at the cut-offs of 2,000 U/L had the highest PPV and NPV for CR-POPF (PPV =71%, NPV =91%; P<0.001).

It should be also noted that in the same post-operative day, PCT at the cut-off of 0.5 ng/mL showed the highest NPV (91%; P<0.045) for clinically relevant pancreatic fistula and was able, when associated with DAL at the cut-off of 2,000 U/L, to increase its PPV for CR-POPF (from 71% to 81%).

In POD3, POD4 and POD5, drains amylase levels (cut-offs 780, 157 and 330 U/L, respectively) showed NPV for CR-POPF >90% (P<0.0001); furthermore, PCT at the cut-off of 0.5 ng/mL showed NPV for clinically relevant pancreatic fistula of about 90%.

Moreover, in post-operative day 5 combining DAL at the cut-off of 330 U/L and PCT at the cut-off of 0.5 ng/mL a PPV for CR-POPF of 81% was found.

Regarding the Odds ratio, in presence of DAL higher than each single cut-off in the first five postoperative days, a significant higher risk of developing CR-POPF was found. Likewise, patients who had PCT levels higher than the cut-offs from postoperative day 2 to 5 had a significant higher risk of developing CR-POPF. Notably, a progressive increased risk of developing CR-POPF from POD2 (OR =3.05; P=0.0348) to POD5 [odds ratio (OR) =4.589; P=0.0082] was observed.

An increased risk of developing CR-POPF in all five postoperative days was also found when drains amylase levels and PCT have been analyzed in combination.

As *Table 2* shows, AUC values for PTC ranged from 54%

Table 2 Results of the ROC curves analysis and the best cut-off values for DAL and PCT and their association, corresponding PPV and NPV and the value of the AUC and P values, from POD1 to POD5. CR-POPFs (grade B+C) have been analysed

POD	Markers	Cut-off value	PPV (%)	NPV (%)	AUC (%)	Sensibility (%)	Specificity (%)	P value	OR	P(OR)
POD1	DAL (U/L)	2300	19	96	75.4	67	72	<0.001	5.133	0.0027
	PCT (ng/mL)	0.5	20	86	54	50	57	0.59	1.14	0.7844
	DAL (U/L) + PCT (ng/mL)		21	83					5.03	0.0031
POD2	DAL (U/L)	2000	71	91	75.6	65	78	<0.001	6.45	0.0004
	PCT (ng/mL)	0.5	26	91	64	70	60	0.045	3.05	0.0348
	DAL (U/L) + PCT (ng/mL)		81	45					6.45	0.0004
POD3	DAL (U/L)	780	28	94	81	75	65	<0.0001	6.45	0.0008
	PCT (ng/mL)	0.5	25	91	69	60	70	0.0041	3.21	0.0196
	DAL (U/L) + PCT (ng/mL)		44	82					6.45	0.0008
POD4	DAL (U/L)	157	33	93	79.8	78	65	<0.0001	6.62	0.0020
	PCT (ng/mL)	0.5	30	90	75.7	62	69	<0.0002	4.39	0.0099
	DAL (U/L) + PCT (ng/mL)		50	79					6.62	0.0020
POD5	DAL (U/L)	330	48	93	79	75	80	0.0001	11.76	0.0002
	PCT (ng/mL)	0.5	54	87	72	44	90	0.0022	4.589	0.0082
	DAL (U/L) + PCT (ng/mL)		81	49					11.769	0.0002

ROC, receiver operating characteristic; CR-POPF, clinically relevant post-operative pancreatic fistula; DAL, drains amylase levels; PCT, procalcitonin; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; POD, postoperative day; OR, odds ratio.

in POD1 to 72% in POD5 with maximum value of 75.7% in POD4.

ROC Curve analysis for grade C POPF

In *Table 3*, ROC curve analysis results focused on grade C POPF have been reported showing that both drains amylase levels and PCT, alone and in combination, reached high NPV (≥92%) for grade C POPF.

Table 3 also shows significant higher risk of developing grade C CR-POPF when drains amylase levels were higher than the cut-off values on postoperative days from 1 to 5 (except in post-operative day 2). Furthermore, patients who had PCT values higher than the optimal cut-offs from POD3 to POD5 were at significant higher risk of grade C postoperative pancreatic fistula.

The association of the two biomarkers confirmed these findings. Notably, in post-operative day 2 combining DAL (cut-off of 2,000 U/L) and PCT (cut-off of 0.5 ng/mL), the risk of developing grade C pancreatic fistula was 23 times higher (OR =23.38; P=0.0037). Similarly, the association of DAL (cut-off of 300 U/L) and PCT (cut-off of 0.4 ng/mL) in POD5 showed significant higher odds of developing this fearful complication (OR =17.05; P=0.0018).

Notably, AUC values for PTC ranged from 63% in POD1 to 83% in POD5 with a maximum of 86% in POD4.

Discussion

POPF represents the main complication after PD and is often responsible for the onset of further, even lethal, complications (18). In order to improve postoperative outcomes, the availability of biomarkers able to early predict the development of CR-POPF, properly defined only in the aftermath based on postoperative outcomes observed in weeks after the PD, and to distinguish these patients from those who will not experience this complication, would be of great utility in clinical practice in order to improve outcomes.

The results of our study show that starting from POD2, drains amylase levels at different cut-offs for each

Table 3 ROC curve analysis results focused on grade C POPF. Best cut-off values for DAL and PCT and their association, corresponding PPV and NPV and the value of the AUC and P values, from POD1 to POD5 have been reported

POD	Markers	Cut-off value	PPV (%)	NPV (%)	AUC (%)	Sensibility (%)	Specificity (%)	P value	OR	P(OR)
POD1	DAL (U/L)	2000	83	75	79.7	87	68	<0.0001	13.8	0.0157
	PCT (ng/mL)	0.5	9	93	63	56	40	0.25	1.43	0.60
	DAL (U/L) + PCT (ng/mL)		86	21					13.63	0.0163
POD2	DAL (U/L)	2000	21	99	79	89	76	<0.0001	0.46	0.62
	PCT (ng/mL)	0.5	14	98	77	78	63	0.016	4.21	0.08
	DAL (U/L) + PCT (ng/mL)		36	92					23.38	0.0037
POD3	DAL (U/L)	1100	23	99	83.7	90	76	<0.0001	53.26	0.0067
	PCT (ng/mL)	0.5	17	99	84	89	67	<0.0001	7.08	0.0176
	DAL (U/L) + PCT (ng/mL)		44	95					9.87	0.0001
POD4	DAL (U/L)	200	20	98	76	87	70	0.0032	16.59	0.0102
	PCT (ng/mL)	0.5	22	98	86	87	72	<0.0001	17.64	0.0088
	DAL (U/L) + PCT (ng/mL)		43	96					16.59	0.0102
POD5	DAL (U/L)	300	25	98	86	87	75	<0.0001	15.90	0.0128
	PCT (ng/mL)	0.4	10	95	83	86	73	<0.0001	8.33	0.0070
	DAL (U/L) + PCT (ng/mL)		27	94					17.05	0.0018

POPF, post-operative pancreatic fistula; DAL, drains amylase levels; PCT, procalcitonin; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; POD, postoperative day; OR, odds ratio.

postoperative day, confirmed to be a valid predictor of clinically relevant pancreatic fistula and this is consistent with what already reported in literature (19-21).

Starting from POD2, procalcitonin at the cut-off of 0.5 ng/mL showed NPV of approximately 90% for CR-POPF. Furthermore, the persistence of PCT levels ≥0.5 ng/mL from POD2 to POD5 was associated to a progressive increased risk of developing clinically relevant pancreatic fistula. ROC curve analysis confirmed the negative predicting ability of PCT for the development of CR-POPF and grade C POPF particularly in postoperative day 4 (AUC values of 75.7% and 86%, respectively).

Therefore, we can assume that when serum PCT levels are below the cut-off of 0.5 ng/mL (which, among other things, represents the maximum normal laboratory level commonly used in clinical practice) in POD2, the development of CR-POPF will most likely not occur.

Furthermore, since PCT showed highest NPV in POD2 and POD3, and considering that it has been proved the role of this biomarker in predicting abdominal infections (21,22), we could speculate that an early infectious process may lay under the development of CR-POPF.

This hypothesis could also be supported by previous experiences that reported the high accuracy of PCT in predicting severe gram-negative sepsis (23) and how the presence of gram-negative rods represents an independent risk factor for threatening Grade C POPF after PD (24). However, the lack of data about drains fluid cultures from POD2 to POD5 in our series do not allow us to confirm this hypothesis.

The high negative predictive ability of PCT was confirmed when the subgroup of grade C pancreatic fistulas was analyzed.

There are few studies in literature (13-15) that investigated relationship between post-operative PCT and development of CR-POPF. Moreover, controversial results have been reported and unique cut-off is still lacking.

In 2014, Giardino *et al*. conducted a prospective study on 84 patients underwent PD. In this experience, PCT in post-operative day 1 identified subjects at risk of developing CR-POPF. Patients with PCT levels higher than the identified cut-off (0.4 mg/dL) had a six times higher risk of CR-POPF (OR 5.62, 95% CI: 1.41–37.7; P=0.030) (15).

However, as already reported in literature (25), PCT

increases after the first 6 hours following major abdominal surgery, regardless of any possible complications. The levels of this marker tend to decrease quickly after the first 24 hours if the inflammation disappears. One day after surgery, elevated PCT values could instead suggest the persistence of inflammation due to possible complications. Therefore, PCT assay before POD2 should not be considered reliable.

More in detail, as previously reported by other Authors (14,26), while C-reactive protein is influenced by inflammation having a half-life of 19 hours, a peak at 48 hours after the stimulation and then decrease in absence of inflammatory stimuli, PCT does not reflect the inflammatory status. PCT levels are influenced more by the presence of bacterial infectious than by other inflammatory injuries.

In disagreement with Giardino, in our experience PCT in POD1 was not associated with significant risk (OR =1.14; P=0.7844) of developing CR-POPF.

Moreover, aware that PCT is affected by surgical trauma in the first 24 postoperative hours, and considering that trauma is reduced in mini-invasive surgery, more recently Ma *et al*. retrospectively analyzed data of 186 patients underwent laparoscopic PD. From this analysis emerged the ability of PCT in POD3 to predict a clinically relevant pancreatic fistula (cut-off values >2.10 ng/mL, sensitivity 88.2%, specificity 92.9%, AUC =0.951; P<0.001) (14). However, it should be noted that, even in attempt to reduce the bias of inflammation due to the open surgical technique, in this study only subjects undergoing laparoscopic surgery were examined and therefore these findings cannot be generalized to all PDs.

In 2020, Zhou *et al*. retrospectively analyzed data of 67 patients underwent PD and 19 patients underwent distal pancreatectomy. The Authors confirmed the ability of postoperative procalcitonin to early detect CR-POPF when compared to other inflammatory markers. The best performance of procalcitonin was observed in POD1 at the cut-off of 0.67 μg/ L (sensitivity 73.68%, specificity 76.12%, AUC 0.77; 95% CI: 0.675–0.860), in POD3 at the cut-off of 0.56 μg/L (sensitivity 89.47%, specificity 64.18%, AUC 0.83; 95% CI: 0.734–0.902), and in POD5 at the cut-off of 0.46 μg/L (sensitivity 68.42%, specificity 76.12%, AUC 0.72; 95% CI: 0.621–0.818) (13). It is clear that in this experience different PCT cut-offs were identified in different postoperative days, suggesting too high variability for the clinical use of this marker. Instead, it should be emphasized that in our study PCT cut-off remained unchanged in various postoperative days, unlike what occurred with DAL.

Regarding DAL, our study confirmed its high positive predictive ability for POPF; however, as already observed by Kanda *et al*., it should be considered that amylase concentration in fluid collected by drains can be strongly influenced by the amount of ascitic exudate and by the effectiveness of the drains themselves. This suggests that DAL do not always increase in parallel with exacerbation of the postoperative pancreatic fistula (25,27). Being PCT levels measured on blood samples, this marker should be less influenced by non-clinical issues. Furthermore, the cut-off that emerged from our study is the maximum value of the range of normality commonly used in clinical practice.

We found interesting to investigate the association of PCT with DAL in identifying patients at higher risk of developing CR-POPF. Even Giardino *et al*. (15) studied this association, but they did not highlight any significant relationship with the development of clinically relevant pancreatic fistula. In our study, PCT at the cut-off of 0.5 ng/mL significantly increased the PPV for CR-POPFs of drains amylase levels in post-operative day 2 and 5. In detail, based on the results we obtained, it is likely to hypothesize that when both drains amylase levels and procalcitonin are above their respective cut-offs of 2,000 U/L and 0.5 ng/mL in POD2, patients will most likely develop a CR-POPF. A similar speculation can be made in post-operative day 5 in presence of DAL and PCT values higher than 330 U/L and 0.5 ng/mL, respectively.

Encouraged by the results obtained from this study, and with particular regard to the ability of the combination of DAL and PCT to identify subjects with extremely high (up to 23 times) risk of developing a grade C POPF, if these data would be confirmed, we could envision the use of both DAL and PCT to identify, as early as POD2, subjects who are more likely to develop severe consequences from their fistula, These high-risk patients may benefit from a more careful clinical observation and a more "intensive" postoperative management. This kind of management could include a late drains removal policy, according to the concept of their dynamic management proposed by Trudeau *et al.* (28), the assessment of early second level diagnostic exams (e.g., CT scan), with early percutaneous drainage of fluid collections and longer in-hospital stay, in order to decrease the failure-to-rescue rates, which according to what reported by van Dongen *et al*. represents a critical determinant of mortality after PD (29).

Furthermore, considering that postoperative PCT correlates with increased intra-abdominal infections

after major surgery (25), this marker would represent an aid in the evaluation of those patients who could benefit from post-PD antimicrobial therapy. This therapy could be oriented on the outcome of the biliary culture intraoperatively collected (30).

Our study is not without limitations that must be identified in its retrospective nature and in the size of the sample, which even small is comparable to that reported in the few other studies published in literature and focused on this topic. Due to the above-mentioned limitations, results found in this study should be carefully considered and need larger and prospective multicenter studies to be confirmed and generalized.

Conclusions

PCT at the cut off-of 0.5 ng/mL may be used as a reliable and easily reproducible marker for identification of patients at highest risk of developing CR-POPF after PD. PCT <0.5 ng/mL could exclude the onset of this complication.

The persistence of PCT levels higher than 0.5 ng/mL from postoperative day 2 to postoperative day 5 is associated with a progressive and significant increased risk of developing this fearful complication.

Furthermore, PCT at the optimal cut-off significantly increases the predictive capacity for CR-POPF of drains amylase levels in POD2 and POD5. Therefore, the association of the two markers in these PODs could be proposed to identify patients at higher risk of CR-POPF, and in particular a grade C postoperative pancreatic fistula, that could benefit of more "intensive" postoperative management (e.g., late drains removal, targeted antimicrobial therapy, early abdominal CT-scan, etc.).

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