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ORIGINAL ARTICLE

C-reactive protein is superior to white blood cell count for early detection of complications after pancreatoduodenectomy: a retrospective multicenter cohort study

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Abstract

Background: Early detection of major complications after pancreatoduodenectomy could improve patient management and decrease the "failure-to-rescue" rate. In this retrospective cohort study, we aimed to compare the value of C-reactive protein (CRP) and white blood cell count (WBC) in the early detection of complications after pancreatoduodenectomy.

Methods: We assessed pancreatoduodenectomies between January 2012 and December 2017. Major complications were defined as grade III or higher according to the Clavien-Dindo classification. Post-operative pancreatic fistula (POPF) was a secondary endpoint. ROC-curve and logistic regression analysis were performed for CRP and WBC. Results were validated in an external cohort.

Results: In the development cohort (n = 285), 103 (36.1%) patients experienced a major complication. CRP was superior to WBC in detecting major complications on postoperative day (POD) 3 (AUC:0.74 vs. 0.54, P < 0.001) and POD 5 (AUC:0.77 vs. 0.68, P = 0.031), however not on POD 7 (AUC:0.77 vs. 0.76, P = 0.773). These results were confirmed in multivariable analysis and in the validation cohort (n = 202). CRP was also superior to WBC in detecting POPF on POD 3 (AUC: 0.78 vs. 0.54, P < 0.001) and POD 5 (AUC: 0.83 vs. 0.71, P < 0.001).

Conclusion: CRP appears to be superior to WBC in the early detection of major complications and POPF after pancreatoduodenectomy.

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Introduction

Pancreatoduodenectomy is the only treatment for tumors of the pancreatic head and periampullary region with curative intent. In high-volume centers, perioperative mortality rates of <3% and morbidity rates of 40–50% are reported.[1–4] As a result of surgical and perioperative improvement in care, mortality rates have dropped significantly over the last decades. However, complication rates remain relatively unchanged.[4,5] Among all, postoperative pancreatic fistula (POPF) is the most threatening complication after pancreatoduodenectomy with an incidence of 10–25%.[1,3,6,7] POPF and intra-abdominal infections can lead to post-pancreatectomy hemorrhage and abdominal sepsis.[8,9] Therefore, early identification of patients at risk might help in decreasing 'failure-to-rescue' rates, which has been identified as an important quality indicator.[10,11]

This paper is not based on a previous communication to a society or meeting.

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Inflammatory biomarkers such as C-reactive protein (CRP) and white blood cell count (WBC) might be suitable for early detection of complications, as they largely reflect the inflammatory status of a patient. Yet, translation and clinical understanding of CRP and WBC in the early postoperative period remains difficult as these parameters are often elevated due to surgical trauma.[12,13] Furthermore, CRP is predominantly used in Europe, while in non-European countries emphasis lies on WBC. However, recent studies demonstrated that both CRP and WBC are useful in the early detection of complications after pancreatoduodenectomy.[14–20]

To our knowledge, no prior study has compared the diagnostic value of CRP and WBC during the early postoperative phase after pancreatoduodenectomy. Therefore, we aimed to determine whether CRP or WBC is superior in the detection of major complications and POPF during the first seven days after pancreatoduodenectomy.

Methods

The Medical Ethical Review Committee of the Erasmus MC in Rotterdam, the Netherlands, approved this study and waived the need for informed consent.

Study population

The cohort for model development included patients who underwent a pancreatoduodenectomy between January 2012 and December 2017 in one academic center in the Netherlands (Erasmus MC). The validation cohort included patients who underwent a pancreatoduodenectomy in one academic (UMC Utrecht) and one non-academic center (Sint Antonius hospital, Nieuwegein) between January 2015 and December 2017. Patients were excluded if they underwent additional concurrent organ resections, such as a hemicolectomy or a liver segment resection, since the height of the postoperative CRP peak is related to the extent of surgical trauma.[21]

Data collection

Demographics, clinical characteristics, operation data and postoperative outcomes were extracted from prospectively maintained databases or collected through systematic reviewed patient's charts. Serum CRP (mg/L) and WBC ($x10^9$/L) from POD 1 to POD 7 were collected. CRP and WBC were routinely measured on POD 3, 5 and 7 according to the postoperative protocol from all participating centres. Postoperative complications, including those after initial hospital discharge, were collected up to POD 30. The diameter of the pancreatic duct was measured on preoperative Computed Tomography (CT) scan at the pancreatic neck anterior to the portal vein and subsequently divided in two categories ($\leq$3 mm and >3 mm). Pathological diagnoses were divided into a low risk (pancreatic adenocarcinoma and pancreatitis) and a high risk group (miscellaneous).[6] Pancreatic texture was determined collected from operation reports of the surgeon (soft/normal or hard).

Definition of complications

The primary endpoint consisted of grade $\geq$ 3a complications according to the Clavien-Dindo Classification (i.e. requiring surgical, endoscopic or radiological intervention under regional-, general- or local anaesthesia, life threatening complications requiring intensive care management, single organ- or multi-organ failure and patients demise).[22] The secondary endpoint was grade B/C POPF.[23] Other complications were post-pancreatectomy hemorrhage,[25] delayed gastric emptying[26] and bile leakage.[27] Intra-abdominal infections were defined as drained fluid collections with a positive culture or purulent output.

Statistical analysis

Frequency distributions of continuous variables were visually assessed with histograms and potential departures from normality were formally assessed using the Shapiro–Wilk test. Normally distributed data are presented as mean ± standard deviation, while non-normally distributed data are presented as median values ± interquartile range (IQR). Categorical data are shown as counts and percentages.

Missing values of CRP and WBC from POD 1 to 7 were imputed using mixed-effects models. Mixed-effects models assess changes in longitudinal data over time, whilst accounting for intra-individual correlations between measurements and patient characteristics.[28,29] Our models consisted of a fixed-effects part and a random-effects part with a random intercept and a non-linear random slope. The fixed-effect parts included (pre-)operative parameters related to CRP, WBC or outcome (i.e. grade $\geq$3) ($P < 0.2$). Pancreatic texture was missing in 113 patients (39.6%); therefore it was not included in the mixed-effects models and multivariable models. All further analyses were performed on the dataset with complete longitudinal data, but were limited to POD 3, 5 and 7 as it had most available actual measurements. CRP and WBC measurements drawn after the incidence of a major complication were excluded from further analyses.

Differences in CRP and WBC between complication groups were tested using the Mann–Whitney U test (non-parametric). We constructed scatterplots for CRP and WBC with the associated Pearson's correlation coefficient. Additionally, receiver-operating characteristic (ROC) curves for CRP and WBC were constructed and area-under-the-curve (AUC) values were determined to assess discriminatory capabilities. Cut-off values were established for CRP and WBC based on the trade-off between sensitivity and specificity using ROC-curve analysis. The diagnostic value of delta CRP and delta WBC was examined in similar fashion. Next, we performed multivariable logistic regression analyses including CRP and WBC, adjusted for age, sex and variables univariably associated with the primary

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endpoint ($P < 0.2$). Bivariable logistic regression models (including only CRP and WBC) were also constructed, and their discrimination and calibration was assessed in the development and validation cohort.

R statistical software (version 3.4.3.; www.r-project.org) was used for all statistical analyses. Two-sided P-values < 0.05 were considered statistically significant.

Results

Study population

In the development cohort, a total of 306 pancreatoduodenectomies were performed. Overall, 21 patients were excluded due to additional concurrent resections, resulting in the final cohort of 285 patients. The validation cohort consisted of 202 patients after exclusion of 14 patients due to additional concurrent resections. Table 1 lists patient characteristics of both cohorts. In the development cohort 103 patients (36.1%) developed a major complication, with a median time of reintervention on POD 8 (interquartile range (IQR) 6–15 days). Furthermore, 51 patients (17.9%) developed POPF in the development cohort. For the validation cohort, 88 patients (40.1%) developed a major complication, with the median time of reintervention on POD 5 (IQR 3–9.5 days). Thirty-five patients (17.3%) developed POPF in the validation cohort. A detailed complication profile of both cohorts is shown in Appendix 1.

CRP and WBC in the development cohort

Patients had a median of 3.5 CRP measurements (IQR: 3–4) and a median of 4 WBC measurements (IQR: 3–5) during the first 7 days after surgery. Before imputation, CRP measurements were available in 83% (POD 3), 58% (POD 5) and 60% (POD 7) of the patients. WBC measurements were available in 83% (POD 3), 60% (POD 5) and 59% (POD 7) of the patients.

Median CRP values were significantly higher in patients who developed major complications on POD 3, POD 5 and POD 7 (all $P < 0.001$), see Fig. 1a. No significant difference in WBC between complication groups was observed on POD 3 ($P = 0.299$). Median WBC was significantly higher in patients who developed major complications on POD 5 and POD 7 (both $P < 0.001$), see Fig. 1b. The positive correlation between CRP and WBC increased from POD 3 towards POD 7, see Fig. 2.

Patients who developed POPF also had significantly higher CRP levels on POD 3 (307 vs. 181 mg/L, $P < 0.001$), POD 5 (240 vs. 101 mg/L, $P < 0.001$) and POD 7 (214 vs. 77 mg/L, $P < 0.001$). No difference was observed for WBC on POD 3 (11.9 vs. 10.7×10^9/L, $P = 0.166$). While, WBC was significantly higher in patients who developed POPF on POD 5 (10.9 vs. 8.9×10^9/L, $P < 0.001$) and POD 7 (16.6 vs. 11.2×10^9/L, $P < 0.001$).

ROC-curve analysis (Table 2) demonstrated that AUCs of CRP were significantly higher on POD 3 and POD 5 compared to WBC for major complications ($P < 0.001$ and $P = 0.032$, respectively) and POPF (both $P < 0.001$). On POD 7, CRP had a similar AUC as WBC for major complications ($P = 0.773$) and POPF ($P = 0.158$). Table 3 displays the diagnostic indices of CRP and WBC for detecting major complications at different cut-off values. Delta CRP and WBC demonstrated to have inferior diagnostic qualities compared to the absolute value of CRP and WBC (Appendix 2).

Multivariable analysis in the development cohort

Univariable analysis demonstrated that BMI, pancreatic duct diameter, soft pancreatic texture and blood loss >1000 ml were associated with major postoperative complications (Appendix 3). The multivariable models (Appendix 4) showed that, CRP was the only independent predictor of major complications on POD 3 and 5 ($P < 0.001$). On POD 7, both CRP and WBC were independently associated with major complications ($P < 0.001$ and $P = 0.002$, respectively). The same was demonstrated in models only containing WBC and CRP, these bivariables models had an AUC of 0.74 on POD 3 (95% CI: 0.67–0.80), 0.78 on POD5 (95% CI: 0.71–0.84), and 0.79 on POD 7 (95% CI: 0.73–0.86).

Calibration and discrimination in the validation cohort

In the validation cohort, AUCs of CRP and WBC were comparable to the development cohort (Table 2). Discrimination of the bivariable models in the validation data proved adequate, with AUCs of 0.75 on POD 3 (95% CI: 0.67–0.82), 0.79 on POD 5 (95% CI: 0.70–0.88) and 0.81 on POD 7 (95%: 0.71–0.90). Calibration of the bivariable models proved adequate in both cohorts (Appendix 5).

Discussion

In this study, we found that CRP and WBC are both useful in the early detection of complications after pancreatoduodenectomy. However, CRP appears to be superior to WBC in the early postoperative phase (i.e. postoperative day 3 and 5). Patients with continuous elevation of CRP levels were consistently at a higher risk of developing major complications and POPF. While, WBC only demonstrated to have a similar diagnostic value on postoperative day 7. Therefore, focus should lie on CRP follow-up rather than WBC when using a biomarker to evaluate the patient's postoperative condition during the first five days after pancreatoduodenectomy.

Biological markers such as CRP are mostly known and used for their value of detecting inflammation.[30] The usefulness of CRP as an early marker of complications has recently been shown during the first 4 days after pancreatoduodenectomy.[14–20] However, in major abdominal surgery, the accuracy of CRP has been shown to significantly increase per day after surgery.[31] Generally, 48–72 h after a single stimulus (e.g. surgical tissue damage) the serum CRP concentration peaks, after which it decreases with a plasma half-life of 19 h if no other stimuli occur.[32] Our observations are in line with this temporal peak.

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Table 1 Patient characteristics of the development and validation cohort

	Development cohort (N = 285)	Validation cohort (N = 202)	P-value
Age in years, median (interquartile range)	68 (58–73)	68 (59–74)	0.288
Male gender, no. (%)	176 (61.8)	110 (54.5)	0.129
Body mass index, median (interquartile range)	24.6 (22.4–27.1)	25.1 (22.7–27.8)	0.173
ASA status 3–4, no. (%)	64 (22.5)	49 (24.2)	0.716
Diabetes Mellitus, no. (%)	71 (24.9)	36 (17.8)	0.080
Smoker, no. (%)	61 (21.4)	28 (13.9)	0.234
Preoperative biliary drainage, no. (%)	180 (63.1)	88 (44.0)	<0.001
Diameter pancreatic duct in millimeters, median (interquartile range)	4 (2–6)	3 (1–6)	0.218
Soft/normal pancreatic texture, no. (%)	90 (52.3)	92 (71.3)	0.001
Pathological diagnoses, no. (%)			
High risk pathology[a]	176 (61.8)	111 (55.0)	0.158
Malignant pathology	219 (76.8)	158 (78.2)	0.804
Pancreatic adenocarcinoma	96 (33.7)	84 (41.6)	0.092
Ampullary carcinoma	45 (15.8)	12 (5.9)	0.001
Cholangiocarcinoma	38 (13.3)	30 (14.8)	0.731
Intraductal papillary mucinous neoplasm (IPMN)	29 (10.1)	20 (10.0)	1
Duodenal carcinoma	19 (6.6)	8 (4.0)	0.278
Pancreatic Neuroendocrine Tumor (pNET)	10 (3.5)	20 (9.9)	0.006
Other pathological diagnoses	48 (16.8)	28 (13.8)	0.401
Classic Whipple procedure, no. (%)	207 (72.6)	88 (43.6)	<0.001
Robot-assisted, no. (%)	27 (9.5)	16 (7.9)	0.665
Blood loss in milliliters, median (interquartile range)	800 (500–1500)	500 (300–100)	<0.001
Length of hospital stay in days, median (interquartile range)	13.5 (9.0–25.0)	14.0 (9.0–21.8)	0.607
Readmissions, no. (%)	31 (10.9)	29 (14.3)	0.250
Time to major complication in days, median (interquartile range)	8 (6–15)	5 (3.0–9.5)	0.003
30-day complications conform Clavien-Dindo, no. (%)			
Grade 0	88 (30.8)	66 (32.7)	0.675
Grade 1-2	119 (42.2)	57 (28.3)	0.002
Grade 3a	61 (21.4)	36 (17.8)	0.390
Grade 3b	10 (3.5)	3 (1.5)	0.280
Grade 4	22 (7.7)	34 (16.8)	0.003
Grade 5	10 (3.5)	6 (3.0)	0.742
Pancreatic fistula, no. (%)[b]	51 (17.9)	35 (17.3)	0.872
Post pancreatectomy haemorrhage, no. (%)[c]	20 (7.0)	18 (8.9)	0.443
Delayed gastric emptying, no. (%)[d]	75 (26.3)	58 (28.7)	0.556
Bile leakage, no. (%)[e]	23 (8.1)	15 (7.4)	0.794
Intra-abdominal infection, no. (%)[f]	78 (27.4)	42 (20.7)	0.098

[a] High risk pathology was defined as any pathological diagnosis other than pancreatic adenocarcinoma and chronic pancreatitis.
[b] Grade B/C fistula according to International Study Group for Pancreatic Surgery criteria.
[c] Grade B/C post pancreatectomy haemorrhage according to International Study Group for Pancreatic Surgery criteria.
[d] Grade B/C post delayed gastric emptying according to International Study Group for Pancreatic Surgery criteria.
[e] Grade B/C bile leakage according to the International Study Group for Liver Surgery criteria.
[f] Intra-abdominal infection was defined as the drainage of pus or a drained fluid collection with a positive culture.

The higher CRP peak observed on POD 3 in patients with major complications suggests that early inflammatory processes, leading to the activation of CRP, precede the clinical manifestation of complications.

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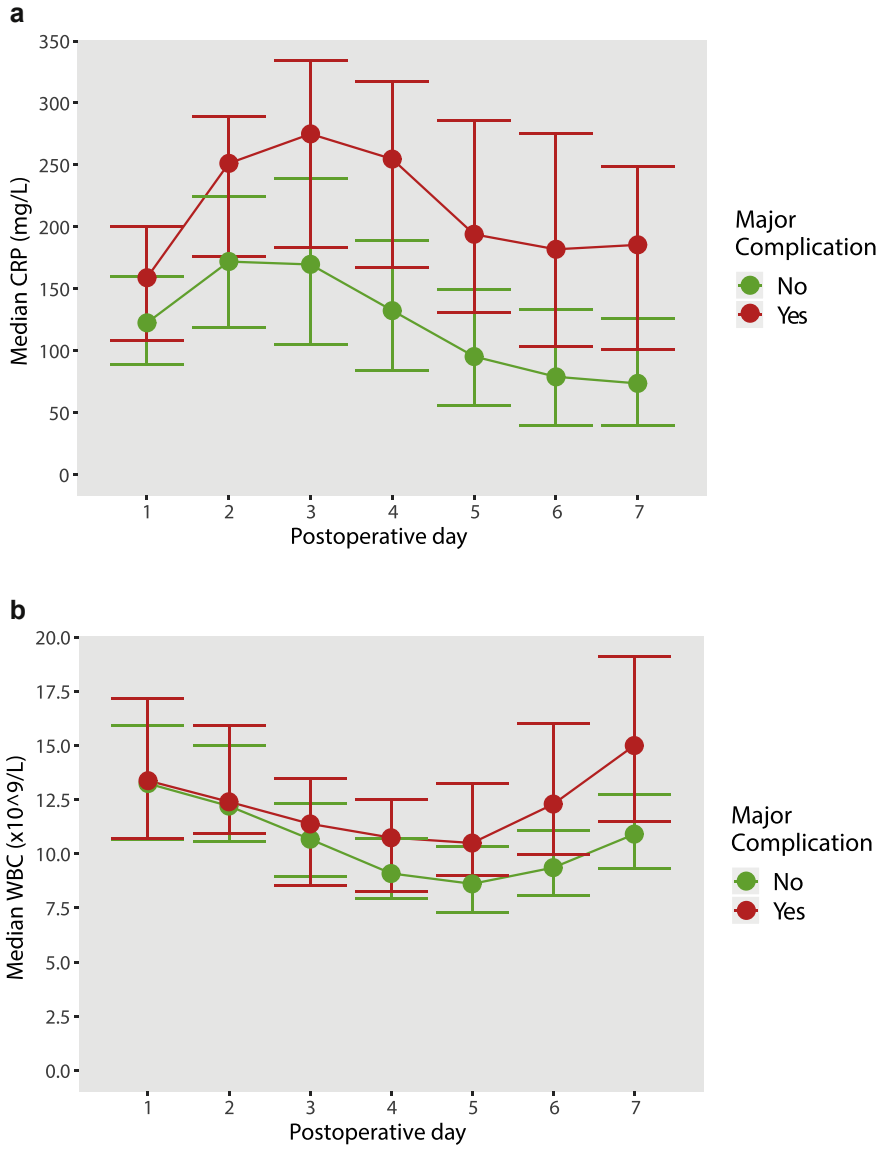

Figure 1 **a**: The median CRP evolution stratified by complications group. **b**: The median WBC evolution stratified by complication group. The median is indicated with the corresponding interquartile range

In addition, recent studies suggest that CRP, besides being a product of inflammation, also aids in bridging the innate and adaptive immune system, by suppressing pro-bacterial processes.[33] Previous studies have shown that major surgeries tend to have transient immunosuppressive effects on the white blood cells, which could account for the delayed immune activation and subsequently less discriminatory ability in the early postoperative phase.[34,35] Our findings are substantiated by previous work in patients after colorectal surgery, which demonstrated no additional value of WBC compared to CRP up to POD 5 in detection inflammatory complications.[36,37] Also, a recent study demonstrated no difference in WBC relating to POPF between POD 1 to POD 5 in 176 patients after pancreatoduodenectomy.[15]

From a historical perspective, although CRP being first discovered in the United States, there was great skepticism initially regarding the clinical utility of CRP. With the discovery that CRP strongly predicts cardiovascular disease in the mid-1990s, it became more widely accepted for this purpose.[30] Yet, in postoperative practice, CRP is still not used much outside of Europe. Interestingly, no cost-effectiveness studies comparing CRP and WBC exist to our knowledge. In the Netherlands, the costs of a CRP measurement is approximately €4.00 compared to €2.00 for a WBC measurement.

Prior studies examining CRP or WBC after pancreatoduodenectomy are mainly limited to POPF.[14,17,38,39] Focus on all major complications may be desired as POPF makes up a mere

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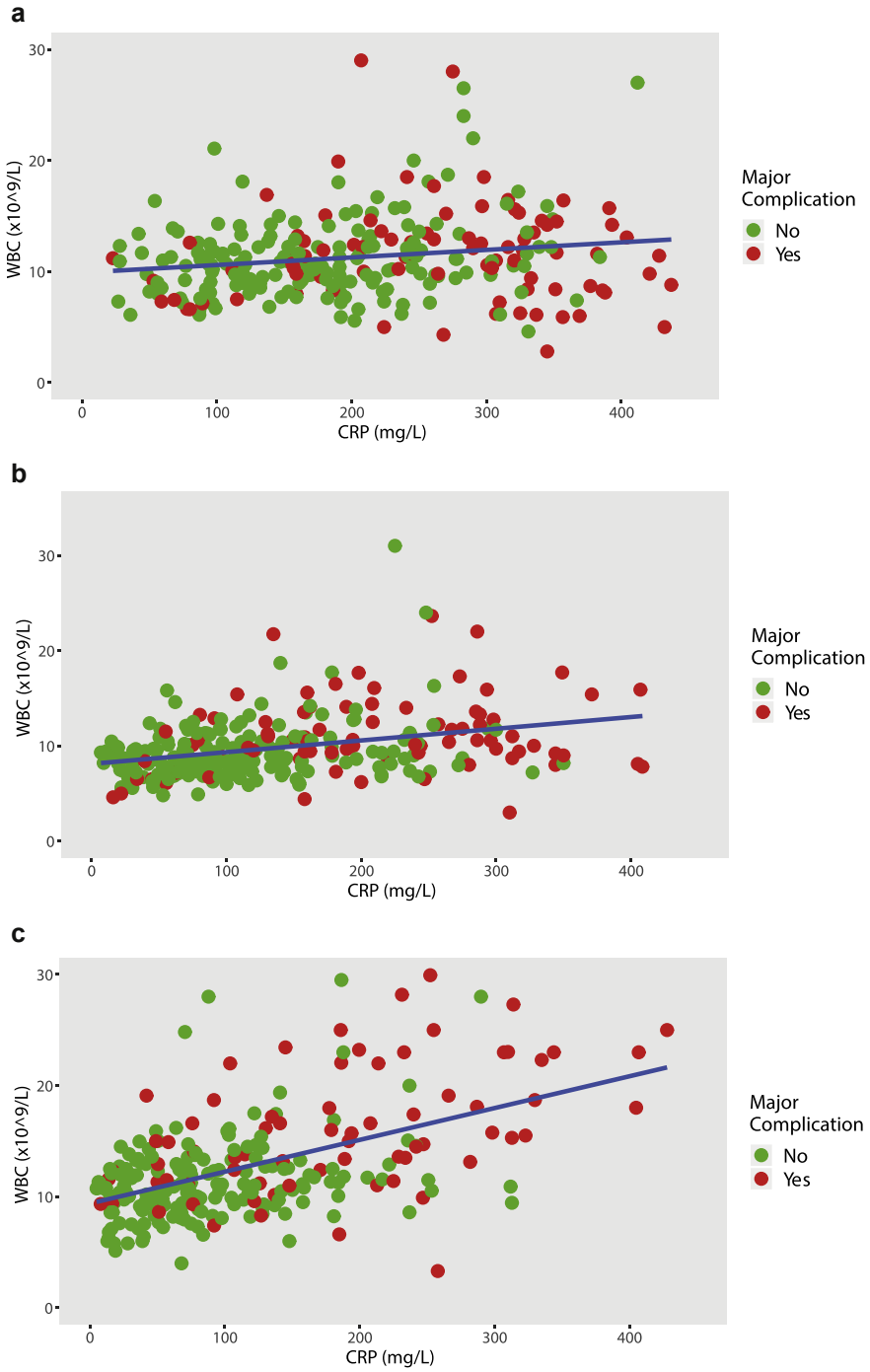

Figure 2 **a**: CRP versus WBC on postoperative day 3. **b**: CRP versus WBC on postoperative day 5. **c**: CRP versus WBC on postoperative day 7

50% of total morbidity in our cohort. Additionally, Prat *et al.* demonstrated that a considerable proportion of POPFs have a latent character and might not be characterized as POPF.[40] Despite the use of broader complication criteria in our study, we found comparable indices of accuracy compared to studies focusing on POPF. Since POPF is a strong driver of most complications it was separately analyzed. We found similar results as those reported in the literature. Recently, Partelli *et al.* found an AUC of 0.80 for CRP on POD 3 in 463 patients after pancreatoduodenectomy.[17] Palani Velu *et al.* demonstrated an AUC of 0.69 for CRP on POD 3 in 230 patients after pancreatoduodenectomy.[14]

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Table 2 Accuracy of CRP and WBC on POD 3, 5 and 7 in detecting major complications and postoperative pancreatic fistula in the development and validation cohort

	The development cohort				The validation cohort			
	Major complications		POPF		Major complications		POPF	
	AUC	95% CI	AUC	95% CI	AUC	95% CI	AUC	95% CI
POD 3								
CRP	0.74	0.67–0.80	0.78	0.71–0.85	0.75	0.67–0.83	0.84	0.77–0.92
WBC	0.54	0.46–0.62	0.56	0.47–0.66	0.56	0.46–0.65	0.54	0.41–0.68
POD 5								
CRP	0.77	0.70–0.83	0.83	0.77–0.89	0.81	0.72–0.90	0.90	0.83–0.96
WBC	0.68	0.60–0.75	0.71	0.63–0.80	0.65	0.54–0.75	0.68	0.54–0.82
POD 7								
CRP	0.77	0.70–0.84	0.85	0.79–0.91	0.79	0.69–0.90	0.85	0.75–0.96
WBC	0.76	0.68–0.83	0.78	0.70–0.87	0.76	0.66–0.85	0.77	0.61–0.93

Abbreviations: POPF = postoperative pancreatic fistula, POD = postoperative day, CRP = c-reactive protein, WBC = white blood cell count, AUC = area-under-the-curve, CI = confidence interval.

Table 3 Diagnostic accuracy of CRP and WBC for detecting major complications at different cut-off values

	Cut-off	Sensitivity	Specificity	Positive predictive value	Negative predictive value	No. of positive patients (%)
POD 3						
CRP	150	0.87	0.42	0.42	0.88	181 (67%)
CRP	200	0.72	0.62	0.47	0.82	132 (49%)
CRP	250	0.57	0.81	0.59	0.80	86 (32%)
POD 5						
CRP	100	0.81	0.52	0.43	0.87	153 (58%)
CRP	150	0.71	0.75	0.56	0.86	104 (40%)
CRP	200	0.47	0.86	0.60	0.79	64 (24%)
WBC	8.0	0.81	0.36	0.36	0.81	184 (70%)
WBC	11	0.40	0.81	0.48	0.75	70 (27%)
WBC	13	0.26	0.93	0.61	0.74	34 (13%)
POD 7						
CRP	100	0.75	0.64	0.47	0.86	116 (47%)
CRP	130	0.65	0.78	0.55	0.84	86 (32%)
CRP	175	0.53	0.88	0.65	0.82	60 (24%)
WBC	10	0.85	0.36	0.36	0.85	173 (70%)
WBC	13	0.66	0.77	0.55	0.85	87 (35%)
WBC	15	0.49	0.90	0.66	0.81	55 (22%)

Abbreviations: CRP = c-reactive protein, WBC = white blood cell count.

"Failure-to-rescue" is an important determinant of mortality after pancreatoduodenectomy, relating to the ineffective management of patients who develop major complications.[10,11] Currently, most complications after pancreaotoduodenectomy are managed with non-operative procedures, such as the administration of antibiotics or the percutaneous drainage of fluid collections.[41] Easily accessible and cheap makers such as CRP and WBC could be useful tools to identify risk groups, especially in case of ambiguity concerning the clinical status of a patient. Vigilance with respect to the development of

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complications warrants a CRP cut-off with a high sensitivity. Notably, the number of false positive results should also be minimized to avoid unnecessary CT-scans. Based on our data, we consider a sensitivity of approximately 70% appropriate. For a patient on POD 5 this is a CRP cut-off of 150 mg/L. Above this threshold, patients have a risk of 56% on major complications, which justifies additional CT-scan examination.This allows for early percutaneous drainage and more liberal administration of antibiotic treatment in case of peri-pancreatic fluid collections.

Noteworthy, reinterventions occurred earlier in the validation cohort than in the development cohort (median POD 8 vs. POD 5, P = 0.003). The incidence and timing of major complications is influenced by the clinical practice, which likely explains the observed difference. Yet, the similar discrimination in both cohorts supports the generalizability of our results despite the difference in clinical practice.

Our study has certain limitations. First, due to the retrospective design we had missing data. However, longitudinal CRP and WBC values could be imputed using a mixed-effects model under the missing-at-random assumption, which is a reliable and established method.[42] An advantage of using a mixed-effects model is that missing longitudinal data can be inferred based on intra-individual measurements and the natural course of a biomarker. Furthermore, pancreatic texture was missing in 40% of the patients. Imputation of this variable was deemed infeasible due to probable violation of the missing-at-random assumption (texture was less likely to be reported if normal/soft). This issue was handled by including postoperative pathology in the multivariable analysis, which serves as an objective, surrogate indicator of pancreatic texture. Second, the occurrence of major complications in this study is related to the clinical practice, which is possibly influenced by CRP and WBC leading to potential verification bias. This could only be circumvented by prospectively blinding clinicians for CRP and WBC values, which is deemed unethical. However, we believe our results are still reliable since the decision to intervene is not solely based on the level of CRP or WBC, rather on the clinical status of the patients in combination with findings on postoperative imaging.

In clinical practice, bedside judgement is an important determinant in postoperative patient management. Therefore, basing decisions solely on CRP or WBC is unlikely, and this also yields substantive groups of patients with an intermediate risk on major complications (Appendix 5). The combination of clinical parameters and CRP or WBC may lead to a more effective risk stratification. Future research will require the development of elaborate models to assess their combined potential. In addition, the effect of early detection and management of complications after pancreatic resection on severe morbidity (relaparotomy, ICU admittance and death) is still unknown. This is currently being investigated in a nationwide stepped-wedge, cluster randomized, superiority trial in the Netherlands (PORSCH trial).

Conclusion

CRP appears to be superior to WBC in the early detection of major complications and postoperative pancreatic fistula after pancreatoduodenectomy. These findings emphasize the clinical value of CRP follow-up during the first days after surgery and the role it may have in decision making.

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Conflicts of interest

None declared.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.hpb.2020.02.005.

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