International Journal of Surgery 17 (2015) 41–47

Contents lists available at ScienceDirect

International Journal of Surgery

journal homepage: www.journal-surgery.net

Original research

Limited utility of inflammatory markers in the early detection of postoperative inflammatory complications after pancreatic resection: Cohort study and meta-analyses

Leonardo Solaini, Bambang T. Atmaja, Jennifer Watt, Prabhu Arumugam, Robert R. Hutchins, Ajit T. Abraham, Satyajit Bhattacharya, Hemant M. Kocher*

Barts and the London HPB Centre, The Royal London Hospital, Barts Health NHS Trust, London, UK

HIGHLIGHTS

- Inflammatory complications after pancreatic surgery are difficult to predict and manage.
- C-reactive protein has the best diagnostic accuracy (74%) in predicting these complications.
- However, CRP on its own it has limited clinical utility.
- Meta-analyses confirmed low accuracy.

ARTICLE INFO

Article history:
Received 21 November 2014
Received in revised form
17 February 2015
Accepted 9 March 2015
Available online 14 March 2015

Keywords:
Pancreas surgery
Inflammatory markers
Pancreatic fistula
Postoperative complications
C-reactive protein
Meta-analysis

ABSTRACT

Purpose: To examine the diagnostic accuracy of systemic inflammatory markers in early prediction of inflammatory postoperative complications (IPC) and clinically-relevant pancreatic fistula (PF).

Methods: Preoperative and postoperative [until postoperative day (POD) 4)] measurements of hemoglobin, white blood cell counts (WBC), neutrophil/lymphocyte ratio (NLR) and C-reactive protein (CRP) were correlated with IPC and PF. Meta-analyses of biochemical predictors were performed.

Results: Ninety-two out of 378 patients developed IPC, PF occurred in 31. Preoperative WBC (OR 1.0001, 95% CI: 1.0001–1.0002, $p = 0.02$), NLR on POD2 (OR 1.05, 95% CI: 1.006–1.1, $p = 0.02$) and CRP on POD4 (OR 1.006, 95% CI: 1.002–1.01, $p = 0.02$) predicted IPC at multivariate analysis. The model including these three variables showed a diagnostic accuracy of 76.8% (sensitivity 20, specificity 97%.14; PPV 71.43, PPN 77.27) and, at logistic regression analysis an OR of 8.5 (95% CI: 2.5–28.6, $p < 0.001$). Only CRP >272 on POD3 (OR 3.32, 95% CI: 1.46–7.52, $p = 0.003$) was associated with PF with a diagnostic accuracy of 74% (sensitivity 54.5, specificity 78.5; PPV 16.88, NPV 94.25). Meta-analyses of available data suggested sensitivity of 75.3% (95% CI 66.7–82.6) and specificity of 75.5% (95% CI 61.3–85.7). However, these studies were significantly heterogeneous.

Conclusions: Readily available, routine tests have limited utility in predicting IPC. Further research is required to develop novel biomarkers to aid management of these patients.

1. Introduction

Morbidity following pancreatic resection is still high. It varies from 30 to 65% and is dependent upon many factors, the chief variables being hospital volume, country and procedure performed [1,2]. Pancreatic fistula following pancreatic resections is the most common, serious inflammatory complication resulting in increased peri-operative mortality rates and, thereby, poorer long-term survival [1,3]. Its early detection is vital in order to commence countermeasures seeking to avoid adverse clinical outcomes. On the other hand, if clinically-relevant pancreatic fistula can reliably be excluded during the early postoperative period, early mobilization and oral feeding with early removal of drains could lead to a shorter hospital stay and reduced treatment costs.

So far, only a few papers have proposed surrogate markers to

* Corresponding author. Barts and the London HPB Centre, The Royal London Hospital, Barts Health NHS Trust, London, E1 1BB, UK.
E-mail address: h.kocher@qmul.ac.uk (H.M. Kocher).

http://dx.doi.org/10.1016/j.ijsu.2015.03.009
1743-9191/

predict the development of pancreatic fistula or other inflammatory complications over the last two decades with variable predictive value. In particular, drain amylase and easily-accessible routine biochemical markers in adjunct to clinical judgment have been the most studied variables [2,4–13].

We investigated the preoperative and postoperative white cell blood count, neutrophils, lymphocytes, serum C-reactive protein (CRP) and albumin alone or in combination to develop a reliable model for early detection of inflammatory postoperative complications and, in particular, pancreatic fistula, following pancreatic resection.

2. Material and methods

All patients referred to the Barts and the London HPB centre (London, UK) undergone pancreatic resection between January 2005 and December 2012 were included in the analysis. Patients' demographics, operative details and postoperative course were prospectively collected at fortnightly audit meeting.

2.1. Definitions and recorded data

Inflammatory complications (IPC) included: pancreatic fistula, leakage of the gastrojejunal, hepaticojejunal or jejuno-jejunal anastomosis, wound infection, pneumonia, *Clostridium difficile* colitis, urinary tract infection, abdominal fluid collection or pleural effusion. Pancreatic fistula was defined and classified according to International Study Group on Pancreatic Fistula definition [14].

Full blood count including Hemoglobin (Hb), white blood cell (WBC) count, lymphocytes and neutrophils counts, serum CRP levels were measured either daily or every other day and recorded preoperatively and during postoperative day (POD) 1–4. Albumin was recorded both preoperatively and on POD1. Biochemical analyses were carried out using Cobas 8000 module c702 (Roche, Basel, Switzerland)). Full blood counts were carried out using hematology automated analyzer xe2100 (Sysmex, Kobe, Japan).

CRP >5 mg/L was considered elevated. WBC count in the range from 4×10^6/ml to 9.8×10^6/ml was considered normal. Perioperative neutrophil to lymphocyte ratio (NLR) was calculated for all patients.

2.2. Procedure and peri-operative clinical management

Thromboprophylaxis was given according to hospital protocol; all patients received anti-thromoboembolism compression stockings from the time of admission to hospital and were given low molecular weight heparin subcutaneously from the day of operation once daily until discharge. Octreotide was given subcutaneously at a dose of 100 mcg 8 hourly with the first dose given at induction of anesthesia. Broad spectrum prophylactic antibiotic cover was given at induction of anesthesia and for two postoperative doses according to hospital protocol.

Whipple's (PD) or pylorus-preserving (PPPD) duodenopancreatectomy was performed as standard procedure for either pancreatic head or peri-ampullary masses. Distal pancreatectomy with or without splenectomy (DP) was performed for masses in the body or the tail of the pancreas. In these latter cases Wirsung's duct, when detected, was always independently sutured. A drain was placed close to the pancreaticojejunostomy in case of PD or adjacent to the pancreatic stump in case of DP. They were removed on POD5 when no clinical signs of abdominal collections or PF (day 5 fluid amylase <3 times upper limit of normal of our laboratory range) were noted and were guided by non-elevated drain fluid amylase.

2.3. Statistical analysis

Preoperative and postoperative laboratory results from patients who developed IPC (or clinically relevant PF only) or non-IPC were independently compared with those from patients who had an uneventful postoperative course. All not-normally distributed continuous variables (D'agostino-Pearson test) were presented as median and inter-quartile range (IQR). Mann Whitney's U-test was used to compare continuous variables between the groups. Fisher exact test was used to compare categorical variables. Logistic regression analysis in a stepwise manner was carried out to identify independent predictor variables of IPC and grade B and C PF. When identified as predictors, the selected variables were assessed by receiver operating characteristic (ROC) analysis. Then, according to the optimal cut-off value a model including all the significant variables was created to evaluate its accuracy in diagnosing IPC or clinically relevant PF. Odds ratio (OR) and positive (PPV) and negative (NPV) predictive values were calculated for the constructed diagnostic models.

All tests were two-sided and a p-value of <0.05 was considered significant. Statistical analysis was performed with statistical software for biomedical research (MedCalc® Software for Windows; version 10.2.0.0).

2.4. Meta-analyses

A literature search of studies assessing the diagnostic accuracy of CRP on POD3 for PF was performed using Medline and Scopus database. The following Mesh search headings were used: “pancreatic resection AND C-reactive protein”, “duodenopancreatectomy AND C-reactive protein” and “pancreatic fistula AND C-reactive protein”. The “related articles” function was used to broaden the search, as well as performing the search using truncated search terms utilizing the wildcard (‘*’) character. Only papers in English were considered and the date of the last search was February 14, 2014. Data were extracted on author, date of publication, institution, study design, patient demographics, and technical aspects of the studies, independently by 2 reviewers (L.S. and H.M.K.). Papers where it was possible to extract the total number of patients, pancreatic fistulas and specificity and sensitivity of CRP on POD3 in detecting PF were included. In papers where this data could not be extracted authors were contacted for further information. A two-by-two table for test outcome and the development of pancreatic fistula was built for each study. Cohran's Q and I^2 were used to verify heterogeneity and, if present, the random effects model was preferred. Freeman-Tukey transformation was used to calculate the weighted summary sensitivity and specificity under the random effects model.

3. Results

Baseline characteristics of the 378 patients (pancreatic cancer ($n = 148$), duodenal cancer ($n = 25$), ampullary cancer ($n = 39$), cholangiocarcinoma ($n = 52$), pancreatic cystic tumors ($n = 29$) and other diagnoses ($n = 85$)) who underwent pancreatic resection are summarized in Table 1. Overall postoperative morbidity rate was 36.9%, 30-day mortality was 4.2% and in-hospital mortality rate was 5%. Six in-hospital (31%) deaths were due to PF while 5 (26%) deaths were due to severe postoperative bleeding. Inflammatory complications ($n = 92$) are listed in Table 2. In-hospital stay was significantly longer for those patients who developed either postoperative inflammatory (median 21.5 days; IQR 14–35.2) or non-inflammatory (median 17; IQR 13–24) complications than those who had an uneventful postoperative course (median 11; IQR 9–15, $p < 0.001$) (Table 1). Patients who had no postoperative