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Distinct risk factors for early and late blood transfusion following pancreaticoduodenectomy

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ABSTRACT

Background: The International Study Group of Pancreatic Surgery (ISGPS) has defined two periods of postpancreatectomy hemorrhage, early (<24 h) and late (>24 h). A previously published Blood Usage Risk Score (BURS) aimed to predict early and late blood transfusion. The primary aim of this study was to define risk factors for early and late blood transfusion after pancreaticoduodenectomy. Secondary aims were to assess the predictive accuracy of the BURS.

Methods: In this retrospective observational study, multivariable analyses were used to identify independent risk factors for both early and late blood transfusion. The predictive ability of the BURS was then assessed using a receiver operating characteristic (ROC) curve analysis.

Results: Among 628 patients, 99 (15.8%) and 144 (22.9%) received early and late blood transfusion, respectively. Risk factors for blood transfusion differed between early and late periods. Preoperative anemia and venous resection were associated with early blood transfusion whilst Whipple's resection (as opposed to pylorus preserving pancreaticoduodenectomy), lack of biliary stent and a narrow pancreatic duct were predictors of late blood transfusion. The BURS was significantly predictive of early blood transfusion, albeit with a modest degree of accuracy (AUROC: 0.700, $P < 0.001$), but not of late blood transfusion (AUROC: 0.525, $P = 0.360$). Late blood transfusion was independently associated with increasing severity of postoperative pancreatic fistula (POPF) (OR: 1.85, 3.18 and 9.97 for biochemical, types B and C POPF, respectively, relative to no POPF).

Conclusions: Two largely different sets of variables are related to early and late blood transfusion following pancreaticoduodenectomy. The BURS was significantly associated with early, albeit with modest predictive accuracy, but not late blood transfusion. An understanding of POPF risk allows assessment of the need for late blood transfusion.

Introduction

Pancreaticoduodenectomy is a major operation with significant morbidity [1–3]. Transfusion of packed red blood cells (PRC) is common. Recent studies [4,5] showed that around half of patients undergoing pancreaticoduodenectomy will receive blood transfusion. Following hemorrhage, PRC transfusion confers benefit by maintaining tissue perfusion, delivery of oxygen to tissues and hemodynamic stability. PRC transfusion therefore aids recovery of patients undergoing major surgery, particularly in the event of postoperative complications [6,7]. However, PRC transfusion has been shown to correlate with poor clinical outcomes in pancreatic surgery, including increased cancer recurrence, increased risk of postoperative pancreatic fistula (POPF), and immunosuppression [8–12]. Some studies [13–15] have shown that restricting PRC transfusion may improve clinical outcomes and lead to potential economic savings through decreased resource consumption.

Hemorrhage after pancreaticoduodenectomy has been defined by the International Study Group of Pancreatic Surgery (ISGPS) [16] as early when it occurs within 24 h of surgery or late after this point.

A recently published nomogram from North America predicts perioperative blood transfusion in major hepatopancreaticobiliary and colorectal surgery [4]. The North American Blood Usage Risk Score (BURS) uses age, gender, race, preoperative hemoglobin,

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preoperative international normalized ratio (INR), Charlson comorbidity index and type of procedure to calculate the risk of PRC use.

It is unclear whether the BURS is useful in pancreaticoduodenectomy, as BURS was developed among patients undergoing a variety of resections. Furthermore, BURS does not differentiate between the need for early or late blood transfusion. Thus, the primary aim of this study was to define risk factors for early and late blood transfusion after pancreaticoduodenectomy. Secondary aims were to assess the predictive accuracy of the BURS among a patient cohort exclusively consisting of those undergoing pancreaticoduodenectomy, and to attempt to generate a new score that may improve the accuracy of the BURS in this cohort.

Methods

The study was conducted and the manuscript prepared in line with guidance set out in the STROBE statement [17]. Institutional audit approval was granted.

Data collection

This was an analysis of consecutive patients undergoing pancreaticoduodenectomy at the Queen Elizabeth Hospital, Birmingham, UK, between January 2007 and December 2015. No patients were excluded. This surgical service was provided by six dedicated hepatobiliary and pancreatic surgeons, who provides support to referring hospitals with a population exceeding 4 million inhabitants. Interventional radiology support was available at all hours.

Data were collected prospectively, with regards to operative variables, outcomes and postoperative complications (stratified by Clavien–Dindo grade) and recorded in an institutional database. Data were collected by a dedicated data manager (Mr. Chris Coldham). Data describing follow-up were obtained from electronic records, case notes or discussion with the patient's general practitioner. Perioperative blood use was identified from a hospital database and all units of PRC transfused within 24 h and 30 d of surgery were recorded.

In general, patients with a hemoglobin above 80 g/L (2007–2012) or above 70 g/L (2013–2015) did not undergo blood transfusion. Blood transfusion was indicated (i) among patients with anemia (hemoglobin $<$ 100 g/L) and symptomatic with this, such as dyspnoea and/or tachycardia, (ii) if the hemoglobin was under 80 g/L (2007–2012) or 70 g/L (2013–2015), (iii) if there were peri- or postoperative hemorrhage with cardiovascular compromise. The decision to give blood products was largely controlled by anesthetists during surgery and by the surgical team following surgery.

Statistical analysis

A range of factors were compared between the patients that did and did not require PRC within 24 h of surgery, in order to identify other potential predictors of PRC usage. Continuous variables that were found to be normally distributed were reported as mean ± SD and compared between groups using independent samples *t* tests, with median and interquartile range (IQR) and Mann–Whitney tests used otherwise. Ordinal variables were compared using Kendall's tau, with Fisher's exact test used for nominal variables.

Multivariable binary logistic regression models were then produced, in order to identify independent predictors of PRC usage. A forwards stepwise approach was used to select variables for inclusion. Only the main effects of factors were considered, with no interactions included in the model. This was due to the fact that a large number of factors were analyzed, hence considering all possible interactions may have led to an increased false positive rate, as well as potential overfitting of the model. As regression is based on complete cases analysis, variables with >25% missing data were not considered for inclusion in the initial model, in order to maximize the available sample size. A second model was then produced, considering only those factors found to be significant independent predictors in the initial model, in order to further increase the available sample size. As a sensitivity analysis, the factors initially excluded due to missing data were considered for inclusion alongside the factors in the final model, to ensure that they were not significant independent predictor of the outcome. The final model was then converted into a risk score, with predictive accuracy assessed using receiver operating characteristic (ROC) curves.

The performance of the BURS for predicting PRC use within 24 h of surgery was assessed using ROC curves. For the subgroup of patients that required PRC, associations between the score and the number of units of PRC used were assessed using Spearman's correlation coefficients. A binary logistic regression model was then produced, with the nomogram score as a covariate, in order to update the predicted values produced by the score, based on this cohort. The area under the ROC curve (AUROC) for the BURS was then compared to our model using the method proposed by DeLong et al. [18].

All analyses were then repeated considering PRC usage on days 1–30 as the outcome of interest, and the predictive accuracy of the BURS has also been calculated for late use of PRC.

All analyses were performed using IBM SPSS 22 (IBM Corp. Armonk, NY) and STATA 14 (College Station, TX: StataCorp LP). Cases with missing data were excluded on a per analysis basis, and $P < 0.05$ was considered statistically significant.

Table 1
Patient demographics.

Variables	*n*	Value
Age (yr)	628	67.7 (60.8–73.5)
Male	628	342 (54.5%)
BMI (kg/m^2)	616	25.9 ± 5.2
Ethnicity	628	
White		589 (93.8%)
Black		3 (0.5%)
Asian		22 (3.5%)
Other		14 (2.2%)
Charlson comorbidity index	628	
0–3		588 (93.6%)
>3		40 (6.4%)
Preoperative biliary stent	620	361 (58.2%)
Preoperative hemoglobin (g/dL)	628	11.6 ± 1.9
Preoperative INR	628	1.1 (1.0–1.2)
Venous resection	555	91 (16.4%)
Transfusion of PRC	628	
<24 h postoperative		99 (15.8%)
1–30 d postoperative		144 (22.9%)
Postpancreatectomy hemorrhage	628	34 (5.4%)
Grade A		4 (0.6%)
Grade B		17 (2.7%)
Grade C		13 (2.1%)
Postoperative pancreatic fistula	562	134 (23.8%)
Biochemical fistula		52 (9.3%)
Grade B		52 (9.3%)
Grade C		30 (5.3%)
Length of hospital stay (d)	628	10.0 (8.0–15.0)
30-day mortality	619	26 (4.2%)

Data reported as *n* (%), mean ± SD or median (IQR), as applicable.

Results

Patient demographics

A total of 628 patients underwent pancreaticoduodenectomy, with a median age of 68 years (IQR: 61–73), and of whom 54%