Perioperative factors impacting intensive care outcomes following Whipple procedure: A retrospective study

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ABSTRACT

Background and Aims: Whipple procedure is associated with perhaps the most perioperative morbidity and mortality amongst surgical procedures. Current data regarding their ICU profile and outcomes are lacking. Thus, in the present study, we aimed to determine perioperative factors affecting patient-centred outcomes following the Whipple procedure. Methods: In a cohort of patients undergoing pylorus-sparing pancreaticoduodenectomies, we strove to determine perioperative variables that may impact outcomes. Unfavourable outcomes (composite of mortality, prolonged ICU stay of more than 14 days or ICU readmission) of patients who underwent the procedure were recorded and logistic regressions analysis of significant variables conducted. Results: Around 68 patients recruited over a 20-month period which included 57 males (83.8%); mean age was 53.4(±11.2) with mean acute physiology and chronic health evaluation (APACHE) II score 12.5 (±6.1). Nineteen patients remained intubated at the end of procedures (27.9%). Median ICU stay was 2 days (IQR 2–3). Unfavourable ICU outcomes were 14 in number (20.6%) and 2 (2.9%) hospital deaths occurred. Pulmonary complications occurred in 12 patients (17.7%) and non-pulmonary complications occurred in 41 patients (60.3%). In a multiple logistic regression analysis, the APACHE score 1.34 (1.09–1.64) and pulmonary complications 17.3 (2.1–145) were variables that were identified as predictors of unfavourable outcomes. Conclusion: The APACHE II score may reliably predict adverse outcomes following Whipple procedure. Although non-pulmonary complications are common, pulmonary complications in these patients adversely impact patient outcomes.

Key words: Intensive care, perioperative complications, Whipple procedure

INTRODUCTION

Whipple procedure performed for pancreatic malignancies presents an audacious task before the surgeons, anaesthesiologists and intensivists as the procedure is technically demanding and perioperative pathophysiological changes associated with breach in the anatomy of the gastrointestinal tract, systemic inflammatory response, fluid shifts as well as preoperative factors such as age, cachexia, biliary obstruction and cholangitis that often impact(s) post-operative morbidity and mortality[1,2]

Factors associated with adverse outcomes related to pancreatic surgery in literature include preoperative irreversible factors such as age, comorbid disease and tumour behaviour, nutritional status, obstructive jaundice, cholangitis and need for stent, intraoperative factors such as surgical technique, stress response, blood loss, duration of surgery and fluid administration[2-7]

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as well as post-operative factors such as development of pulmonary and non-pulmonary complications.[8-11] We hypothesise that some of these variables could be more predictive of outcomes than others in our patient population. However, data related to outcomes from our country is scarce. Therefore, in a cohort of patients admitted to the intensive care unit (ICU) at a tertiary level centre in India, we aimed to determine perioperative factors that may be associated with unfavourable ICU outcomes.

**METHODS**

This is a retrospective study of a cohort of patients undergoing Whipple procedure admitted to ICU over a 20-month period. The setting of the study was a 19-bedded tertiary level ICU and 9-bedded high dependency unit. We made a priori set-up following definitions related to the study before retrospective data collection.

Whipple procedure: Open pancreaticoduodenectomy (PD) performed for the head of pancreas or periampullary carcinoma malignancy (pylorus sparing techniques were used). Conventional pancreaticoduodenectomy involves removal of the pancreatic head along with duodenum, first 15 cm of the jejunum, common bile duct as well as the gallbladder and partial gastrectomy. Although there are no controlled studies to confer superiority, pylorus sparing pancreaticoduodenectomy has become the preferred operation as it is less radical with preservation of the gastric antrum, pylorus and proximal duodenum. Thus, perhaps reducing biliary reflux and post-operative dumping phenomenon.[12] For all cases, general anaesthesia with inhalational anaesthetics was used with or without epidural along with administration of 6–8 mL/kg tidal volumes and positive end-expiratory pressure (PEEP) of 5 cm of H₂O. Use of opiates, muscle relaxants, intravenous fluids and vasopressors were left to the discretion of the anaesthesiologist as well as the need for extubation at the end of surgery. The surgical team performing the procedure were from a team specialising in hepatobiliary surgery with chief surgeons recording numerous years of experience at this high volume academic centre.

Some other definitions of relevance include the following:

Tumour grade: High-grade, if stage more than T2 or poorly differentiated.

Preoperative Jaundice: Clinical features of jaundice or icterus with laboratory confirmation of a total Bilirubin >2 mg/dL.

Preoperative cholangitis: Clinical features consistent with an infection arising from the biliary tract such as jaundice, abdominal pain and fever.

(The above definitions relate to a time period during the evaluation of the malignancy or optimisation for surgery).

Intraoperative Fluid use: Total volume of crystalloid and or colloid administered during the procedure.

Estimated blood loss: Blood loss as estimated by the anaesthesiologist assigned to the procedure.

Perioperative red cell transfusion requirement: Number of packed red cells transfused within 24 h of the surgery.

Mean P/F ratio: Ratio of the partial pressure of oxygen (PaO₂) to fraction of inspired oxygen (FiO₂) on samples taken during the procedure.

Pulmonary Complication (PC): Clinical features of hypoxaemic (PaO₂/FiO₂ ratio < 300) and or hypercapnic respiratory failure (PCO₂ > 45 mmHg) encountered post-operatively requiring mechanical ventilation.

Non-Pulmonary Complication (NPC): Post-operative complication that develops directly or indirectly as a result of surgical procedure e.g., pancreatic fistulae, anastomotic leak/collections/intra-abdominal abscesses, significant post-operative bleeding requiring transfusions or radiological or surgical intervention, wound dehiscence, bedsores, deep vein thrombosis (DVT) etc.

ICU free days: Twenty-eight minus days in ICU. The number of ICU free days equals 0 in death.

Unfavourable outcomes: Composite of mortality, prolonged ICU stay of more than 14 days or ICU readmission (which is associated with adverse outcomes at 90 days).[4,13] This was the primary outcome of interest.

Data collection was done with a review of electronic medical records, ICU database as well as patient notes. The institutional review board for research and ethics approved the study design before the
commencement of data collection (IRB no: 11546) on September 26th 2018. Informed consent was waived for the study.

Descriptive statistics were expressed as mean and SD/median with IQR for continuous variables depending on the normality. Categorical data were expressed as frequency along with percentage. The continuous variable among the favourable and unfavourable outcome using independent t-test/Mann-Whitney U test depending on the normality and the categorical variables were compared using Chi-square statistics. Logistic regression was performed to determine the predictors of outcome amongst clinically and statistically significant variables. A priori sample size was not calculated. Cases were recruited every month and at the end of 20 months, Post-op pulmonary complications were taken as the main exposure and power analysis was done to check the adequacy of sample size. The multiple regression \( r^2 \), which was 0.3758 and the adjusted significance level of POPCs, which was 0.012. With the available information, the calculated power was 96.8%. Thus, it was concluded that the sample size of the study was adequate. All the statistical analysis was done using STATA IC/15.1 and the power analysis is carried out using G-Power analysis software.

**RESULTS**

A total of 68 patients were recruited during the study period extending from April 2016 to November 2017. The clinical profile of patients is displayed in Table 1. Most patients were males with jaundice and/or cholangitis. In fact, stent placement was required in 48% of patients prior to surgery (median stent duration was 62 days [32–100 days]). Most patients had high-grade tumours (76.5% of all tumours) with an average; 47 were American Society of Anaesthesiologists (ASA) 2 (69.1) and duration of surgery being 9.9 (±2.3) h with an estimated blood loss of 350 mL (interquartile range 300–650 mL). Forty-one (60.3%) patients had at least one post-op surgical (Non-pulmonary) complication [Table 2] of which seven required re-exploration; five patients for infections and two for bleeding. Twelve (17.7%) PCs were recorded for which mechanical ventilation was administered (related to acute respiratory distress syndrome [ARDS], fluid overload, atelectasis, or pneumonia) [Table 2]. These were diagnosed through clinical, radiological (ultrasound/echocardiography/X-ray) means and microbiological information.

### Table 1: Clinical profile of patients in the cohort (n=68)

| Clinical parameters                        | n (%) Or Mean (±SD/Median [IQR]) |
|-------------------------------------------|----------------------------------|
| Age                                       | 53.4 (+11.2)                     |
| Male                                      | 57 (83.8%)                       |
| APACHE                                    | 12.5 (+6.1)                      |
| Previous Cholangitis                      | 41 (60.3%)                       |
| Previous Jaundice                         | 58 (85.3%)                       |
| Preoperative stent                        | 33 (48.5%)                       |
| Median stent days                         | 63 (36–100)                      |
| High-grade Tumour                         | 52 (76.5%)                       |
| Duration of surgery in hours              | 9.9 (±2.3)                       |
| Epidual use                               | 58 (85.3%)                       |
| Estimated blood loss in mL                | 350 (300–650)                    |
| Intraoperative Fluid in L                 | 4.1 (±1.0)                       |
| Blood transfusion required periopeatively | 20 (29.4)                        |
| Vasopressor Use                           | 31 (45.6%)                       |
| Hyperlactataemia >2 mmol/L                | 33/69 (48.5%)                    |
| Mean P/F ratio in the first 24 h          | 316 (±87.3)                      |
| Pulmonary Complications                   | 12 (17.7%)                       |
| Non-Pulmonary Complications*              | 41 (60.3%)                       |
| Duration of ICU free stay‡                | 22.7 (7.6)                       |
| Death in Hospital                         | 2 (2.9%)                         |
| Unfavourable outcomes†                    | 14 (20.6%)                       |

*Pancreatic fistula, bleeding, abdominal collections, anastomotic leaks, wound dehiscence, DVTs. †ICU 28 days minus ICU stay; ICU free stay=0 if a patient dies. ‡Death/ICU readmission/Prolonged ICU stay (>2 weeks)

In order of frequency, NPCs complications included pancreatic fistulae [\( N = 20 \) (29.4%)], anastomotic leak/collections or intra-abdominal abscesses [\( N = 16 \) (23.5%)], significant bleeding [\( N = 8 \) (11.7%)] and others [\( N = 6 \) (8.8%)] such as wound dehiscence, bedsores or DVTs [Table 3]. One patient had atrial fibrillation requiring antiarrhythmic therapy. Patients on occasion had a combination of the aforementioned complications. A total of 9 patients required radiological procedures and 7 patients had unplanned reoperations related to one or more of these complications.

Unfavourable ICU outcomes were 14 in number (20.6%) and 2 (2.9%) hospital deaths occurred.

In a univariate and multivariate analysis [Tables 3 and 4, respectively] the APACHE II score (performed within 24 h of ICU admission) and pulmonary complications were variables that were identified as predictors.
of adverse outcomes (amongst other statistically significant variables from univariate analysis as well as clinically significant variables were assessed; authors felt ‘previous cholangitis’ was a clinical variable that was worthy of logistic analysis).

**DISCUSSION**

In a concurrent cohort of patients, who underwent PDs and were admitted to our ICU or HDU, we strived

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Table 3: Variables associated with unfavourable outcomes

| Variable                          | Favourable (Total number=54) | Unfavourable (Total number=14) | P (significance <0.05) |
|-----------------------------------|------------------------------|--------------------------------|------------------------|
| Age-Mean (± SD)                   | 52.5 (± 10.6)                | 57.1 (± 8.9)                   | 0.19                   |
| Gender (Male)                     | 45                           | 12                             | 0.82                   |
| (Female)                          | 9                            | 2                              |                        |
| Tumour Grade                      |                              |                                |                        |
| High-grade Tumour                 | 41                           | 11                             | 0.84                   |
| Low Grade                         | 13                           | 3                              |                        |
| Previous Cholangitis              |                              |                                |                        |
| Present                           | 35                           | 6                              | 0.14                   |
| No cholangitis                    | 19                           | 8                              |                        |
| Previous Jaundice                 |                              |                                |                        |
| Present                           | 47                           | 11                             | 0.93                   |
| No Jaundice                       | 8                            | 2                              |                        |
| Pre-op Stent                      |                              |                                |                        |
| Present                           | 26                           | 7                              | 0.90                   |
| No stent                          | 28                           | 7                              |                        |
| Stent days-Median (IQR)           | 75 (54-180)                  | 59.5 (35-100)                  | 0.4                    |
| Pre-op Albumin                    | 4.0                          | 3.7                            | 0.13                   |
| ASA 1                             | 18                           | 3                              | 0.73                   |
| ASA 2                             | 36                           | 11                             | 0.50                   |
| Duration of surgery in hours - Mean (± SD) | 10.0 (2.5)         | 9.8 (1.1)                      |                        |
| Epidural                          |                              |                                |                        |
| Used                              | 49                           | 9                              | 0.01*                  |
| No Epidural                       | 5                            | 5                              |                        |
| Estimated blood loss in mL - [Median (± IQR)] | 400 (300-700)           | 300 (300-600)                  | 0.60                   |
| Intraoperative Fluid in L - Mean (± SD) | 4.0 (±1.0)                           | 4.3 (±1.0)                      | 0.27                   |
| Blood transfusion required perioperatively (first 24 h) [n=20] | 14                          | 6                              | 0.34                   |
| Vasopressors                      |                              |                                |                        |
| Used                              | 25                           | 6                              | 0.81                   |
| No Vasopressors                   | 29                           | 8                              |                        |
| Hyperlactataemia                  |                              |                                |                        |
| Present                           | 25                           | 8                              | 0.47                   |
| Absent                            | 29                           | 6                              |                        |
| Immediate Post op ventilation required | 11                        | 2                              | 0.28                   |
| APACHE - Mean (±SD)               | 11.1 (±5.2)                  | 18.4 (±5.7)                    | <0.01                  |
| Mean P/F ratio in 24 h - Mean (± SD) | 317.3(±80.5)                  | 310.7 (± 118.9)                | 0.4                    |
| Pulmonary complications           |                              |                                |                        |
| Present                           | 5                            | 7                              | <0.01                  |
| Absent                            | 49                           | 7                              |                        |
| Non-Pulmonary complications       |                              |                                |                        |
| Present                           | 29                           | 12                             | 0.03                   |
| Absent                            | 25                           | 2                              |                        |

*Had the favourable outcome. ASA – American Society of Anaesthesiologists

Table 4: Multiple Logistic regression analysis of significant variables

| Variable                  | Odds ratio (95% CI) | P (significance <0.05) |
|---------------------------|---------------------|------------------------|
| Age                       | 0.94 (0.86-1.03)    | 0.21                   |
| Pre-op Cholangitis        | 0.43 (0.07-2.57)    | 0.43                   |
| APACHE II score           | 1.34 (1.09-1.64)    | 0.01                   |
| Pulmonary complications   | 17.3 (2.1-145)      | 0.01                   |
| Non-pulmonary complications | 4.3 (0.66-28.3)     | 0.13                   |
| Epidural                  | 1.96 (0.14-27.43)   | 0.62                   |
to look at factors affecting patient-oriented outcomes. Our adverse outcome rate was 20.6% and the hospital mortality rate was 2.9%.

We found that with multiple logistic regression analysis, the APACHE II score and presence of pulmonary complications requiring invasive ventilation were independent predictors of adverse outcomes.

The APACHE II score, a well-studied ubiquitous score that is a conglomeration of chronic health factors and acute physiological derangements (taken within the first 24 h in ICU), was a predictor of adverse outcomes in our cohort of patients undergoing pancreaticoduodenectomy. The score thus underlines the role of early organ failure in the ultimate outcome of patients. The score may also be useful in predicting patients with a high risk of death or long ICU stay or ICU readmission. This may facilitate appropriate therapy, triage and disposition of patients from the ICU.

The utility of APACHE II scoring in the field of hepatobiliary procedures as a prognostic tool has been supported by studies related to liver transplant,[14-16] liver resection[17,18] and portosystemic shunt procedures[19]

We also found pulmonary complications impacted outcomes, not unlike other studies.[4] Twelve patients (17.6%) had post-operative pulmonary complications requiring mechanical ventilation secondary to ARDS, fluid overload, atelectasis or pneumonia. The findings, however, should be taken in light of broad confidence intervals reflecting small sample size. However, these findings stress the need for intraoperative and post-operative lung protection with appropriate manoeuvres (such as recruitment and positioning), appropriate application of PEEP, FiO2, plateau pressure, driving pressure and tidal volumes. In our study, fluid administration did not impact on outcomes (possibly as it was universally judicious); however, other studies have underlined its importance.[5]

Common non-pulmonary complications included pancreatic fistulae (N = 20 [29.4%]), anastomotic leak/collections or intra-abdominal abscesses (N = 16 [23.5%]), significant bleeding (N = 8[11.7%]) requiring post-op blood transfusion or surgical/radiological intervention. These complications did not significantly impact outcomes adversely.

Data from the west indicate the immediate post-operative mortality for PDs to be about 2–5%.[10,20,21] and morbidity to be 12.1–60%. [5,10,20]

Regarding studies from closer to the Indian subcontinent, a Thai study depicted a similar rate of morbidity but higher perioperative mortality at 23.08%.[22]

Outcomes from two other studies done in Indian centres have a similar rate of adverse outcomes and mortality; however, classifications of morbidity and complications were difficult to compare. One of these, a negative randomised control trial concerning the utility of octreotide in reducing pancreatic fistula rate depicts a mortality rate of 1.8% and a morbidity rate of 18–30%. Respiratory complications in this study were about 14% compared to about 17% in ours. Non-pulmonary complications including wound infections, intra-abdominal collections occurred in 32 of 109 patients (29.4%).[23] The only other study from an Indian centre was a small-randomised trial investigating laparoscopic technique versus an open technique. The open group, which had 32 patients, had a complication rate of 31.3% (the laparoscopic group had similar outcomes). Each arm recorded one death (overall mortality of 3%).[24]

Limitations of our study include the small sample size reflected by relatively wide confidence intervals in our findings plus the observational nature of our study from a single centre. Our findings, however, are useful to the domains of hepatobiliary surgery, anaesthesia, intensive care as well as perioperative medicine and builds upon findings from other high-volume centres in an attempt to achieve better intensive care outcomes.[25]

**CONCLUSION**

The APACHE II score may prove useful in predicting death, long ICU stay or ICU readmission following pancreaticoduodenectomy. Non-pulmonary complications are common but pulmonary complications, in particular, adversely impact patient outcomes.

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**Conflicts of interest**

There are no conflicts of interest.
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