

ASSESSMENT OF RISK FACTORS FOR COMPLICATIONS FOLLOWING WHIPPLE OPERATION

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Abstract

Background: Studies on the risk factors for complications following pancreaticoduodenectomy (Whipple operation) are rare and there is no consensus regarding the role of different perioperative factors in the development of postoperative complications. The objective of this study is to determine the predictive risk factors for major complications for this surgery based on the definition by the international study group. **Materials and Methods:** Between February 2007 to April 2011, data from 57 consecutive patients who underwent a PD in the Jagjivanram Railway Hospital were collected. Medical records and specific charts from surgical procedures, histopathology reports, and intensive care units were continually scrutinized and all data's collected. 12 variables are taken for univariate analysis using chi-square test for two main complications of Whipple operation ie, pancreatic leak and septic complications and factors which were found to be significant are taken for multivariate analysis using binary logistic regression method to assess the independent risk factors. **Result:** Among 57 patients undergoing PD, 32 (56.1%) experienced at least one complication. Among these 20 patients had pancreatic leak (34%) and 31 patient had septic complications which include minor wound infection to major sepsis. 7 patients had grade C pancreatic fistula. mortality 4 patients (7%). Cause of death 2 uncontrolled sepsis following PF, one pneumonia and one bleed. Univariate analysis on pancreatic fistula showed statistically significant association with elderly patient (p. Value-.0035), Hypoalbuminemia (p value-.0011, multiple blood transfusion (p value.027), smaller pancreatic duct (p value.0076) and soft pancreas (p value.011). **Conclusion:** Pancreatic head resection for neoplastic lesions of the pancreatic head is still a major surgical procedure with significant morbidity but decreasing mortality. In our institute we could achieve an acceptable morbidity and low mortality in these group of patients.

INTRODUCTION

Pancreaticoduodenectomy (PD) is one of the standard treatments for various benign and malignant diseases of the pancreatic head and periampullary region. It is the only established curative treatment for the majority of peri-ampullary and head of pancreas carcinomas.^[1] A major problem is that the required surgery is extensive and entails a considerable risk of serious complications.^[2] The operative mortality rate after PD has significantly declined during the last 2 decades in experienced centres (most of the studies it is <5% while the incidence of post operative morbidity still remains high, from 40% to 50%.^[1-3]

Recent literature suggests that many factors influence pancreatic leakage after PD, like sex, age, jaundice,

operation time, intra operative blood loss, pancreaticojejunal anastomotic technique, texture of the remnant pancreas, pancreatic duct size, use of somatostatin, and surgeon experience etc. However, no definite factor has yet been identified.^[4,5] Studies defining the role of potential risk factors for the development of postoperative complications are rare, and sometimes with conflicting results. One of the main reason for this is the lack of a universally accepted definition of pancreatic surgery complications like pancreatic fistula, delayed gastric emptying, biliary leak, bleeding etc.^[6,7] Now international study group on pancreas has given a clear definition of these complication.^[7] The aim of this study is to analyze pre and perioperative risk factors in these patients and to study their influence in the development of complication after whipple

operation in 57 cases that underwent PD at our hospital.

MATERIALS AND METHODS

The following retrospective and prospective study was conducted in Jagjivanram Railway Hospital, Mumbai Central with the aim to identify the risk factors for complications following Whipple operation. Time period for collection of data was from February 2007 to April 2011. The study was commenced after due approval from the hospital ethics committee. All patients operated during this period were considered and final sample size was decided after applying the inclusion and exclusion criteria which are as follows.

Inclusion Criteria

- All elective pancreaticoduodenectomy (Whipple) cases which are operated for benign or malignant disease during this period are included.

Exclusion Criteria

- Other type of pancreatic head resection like enucleation/coring etc
- Emergency cases
- Locally advanced or metastatic patients
- Patients who had received neoadjuvant therapies

Methodology

History of present illness, detailed personal history, past medical and surgical history noted. Thorough physical and clinical assessment of the patient done. Baseline laboratory tests including Haemoglobin, PCV, DC, TC, LFTs, RFTs, electrolytes, blood sugars, urine examination, etc. X ray chest, ECG, USG, PFT, echocardiography (optional). Imaging – all patients are evaluated with high quality pancreatic protocol CT scan for confirming the diagnosis as well as assessing respectability. Tumor markers including CA-19-9 and CEA. EUSG – in special cases were CT scan reports are confusing regarding respectability or diagnosis is doubtful and also there is a possibility of taking biopsy preoperatively. Specialized investigations like PET scan and diagnostic lap when suspecting metastatic or locally advanced disease. Co morbid illnesses were controlled before surgery. Incentive spirometry started in all patients at least 1 week before surgery.

At the time of operation antibiotic administered just before induction of anaesthesia. Patient preparation with povidone iodine scrub and absolute alcohol. All cases are operated by a single surgeon trained in pancreatic surgery. Midline incision is preferred with Thompson self retaining retractors. After ruling out metastatic disease aortocaval lymph node sampling is done for frozen section to rule out locally advanced disease. Procedure abandoned if turns positive

Reconstruction: done using single loop of jejunum passed retro colically. First end-side pancreatico-jejunosomy done using 4 layer modified Heidelberg technique using special sutures. 10 cm distal to PJ end-side Hepatico jejunostomy in single layer. Next antecolic duodeno-jejunal anastomosis completes the

GI continuity. Special 3 lumen nasojejun tube is placed for gastric decompression and feeding so that feeding jejunostomy could be avoided. Antibiotic are continued for 3 days post op. Prophylactic octreotide infusion not given. All vitals and other biochemical parameters are monitored closely and recorded. Postoperative events are observed and recorded, complications are diagnosed based on std definition by the International study group mentioned earlier.

Statistical Analysis: Data were entered in MS Excel and Statistical Package for Social Sciences (SPSS) version 25. The statistical analysis was done by applying descriptive statistics i.e., mean \pm S.D. Comparison of blood pressure indices between patients was done by using Student's t test. Correlation of VRT and ART indices in patients with alcoholic and non-alcoholic was made by using Spearman's rho correlation test and 'p' value of less than 0.05 was considered significant.

RESULTS

During the study period, 57 patients who had undergone PD were enrolled. Of these patient, there were 35 (61.4%) male and 22 (38.6%) were female patients. The patients had a median age was 55 years with a range from 30 to 73 years. Jaundice was the most common presentation, followed by abdominal pain, duodenal obstruction, and others. Many patients exhibited more than one symptom. Co morbidities included diabetes mellitus (19 patients) hypertension, COPD etc. Laboratory tests showed cholestatic jaundice with a mean bilirubin level of 5.53 mg/dL (range, 1–22 mg/dL). If total serum bilirubine level was over 10 mg/dL, the patients were considered to be severely jaundiced. Hypoalbuminemia, defined as a serum albumin level less than 3.5 g/dL, was found in 12 (21.1%) patients. 34 patients (59.6%) had history of preoperative cholangitis (pre or post stenting). 31 patients had under gone biliary stenting preoperatively mainly endoscopic. [Table 1]

The overall post-resection morbidity rate in our series was 56.1% (32 patients) and mortality 7% (4 patients). Septic complications were the most common complications 31 patients, followed by Pancreatic fistula, presenting in 20 (34%). Among the 31 patients with septic complications 25 had just wound infection which required just removal of sutures and dressing and later secondary suturing. Only 6 patients had significant intra-abdominal collection which required some form of drainage. Among the 20 patients with pancreatic fistula 7 had grade C and rest had grade B fistula. Five patients with pancreatic fistula required re-operation. With redo anastomosis and two patient died of sepsis. Postoperative haemorrhage was found in 3 patients, and among this 1 patient died of massive bleed and rest 2 were managed with angio embolisation. Systemic complications were less frequent, presenting in 2 (3.5%) patients as pneumonia, and one of those died. Both patients had history of COPD.

Rest of the two deaths was due to uncontrolled septicaemia following pancreatic leakage. [Table 2] As per [Table 3] the mean age was 56 with a minimum of 30 and maximum of 73 years. The results of the univariate analysis conducted to assess the influence of the putative risk factors on the risk of complications mainly pancreatic leak and septic complications. As the age progresses >65 show more chances of pancreatic fistula and it is statistically significant.

The cases were in Female: Male as 40:60 ratios according to sex. We had male patients more than females as per world standards. But this difference is not significant. [Table 4]

As per [Table 5] septic complications are more in soft factors as compared to firm but this is not statistically significant.

As per [Table 6] binary Logistic Regression with 'Pancreatic fistula' as dependent variable and pancreatic texture, S. Albumin, Blood transfusion, PD size and Age as independent (Predictor) variables, all the variables are not significant except blood transfusion.

As per [Table 7] Binary Logistic Regression with 'Septic complication' as dependent variable and Operation time, Previous Cholangitis, Stenting and Age as independent (Predictor) variables. Only Operation time was considered as significant with septic complication.

Table 1: Site of Tumour and Demographic details

| Site of tumor | No. | Percentage |
|--|-----|------------|
| Periampullary | 32 | 56.1% |
| D2 adenoca | 7 | 12.3% |
| Distal cholangiocarcinoma | 7 | 12.3% |
| Head of pancreas | 6 | 10.5% |
| Uncinate adenoca | 3 | 5.3% |
| Head of pancreas due to Chronic pancreatitis | 2 | 3.5% |
| Total | 57 | 100.0% |

Table 2: Complications and Cause of death

| Cause of death | No. | Percentage |
|---------------------|-----|------------|
| Massive bleed | 1 | 25.0% |
| Respiratory failure | 1 | 25.0% |
| Septicemia | 2 | 50.0% |
| Total | 4 | 100.0% |

Table 3: Univariate analysis as per age

| | Pancreatic fistula | No Pancreatic fistula | |
|---------------------|--------------------|-----------------------|-----------------|
| < 65 | 27.1% | 72.9% | 100.0% |
| >= 65 | 77.8% | 22.2% | 100.0% |
| Total | 35.1% | 64.9% | 100.0% |
| | df | p-value | Association is- |
| Pearson Chi-Square | 1 | 0.01097 | Significant |
| Fisher's Exact Test | | | |

Table 4: Univariate analysis according to Sex in terms of Pancreatic Fistula

| | Pancreatic fistula | No Pancreatic fistula | |
|---------------------|--------------------|-----------------------|-----------------|
| Female | 27.3% | 72.7% | 100.0% |
| Male | 40.0% | 60.0% | 100.0% |
| Total | 35.1% | 64.9% | 100.0% |
| | df | p-value | Association is- |
| Pearson Chi-Square | 1 | 0.487 | Not significant |
| Fisher's Exact Test | | | |

Table 5: Univariate analysis of factors influencing septic complications

| | Septic complication | No Septic complication | |
|---------------------|---------------------|------------------------|-----------------|
| Firm | 42.9% | 57.1% | 100.0% |
| Soft | 58.1% | 41.9% | 100.0% |
| Total | 54.4% | 45.6% | 100.0% |
| | df | p-value | Association is- |
| Pearson Chi-Square | 1 | 0.491 | Not significant |
| Fisher's Exact Test | | | |

Table 6: Multivariate analysis of factors influencing pancreatic fistula

| Variables | B | S.E. | Wald | df | Sig. | Exp(B) |
|----------------------------|---------|-----------|-------|----|-------|----------|
| Age (years) (>= 65) | -41.296 | 10420.881 | 0.000 | 1 | 0.997 | 0.000 |
| S. Albumin (gm%) (Low) | -36.634 | 8602.24 | 0.000 | 1 | 0.997 | 0.000 |
| Blood transfusion (0 or 1) | 4.654 | 1.486 | 9.803 | 1 | 0.002 | 105.000 |
| Pd size (mm) (Dilated) | 56.597 | 11905.623 | 0.000 | 1 | 0.996 | 3.80E+24 |

| | | | | | | |
|---------------------------|--------|-----------|-------|---|-------|-------|
| Pancreatic texture (Soft) | -0.573 | 10484.067 | 0.000 | 1 | 1.000 | 0.564 |
| Constant | -1.372 | 10484.067 | 0.000 | 1 | 1.000 | 0.253 |

Table 7: Multivariate analysis of factors influencing septic complications

| Variables | B | S.E. | Wald | df | Sig. | Exp(B) |
|-------------------------------|---------|-----------|-------|----|-------|----------|
| Age (years) (>= 65) | -42.190 | 14624.687 | 0.000 | 1 | 0.998 | 0.000 |
| Previous Cholangitis (No) | -1.897 | 24652.078 | 0.000 | 1 | 1.000 | 0.150 |
| Stenting (No) | 23.100 | 23205.422 | 0.000 | 1 | 0.999 | 1.08E+10 |
| Operation time (hours) (<= 6) | 2.303 | 1.103 | 4.358 | 1 | 0.037 | 10.000 |
| Constant | -1.897 | 0.619 | 9.389 | 1 | 0.002 | 0.150 |

DISCUSSION

This study has concentrated on mainly the risk factors which are associated with these complications. This will definitely help us in identifying the high-risk patients and allow us to put more attention on these patients to prevent further aggravation of the problem thus decreasing the morbidity and mortality. There are some previous studies which addressed these issues but a uniform consensus on the definition post op complications like PF, DGE etc were not there. In this study it has been solved by adopting the definition of International study group.

This study consists of 57 patients who had undergone this operation in our hospital the overall morbidity was around 56% which is almost matching with many other studies.⁸ Many studies have given confusing result because of the different definition they used for diagnosing complications. Major complications in this study were pancreatic leak and septic complications.

Pancreatic leak as is still a dreaded complication. Many surgeons are still staying away from pancreatic surgery just to avoid facing this tricky situation. In this study there were 20 patients with pancreatic leak. Among this 7 had severe leak that is grade C according to the definition of international study group out of this 7 patients 2 patient died of septicaemia (mortality 29%) and rest 5 had reoperation including redo anastomosis which shows the seriousness of this complication. Patients who had other complications like delayed gastric emptying, bleeding etc many of them had pancreatic leak¹² which shows that these are all secondary to leak. The overall pancreatic leak seen in our patients are around 35% which is also matching with many other studies. In this study the risk factors are evaluated separately for pancreatic leak and septic complications because of the observation that different factors influence the development of these complications. Factors are classified like preoperative patient related factors, disease related factors and intra operative factors etc following are the findings.^[9-11]

Initial univariate analysis on the factors which influence development of pancreatic leak we observed many interesting finding. Analysis showed following factors like age greater than 65, Hypoalbuminemia, perioperative multiple transfusion, pancreatic duct size 3mm or less (undilated), soft pancreas, are associated with increased risk of pancreatic leak. Age greater than 65

is a known risk factors for any type of major surgery so this finding is makes sense and it has been proven in many other studies that as age advances the capacity of the body in healing, immunity, containing anastomotic leaks etc decreases significantl.^[12] Most of the elderly patients are having nutritional deficiency which is very difficult to correct it preoperatively because of multiple reasons.^[14] More importantly as age advances there is fat infiltration of pancreas which makes it very friable and delicate which cannot hold sutures leading to additional risk of leak. In a study by Sebastien Gaujoux et al,^[8] it is clearly shown that fatty pancreas commonly seen in obese patients and old patient is a significant risk factors for pancreatic leak there are other studies also proved the relation of fatty pancreas in older age and increased leak rate.^[13,14]

Intra op multiple blood transfusion (more than 1) is the other factor which showed statistical significance. Both univariate (p value-.027) and multivariate analysis (p value .002) showed increased incidence of pancreatic leak following multiple transfusion. This is an interesting finding in this study. There are reports in the literature regarding the harmful effects of blood transfusion in operative patients and it has been proven in colonic surgeries that this causes increased rate of recurrence and other complications,^[14,15] in addition to this multiple transfusion itself shows that the surgery was difficult and complicated and its natural to have more complications associated with such patients. Per operative blood transfusion is a symptom of per operative difficulties (proximity of vessels, difficulty of retroperitoneal lymphadenectomy, obese patients) which are linked to the postoperative course.^[16] This factor suggests that PD is a surgery requiring meticulous intra -operative haemostasis. There are many problems with transfusion and multiple transfusions have even severe side effects. The present guidelines shows very high threshold for transfusion in operative patient s but unfortunately rarely these guidelines are followed in the daily practice and that there is a negative correlation between pancreatic fibrosis and fat there are studies that identified pancreatic fibrosis as a preventive factor.^[17]

Over all this study assessed many important factors for this highly morbid procedure and we could identify few potential risk factors. Multivariate analysis did not show statistical significance with all of them probably because of smaller number of patients and many variables are involved. This kind

of studies are helpful because if we can predict serious complication in these patients we can offer these high-risk patients a specific, standardized clinical management approach like meticulous and careful surgery, early identification of Intra-abdominal peri-anastomotic collections and if possible fully drained (as judged radiologically).

CONCLUSION

In conclusion, our study confirms the results from recent reports that pancreatic head resection can be performed with a low mortality rate and acceptable morbidity. Many factors are studied and analysed in this study and multiple blood transfusion in pancreatic leak and prolonged surgery in septic complication are attained statistical significance in multivariate analysis as a risk factor for these complications respectively. There are few other potential risk factors also noted but they did not attain statistical significance probably due to relatively smaller study group and numerous factors are evaluated. Larger studies are required to confirm their role. Accurate and early predictive criteria for these major complications must be identified because these patients have to be managed differently from others with low risk undergoing Whipple. It is critical that each centre and each surgeon knows the risk factors for each patient. Such information can provide good quality controls for the doctor and hospital and allow patients to receive more realistic information about surgical risks.

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