

# Postoperative Mortality Rate Following Whipple's Procedure for Periapillary Carcinoma: A 5 Year Cohort Study

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## ABSTRACT

**Background:** The mortality rates for Whipple's procedure has come down during the last few years. This study was intended to assess perioperative mortality rates in a tertiary care centre and to compare it with other centres. **Methods:** Data was collected from various registers and medical records for this retrospective cohort study. All Whipple's procedures for 5 years were included in the study. Statistical analysis was done using R statistical software and the results were tabulated. **Results:** There were 48 patients and 8 of them died. A median serum bilirubin level of 16.9 mg% was found statistically significant with respect to mortality. Similarly placed was median serum albumin levels of 2.71 gm% and poor differentiation of tumour. **Conclusion:** In this study the mortality rates were comparable to other centres. Hypoalbuminaemia is a significant predictor of mortality. Tumour size of more than 3 cm is associated with high mortality. High serum bilirubin levels is an independent predictor of mortality. Several studies also show similar predictors of death in Whipple's procedure. Pulmonary complications were the most common cause for death. Mortality rate is comparable to other centres and Whipple's procedure is a safe surgery in the tertiary centre where it was studied.

**Keywords:** Pancreatoduodenectomy, Mortality, Whipple's procedure, Periapillary carcinoma.

## INTRODUCTION

Periapillary carcinoma is a group of malignant tumours arising in the region of ampulla of Vater. These are mainly adenocarcinomas of the head of pancreas, the ampulla of Vater, the distal bile duct and the adjoining portions of duodenum. The mode of presentation of these tumours is similar. The prognosis of these patients is poor and most of them present at an advanced age.

Dr Whipple, in 1935, with an intention to demonstrate his skills at gastrectomy before an august audience stumbled upon not a stomach cancer but a pancreatic one. With his pride at stake, he had to improvise. The close proximity of pancreas to several structures forced him to take out the duodenum, pylorus, a portion of the bile duct and a portion of the jejunum along with the pancreas. This was in fact the first pancreatoduodenectomy. Later it was labelled the Whipple's procedure and has stood the test of time. It is now a common operation in major centres across the globe.<sup>[1]</sup> However until

early 90s this procedure had high mortality.<sup>[2]</sup>

The indications for Whipple's procedure are periampillary cancer and mass lesions in the head of pancreas in chronic pancreatitis. Centres carrying out 20 cases per year are defined as high volume centres for Whipple's. Mortality rates are low in high volume centres. The mortality rate has decreased from 50% at the beginning years of this operation to 16-20% during last few years. In a retrospective study by Distler M et al, in a total of 195 patients who underwent Whipple's surgery, the overall mortality was 4.1%.<sup>[3]</sup>

In Government Medical College, Thrissur there is increasing number of cases of periampillary carcinoma every year and more of Whipple's surgery is being done compared with many other referral centres. This study was intended to assess perioperative mortality rates and to compare that with those of high volume centres, so that patients are benefitted.

## MATERIALS AND METHODS

This retrospective cohort study was a record based study done in the department of General Surgery at the Government Medical College, Thrissur, Kerala, India. Ethical clearance was obtained from the Ethics Committee of the institution. The principles laid down in the Declaration of Helsinki were observed.

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The study was intended to assess mortality rate in patients who had undergone Whipple's procedure for periampullary carcinoma. The safety of this procedure in the institution was also assessed in the background of the fact that pancreatoduodenectomy is the only potentially curative treatment for periampullary carcinoma.

Data regarding Whipple's surgery was extracted from the registers maintained at the department of General Surgery and that regarding histopathology from registers in the department of Pathology. Further information was retrieved from medical records. All patients who had undergone Whipple's procedure from January 2012 to December 2016 were included in the study. Data was gathered using a checklist designed for this study. Details of patients like complications, readmissions and death up to a period of 30 days following surgery were noted and were followed up with histopathological report. Patients whose histopathological report was of benign pathology were excluded from the study. Data was collected in a pretested data collection form and later entered into excel with careful attention to avoid data collection errors. All statistical analysis were done in R statistical software. Continuous data were summarised as

mean and standard deviation or median and interquartile range. The results were tabulated and discussed after completion of the study.

## RESULTS

There were 48 patients in the study. The mean age was 61 years within a range of 33-75 years. Males numbered 31(64.6%) while 17(35.4%) were females. Jaundice was the predominant symptom in 25(52.1%) of patients studied. Abdominal pain was the presenting symptom in 18(37.5%), vomiting in 3(6.2%) and fever in 2(4.2%) (Fig.1). Comorbidities were absent in 32(66.7%) patients and in 2(4.17%) patients the records failed to mention as to whether comorbidities were present or not. The mean serum bilirubin value was 4.8 (IQR: 1.08-11.8) mg% [Figure 2]. Serum albumin showed a median of 3.37(±0.56) gm% The pathological tumour size was less than 3 cm in 43(89.6%) cases and more than 3 cm in the rest. At histopathology, only 6(12.5%) patients had lymph nodes harbouring malignancy. Regarding tumour differentiation 29(60.4%) had well differentiated tumours, 10(20.8%) had poorly differentiated tumours and the remaining ones had moderately differentiated tumours.

**Table 1: Comparison of various factors affecting mortality**

	(ALL) N=48	No mortality N=40	Mortality N=8	p. overall
Gender :				1.000
F	17 (35.4%)	14 (35.0%)	3 (37.5%)	
M	31 (64.6%)	26 (65.0%)	5 (62.5%)	
Bilirubin:	4.80 (1.08;11.8)	3.75 (0.90;9.07)	16.9 (9.90;24.8)	0.003
Albumin:	3.37 (0.56)	3.50 (0.49)	2.71 (0.44)	0.001
Tumour size:				<0.001
<3 cm	43 (89.6%)	40 (100%)	3 (37.5%)	
>3 cm	5 (10.4%)	0 (0.00%)	5 (62.5%)	
Lymph node:				<0.001
Negative	42 (87.5%)	40 (100%)	2 (25.0%)	
Positive	6 (12.5%)	0 (0.00%)	6 (75.0%)	
Differentiation:				<0.001
Moderate	9 (18.8%)	6 (15.0%)	3 (37.5%)	
Poor	10 (20.8%)	5 (12.5%)	5 (62.5%)	
Well	29 (60.4%)	29 (72.5%)	0 (0.00%)	

**Table 2: Causes of death in Whipple's procedure**

Causes of death:	N=8
ARDS	3 (37.5%)
Bile sepsis	1 (12.5%)
Liver failure	1 (12.5%)
MI	1 (12.5%)
Pancreatic	1 (12.5%)
SAH	1 (12.5%)

In all, 8 patients died. The median age at which patients died after Whipple's procedure for periampullary carcinoma was 65.0(IQR: 57.8-69.2). Males constituted 5(62.5%) of those who died while the rest were females [Table 1]. While only 1(5%) patient among 18 who reported with abdominal pain met with mortality, 7(28%) of those who presented with jaundice died within the period studied. Even as 14(29.2%) patients had comorbidities only 4 patients

among them died. A median serum bilirubin level of 16.9 (IQR: 9.90-24.8) mg% was associated with mortality with p-value of 0.003. The median serum albumin level associated with mortality was 2.71 gm% (p-value of 0.001) [Figure 3]. Of those who died, 62.5% had tumour size more than 3 cm while the rest had tumour size less than 3 cm which was statistically significant (p-value of <0.001). The association of mortality with tumour differentiation was also statistically significant (p-value of < 0.001) [Table 1].

Acute Respiratory Distress Syndrome was the cause of death in 3(6.25%) patients. One among bile sepsis, liver failure, myocardial infarction, pancreatic leak, subarachnoid haemorrhage was the cause of death in remaining patients [Table 2].

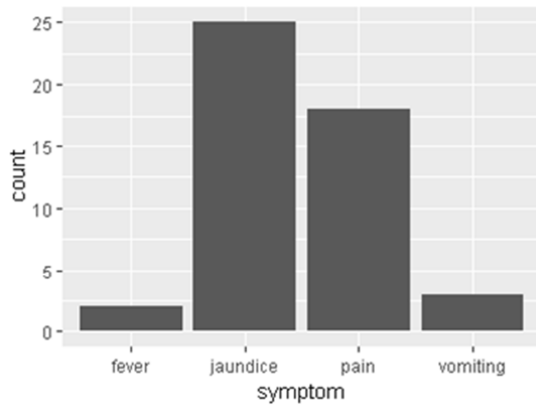


Figure 1: Presenting symptoms

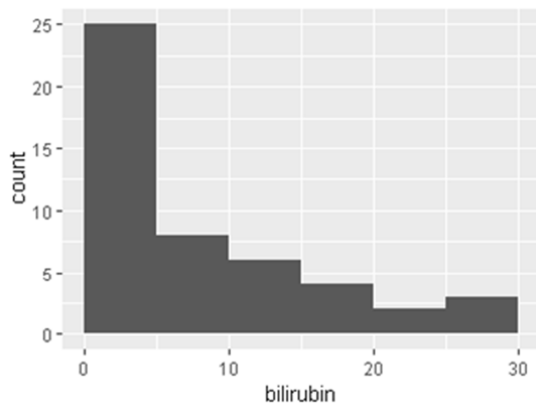


Figure 2: Serum bilirubin levels

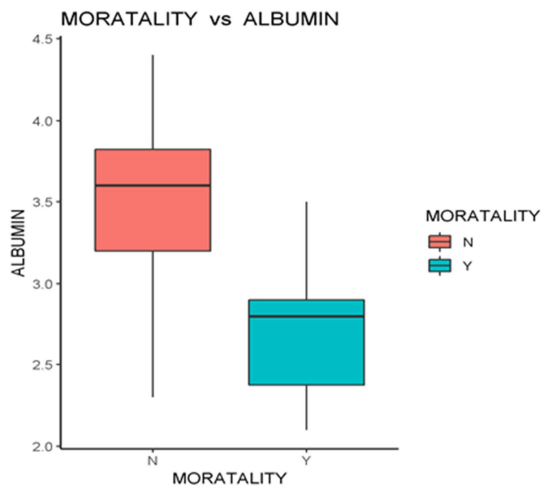


Figure 3: Association of serum albumin levels to mortality

## DISCUSSION

Whipple's resection remains the only potential curative option for patients with periampullary carcinoma. Ever since its inception into surgical practice this procedure has been a subject of repeated research to find out the mortality. This study was done to assess the rates of mortality following this procedure in patients with periampullary carcinoma in a tertiary care centre which caters to a large

segment of population in central Kerala. The study was conducted in the background of increasing evidence of association of tropical pancreatitis with pancreatic cancer considering the fact that tropical pancreatitis is prevalent in Kerala.<sup>[4,5]</sup>

All patients who had undergone Whipple's procedure in Government Medical College, Thrissur during the study period was for periampullary carcinoma, mainly carcinoma of head of pancreas. Even though the age range was 33-75 years the mean age was 61. Over the years mortality rates following pancreatoduodenectomy have been declining but the morbidity rates have remained high. In 1999 Bottger et al reported that surgical complications happened in 25% and general complications in 18.5%.<sup>[6]</sup> Gordan et al in their study found out that as the number of cases of pancreatoduodenectomy increased, the in-hospital mortality rate decreased. In the study titled 'effect of hospital volume on in-hospital mortality with pancreatoduodenectomy' Birkmeyer identified that mortality rates were 3 to 4 fold higher in low volume centres compared to high volume centres.<sup>[7,8]</sup> Ho et al, Topal et al and Kim et al also had similar findings in their studies.<sup>[9-11]</sup> In the retrospective study conducted by Saraee et al the mortality rate was found to be 16-20% after pancreatoduodenectomy. In our study the mortality rate was 16.7% which is comparable to other centres.<sup>[12]</sup>

There are several causes of mortality. Hypoalbuminaemia is a significant factor contributing to mortality in our study. The median serum albumin contributing to post-operative death is 2.71 gm% (p-value of 0.001). In various other studies also hypoalbuminaemia is a cause for mortality. A study by Chou et al in 1996 concluded that an albumin concentration of less than 30 gm/L before surgery influenced surgical mortality.<sup>[13]</sup> Four parameters were found to be independently correlated to mortality in a study by Su et al, one among them was serum albumin levels less than or equal to 3.0 gm%.<sup>[14]</sup> A pre-operative serum albumin level of less than or equal to 3.5 gm% was seen significantly associated with mortality in a study by Winter et al in 200.<sup>[15]</sup> In the same study mortality was higher (7%) when the albumin levels fell to less than 2.5 gm% compared to a mortality rate of 3% when the same was between 2.6 and 3.5 gm%. Hypoalbuminaemia as a significant predictor of death was also confirmed in 2011 in a study by Greenblatt et al.<sup>[16]</sup>

In study by Bottger et al, high serum bilirubin levels was found to be an independent risk factor for death.<sup>[6]</sup> Our study also showed a significant association between mortality and hyperbilirubinaemia. However a study by Feng et al in 2012 showed that depth of jaundice did not have an influence on mortality.<sup>[17]</sup> Tumour size, in our study, also is having an effect on mortality with sizes more than 3 cm having a high mortality compared to

those with less than 3 cm. Su et al has also reported that lower the tumour size longer is the patient survival.<sup>[14]</sup> The same study had revealed that patients with well differentiated tumours have good prognosis. In our study poorly differentiated tumours are found to be significantly related to mortality.

Among other causes of post-operative death pulmonary complications contributed to death in 3 patients in our study. In a study conducted in 2017 Nagale et al has reported a very high mortality owing to pneumonia.<sup>[18]</sup>

In the current study, details were extracted from patient records and histopathology records. Being a retrospective study there were no omission of cases. The limitation was that the number of pancreatoduodenectomies fell marginally short of being characterised as high-volume. In all there were 48 patients in this study. Pallagrini et al in 1989 studied 51 patients to assess mortality rates.<sup>[19]</sup> In 1997 Gouma et al classified centres performing pancreatoduodenectomies as high volume and low volume centres. More than 25 procedures in one year was taken as criterion for a high volume centre. They also concluded that in high volume centres mortality rates are less.<sup>[20]</sup> Kotwall et al in 2002 also arrived at a similar conclusion.<sup>[21]</sup> A 6 year study by Rosemurgy et al in Florida found that surgeons who perform pancreatoduodenectomy frequently serve patients better.<sup>[22]</sup>

## CONCLUSION

Being the only curative option for periampullary carcinoma, pancreatoduodenectomy was studied with regards to mortality in a hospital which is depended upon by a large population. The mortality rate is comparable to that of other centres. It is a safe operation for those patients depending on the institution, a tertiary care centre, where it was studied.

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