A study of factors associated with high mortality of pancreatic carcinoma: A single institutional study from North East India. A study of factors associated with high mortality of pancreatic carcinoma

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ABSTRACT

<u>INTRODUCTION</u>: Pancreatic cancer is a highly lethal cancer, with 4,58,918 new cases occurring in 2018 worldwide, it is ranked as 13th most common cancer worldwide. However it is the 7th most common cause of cancer related deaths.

<u>OBJECTIVE:</u> To study the factors associated with high risk of mortality from pancreatic cancer, an Indian perspective.

<u>MATERIALS AND METHODS</u>: This is a retrospective study. Data of patients presented with pancreatic cancer in one year period was analyzed. Demographic data, socio-economic status, presenting symptoms, performance status, and radiological findings were noted. Treatment given, delay in starting treatment and date of last follow up were also noted. Survival was taken as time between date of diagnosis and date of last follow up.

<u>RESULTS</u>: A total of 343 case record files were available for analysis. The median age at presentation was 55years. Males were more commonly affected than females (1.5:1). Approximately 68% of our patients belonged to rural area. Almost half of the cases in our study belonged to lower socioeconomic status(48.9%). The median survival was 1.1 months(0.03-12.3). The 30-day mortality rate was 47.4%. One year overall survival was 15%. All patients who had curative surgery are alive at the time of analysis.

<u>CONCLUSION</u>: To summarize our study we can say that besides performance status, stage at presentation and treatment received; locality and socio-economic status of the patient have significant effect on the survival. Although delay in treatment didn't have significant effect on survival, patient with earlier starting of treatment tends to have better outcomes

I. INTRODUCTION

Pancreatic cancer is a highly lethal cancer, with 4,58,918 new cases occurring in 2018worldwide, it is ranked as 13th most common cancer worldwide. However it is the 7th most common cause of cancer related deaths. Pancreatic cancer is 24th most common cancer and 18th most common cause of death in India.[1] Age standardized rate for Indian female and male is 0.88 and 0.81 per 100000 respectively(compared to 4.0 and 5.5 in world; 6.3 and 7.9 in UK, and 6.6 and 9.0 in USA).[2] Many risk factors for pancreatic cancer have been identified like smoking, old age, family history, and diabetes, however this knowledge didn't lead to much improvement in early detection or survival in pancreatic cancer patients.[3] This cancer is associated with an extremely poor prognosis, as shown by a 1-year survival rate of around 18% for all stages of the disease, falling to less than 4% at 5years . [4]The tumor microenvironment is highly dynamic and has been found to promote tumor

progression, metastasis niche formation and therapeutic resistance. [5] Besides this inherent aggressive nature of cancer, many other factors are related to high mortality. Majority of patients with pancreatic adenocarcinoma present with unresectable disease as a result of either local invasion or distant metastasis. [6] Low socioeconomicstatus (SES) has been found to be an independent risk factor for mortality in a population-based study of pancreatic adenocarcinoma cases.[7] Locality of patient has also been found to have effect on pancreatic cancer related mortality. In our study we have studied various factors associated with high risk of mortality in pancreatic cancer patients, from an Indian perspective. Our study highlights the need of resource development in rural area and conducting cancer awareness campaigns for people belonging to lower SES.

II. MATERIAL AND METHODS

This is a retrospective study. Institutional ethical committee clearance was taken. As this is a retrospective analysis, patient's written consent was not obtained and study was not registered in clinical trial registry.

Study participants: Patients registered with a diagnosis of pancreatic cancer at a public (government-run) tertiary care cancer centre from May 2019 to April 2020 (one year) were found through electronic medical record.

Study methodology: Patients registered with a diagnosis of pancreatic cancer at a public (government-run) tertiary care cancer centre from May 2019 to April 2020 (one year) were found through electronic medical record. Data was then collected from the case records. Diagnosis of pancreatic cancer was based on radiological findings. Demographic data, socio-economic status, presenting symptoms (pain, jaundice, anorexia, fatigue or ascites), performance status, and radiological findings were noted. Available Biopsy/FNAC reports were recorded. Treatment given, delay in starting treatment and date of last follow up were also noted. Survival was taken as time between date of diagnosis and date of last follow up. Modified Kuppuswamy scale was used to classify patients into different socio-economic groups.

Study statistics: Statistical analysis was done using Statistical Package for Social Sciences 20.0 (SPSS Version 20.0). Survival was calculated using Kaplan-Meier analysis.

III. RESULTS

A total of 354 patients were registered with pancreatic cancer (1.41% of all cancer patients presented at institute) in one year duration. However 11 cases were excluded due to lack of complete data and hence 343 cases were included in this study. Among them, mean age was 54.4years and median was 55years. Males were more commonly affected than females (1.5:1). Approximately 68% of our patients belong to rural area. Almost half of the cases in our study belonged to lower socioeconomic status. (48.9%) (Table 1)

Characteristics	Results
Age(Mean)	54.4years
Age(Median)	55years
Sex	
Male	206(60%)
Female	137(40%)
Locality	
Rural	233(67.9%)
Urban	110(32.1%)
Socio-economic Status	
Upper	0
Upper middle	30(8.7%)
Lower middle	55(16%)
Upper lower	90(26.2%)
Lower	168(48.9%)

Table 1: Demographical characteristics

`Most common presenting complaint was anorexia and weight loss (57.7%) followed by fatigue (35.2%).Patients most commonly presented with performance status 1(38.2%) followed by 3(30%). The most common location of tumor was in head of pancreas (33.8%) followed by head and

uncinate process (26.8%). Almost half of the patients presented in metastatic stage (48.1%). Most common site of metastases was liver (72.7%) followed by liver and lungs (12.1%). (Table 2)

Biopsy/FNAC was available in 149 patients, with adenocarcinoma being the most common histology, seen in 87.2% cases followed by poorly differentiated carcinoma in 8.1 %.(Table 2)

Characteristics	Results
Presenting complaints	
Anorexia and weight loss	198(57.7%)
Fatigue	121(35.2%)
Pain	103(30%)
Jaundice	62(18%)
Ascites	24(6.9%)
Referred cases(after curative surgery)	15(4.3%)
Performance status	
1	131(38.2%)
2	72(20.9%)
3	103(30%)
4	37(10.7%)
Location of tumor	
Head of pancreas	116(33.8%)
Head and uncinate process	92(26.8%)
Head and body	40(11.7%)
Periampullary	38(11.1%)
Tail	36(10.5%)
Body and tail	21(6.1%)
Stage	
Localized	53(15.4%)
Regional	125(36.4%)
Metastatic	165(48.1%)
Liver	127(72.7%)
Liver and lungs	20(12.1%)
Peritoneal/omental	7(4.2%)
Supraclavicular lymph node	8(4.8%)
Adrenal glands	3(1.8%)
Biopsy/FNAC(done/available in 149)	
Adenocarcinoma	130(87.2%)
Poorly differentiated carcinoma	12(8.1%)
Pancreatic NET	5(3.3%)
Solid Pseudopapillary tumor	2(1.3%)
Total	149
Treatment given	

Palliative chemotherapy	60(41.3%)
Biliary drainage	40(27.5%)
Curative surgery	29(20%)
Adjuvant chemotherapy(for referred cases)	16(11.0%)

Table 2: Clinico-pathological factors

In our study, 145(42.3%) patients received some form of treatment, with most of the patients receiving palliative chemotherapy (41.3%) followed by biliary drainage (27.2%) and curative surgery (20%). Overall 39 patients were taken up for surgery but only 29 cases were resectable. Remaining 10 patients received palliative chemotherapy. Sixteen (10.9%) patients who presented after curative surgery from outside received adjuvant chemotherapy at our centre(Table 2).

Mean and median survival was 3.5 and 1.1 months respectively. 30 day mortality rate was 47.4%; age specific 30 day mortality rate was significantly ($p<0.05$) more in patients with age >50 years (52.6%) than those with age≤50 years (36.3%). One year overall survival was 15%. Table 3 shows mean and median survival in different age groups, sex, locality, socio-economic status, performance status, stage of the tumor and treatment received.

Characteristics	Mean survival(months)	Median survival(months)	Range(months)
Age(years)			
≤50	4.3	1.13	0.13-11.06
51-70	3.4	1.00	0.03-12.30
>70	1.0	0.70	0.10-0.833
Sex			
Male	3.8	1.13	0.03-12.30
Female	2.9	0.90	0.03-11.06
Locality			
Rural	3.1	0.90	0.03-7.80
Urban	4.8	1.10	0.13-12.30
Socio-economic Status			
Upper middle	7.6	-	3.80-12.30
Lower middle	4.9	2.97	0.33-11.50
Upper lower	3.4	1.16	0.43-8.76
Lower	2.3	0.46	0.03-5.16
Performance status			
1	7.2	3.03	1.03-12.30
2	1.9	0.96	0.16-6.16
3	1.0	0.60	0.03-2.97
4	0.3	016	0.03-1.00
Stage			
Localized	8.7	6.43	3.86-12.30
Regional	2.8	1.13	0.03-9.00
Metastatic	1.8	0.70	0.03-6.16
Treatment received			
Curative surgery	-	-	2.23-12.3
Adjuvant chemotherapy(for referred cases)	9.9	-	3.86-11.06
Palliative chemotherapy	6.9	6.16	0.76-9.00
Biliary drainage	1.7	0.96	0.13-5.1

Best supportive care	1.1	0.63	0.03-2.97

Table 3: Mean survival in different age groups, sex, locality, socio-economic status, performance status, stage of the tumor and treatment received. Note: Missing values depicts the values which could not be computed by Kaplan-Meier.

For patients who received palliative chemotherapy survival was 7.8 months in patients with delay in treatment ≤21 days and it was 6.9 months in patients with delay of >21 days. Although it was not statistically significant.

IV. DISCUSSION

Pancreatic carcinoma is a highly aggressive cancer and is very hard to treat. The tumor microenvironment is highly dynamic and has been found to promote tumor progression, metastasis niche formation and therapeutic resistance. [5] Besides inherent aggressiveness of pancreatic cancer, various additional factors are responsible for high mortality in pancreatic cancer. In a developing country like ours, our study has found socio-economic status(SES) and locality of the patient have a significant effect on survival of pancreatic cancer patients. This finding highlights the need of resource development in rural areas. Our study also found that patients from lower SES tend to present in later stages of the disease, showing lack of social and financial support. We also found that early treatment has trend toward better survival (although not statistically significant)

Patients presenting with pancreatic carcinoma were younger in our study (median age-55yrs) as compared to the western patients(median-71yrs)[8]. In our study 40% patients were females similarly to a study conducted by Yeo et al[8] , in which also 40.1% patients were females. However in a study conducted by Zell et al[7] 48.5% were females.

Most common histology was adenocarcinoma, seen in 87.2% patients of our study; however in a study conducted by Gajalakshmi et al 76% patients had adenocarcinoma.[8] In our study 15.4% of patients had localized disease at presentation (although sixteen of them have already had underwent curative surgery and were referred cases who came for adjuvant chemotherapy only), 36.4% presented with regional disease and 48.1% with metastatic disease. Similarly in a study by Cheung et al 9.5%, 39.2% and 51.2% patients presented localized, regional and metastatic disease respectively.[9]

Many factors are associated with high mortality in pancreatic carcinoma. We have studied change in survival depending upon change in different factors. In our study, mean and median survival was 3.5 and 1.1 months respectively which is lower as compared to study by Cheung et al(median survival-5.7 months)[10]. In this same study median survival for patients <40yrs of age was 8.8months (vs. 4.3 months in our study).

The reason for low median survival in our study could be attributed to one of the many factors contributing to high mortality. For instance patients with poor performance status were associated with significantly poor survival and there were a high proportion of patients presented with poor performance status.

Old age is amongst the most important factor associated with high mortality. There was significant difference found in 30 day mortality and one year overall survival in patients with age ≤50 yrs and those with age >50 years. Survival when seen in three different age groups, ≤50yrs, 51-70 and >70 was 4.32, 3.46 and 0.96 months respectively. Similar finds were seen in a study conducted by Sunil Amin et al in which survival significantly decreased with increasing age at diagnosis, from a mean of 10.4 months for those younger than 50 to 9.1 months for those 50 to 70 years to 6.4 months for those older than 70 years.[11]

Survival was also found to be slightly more in males than females (3.79 vs 2.95 months), although the difference was not statistically significant. In a study conducted by Fesinmeyer MD et al survival was found to be more in males (4 vs 3 months).

In our study 67.9% of population was rural as compared to 38.3% in a study from Denmark by JakobKirkegård et al. [12]In our study we found significant difference in survival between patients from urban and rural areas(4.8 vs 3.1 months). This is similar to the finding seen in the study by JakobKirkegård et al where survival in urban and rural population was 4.1 and 3.5 months respectively. However this can be seen that disparity in survival is more in our study. This is most probably due to the reason that resources were more lacking in rural population of developing country like ours versus developed country of Denmark.[12]

As expected, patients with good performance status (1 or 2) had better survival (than those with poor performance status that is 3 or 4); those with localized disease had better survival (than those with regional or metastatic

disease) and those who received treatment had better survival than those who didn't.

Almost half (48.9%) patients in our study belonged to lower socioeconomic status(SES). Patients belonging to upper lower, lower middle and upper middle SES were 26.2%, 16% and 8.7% respectively. (Table 4) In our study, none of the patients belonged to upper SES.

SES	Zell et al[7]	Puri et al[13]	Van Roest et al[43]	Present study
Upper	15.3%	6.6%	30%	0
Upper middle	18.8%	8.9%		10.2%
Lower middle	20.5%	15.1%	40%	14.6%
Upper lower	22.3%	28.7%		23.4%
Lower	23.2%	33.5%	30%	51.8%

Table 4: Distribution of patients in different socio-economic groups in different studies

In our study significant survival differences were found in patients of different socio-economic groups. In a study conducted by Jason A Zell et al similar disparity in survival rates was found. In their study they found that upper SES was associated with a hazard ratio of 0.86 when lower SES was taken as reference.[7] Similar disparities has also been seen in studies done for other cancers. For instance in a study by Hoa Le et al in colon cancer by median survival I different SES groups were as follows: lowest (50 months) second lowest (58 months), middle (62 months), high (67 months), and highest (80 months). In the same study, for rectal cancer median OS in different SES were as follows: lowest (53 months), second lowest (61 months), middle (68 months), high (82 months), and highest (104 months). [15]

It can be seen that patients in upper middle SES presented with good performance status and in earlier stage. They were also more likely to receive treatment. And those from lower SES were more likely to present in poor performance status and in advanced stages.

We divided patients according to time to treatment initiation treatment, whether ≤21 days or >21 days and calculated mean survival. In patients undergoing curative surgery mean survival could not be computed because all patients were alive at the end of study. There was a trend toward better survival in patients receiving palliative chemotherapy within 21 days, although it was not statistically significant. Similarly in a study by Stephan Kruger et al, it was found that prolonged time to treatment initiation had no major effect on treatment outcome in patients with advanced pancreatic cancer. [16]

We acknowledge that our study has several possible limitations like the small sample size, retrospective nature, unavailability of data on quality of life and long term survival, the major strength of this study is that it comes from a three-tier institute of North-east India which covers a population from a large geographical area. Our study shows the need of public awareness regarding cancer and development of social support groups for population belonging to lower SES group and rural area.

V. CONCLUSION

Pancreatic cancer portends a very poor prognosis, more so in a developing country like ours. Most of the patients come from the rural population with very little resources. These patients present mostly in advanced stage with poor performance status, due to which they are not able to get any treatment. To summarize our study we can say that besides performance status, stage at presentation and treatment received; locality and socio-economic status of the patient have significant effect on the survival. Although delay in treatment didn't have significant effect on survival, patient with earlier starting of treatment tends to have better outcomes.Further research should be directed to identify the ways to decrease the gap between the resource allocation between different SES groups and between rural and urban population.

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