

One-year Survival Rate of Pancreatic Cancer and the Mortality Affecting Factors

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ABSTRACT

Background: Pancreatic cancer is the fourth leading cause of death associated with malignancy in the United States, and is thought to be the second leading cause of death in 2030 in the United Kingdom. In Asia, pancreatic cancer is the most fatal cancer with the lowest survival of all malignancies, 25-30% survival five years after surgery. Indonesia has no data on the survival of pancreatic cancer and the factors that affect it. The aim of this study is knowing the 1-year survival of pancreatic cancer and its influencing factors in Cipto Mangunkusumo Hospital, Jakarta.

Method: A retrospective cohort study was performed using data from the medical records of pancreatic cancer patients Dr. Cipto Mangunkusumo Hospital between January 2012 - December 2016. Factors age, sex, metastasis, stage, comorbid and treatment were analyzed bivariate and multivariate using Cox proportional Hazards Regression to obtain hazard ratio (HR) for each prognostic factor. The cumulative survival of 1 year after diagnosis is expressed by the Kaplan-Meier curve.

Results: Of 83 subjects the proportion of males was 62.7%, age ≥ 50 years 68.7%, with age range 33-79 years, and 55 years on average. In bivariate analysis, there was a statistically significant relationship of survival with comorbid variables (HR = 2.116; 95% CI: 1.335-3.513, $p < 0.002$), metastasis (HR = 3.802; 95% CI: 1.995-7.249, $p < 0.001$), palliative treatment (HR = 2.108; 95% CI: 1.077-4.125, $p = 0.029$) and group without treatment (HR = 2.924; 95% CI: 1.496-5.716, $p = 0.002$). Multivariate analysis showed that metastasis provided the greatest risk of death with HR = 4.306 (95% CI: 2.125-8.724; $p < 0.001$). Palliative group HR was 2.510 (95% CI: 1.245-5.061 $p = 0.010$) while the group without treatment gave HR = 2.535 (95% CI: 1.277-5.032; $p = 0,008$). The 1-year survival rate is 14%, with a median survival of 6 months.

Conclusion: The overall survival of one year of pancreatic cancer patients was 14%, with a median survival of 6 months. The presence of metastasis and not the curative therapy of Whipple surgery in patients with pancreatic cancer in Dr. Cipto Mangunkusumo Hospital is the main factor that negatively affect the survival of 1 year

Keywords: pancreatic cancer, survival, influencing factors

ABSTRAK

Latar belakang: Kanker pankreas adalah penyebab kematian keempat yang berhubungan dengan keganasan di Amerika Serikat, dan diperkirakan akan menjadi penyebab kematian kedua di years old 2030 di United Kingdom. Di Asia, kanker pankreas adalah kanker yang berakibat paling fatal dengan kesintasan terendah di antara semua keganasan, yaitu 25-30% kesintasan lima years old setelah tindakan operasi. Indonesia belum memiliki data kesintasan kanker pankreas dan faktor-faktor yang memengaruhinya. Tujuan penelitian ini adalah untuk mengetahui kesintasan 1 years old kanker pankreas dan faktor-faktor yang memengaruhinya di RS Dr. Cipto Mangunkusumo, Jakarta.

Metode: Dilakukan penelitian kohort retrospektif menggunakan data dari rekam medis pasien kanker pankreas RS Dr. Cipto Mangunkusumo antara Januari 2012 - Desember 2016. Faktor age, jenis kelamin, metastasis, stage, Comorbidity dan pengobatan dianalisis secara bivariat dan multivariat menggunakan Cox Proportional Hazards Regression untuk mendapatkan hazard ratio (HR) setiap faktor prognosis. Kesintasan kumulatif 1 years old setelah diagnosis dinyatakan dengan kurva Kaplan- Meier.

Hasil: Dari 83 subyek penelitian, proporsi male adalah 62.7%, usia ≥ 50 years old 68,7%, dengan rentang usia 33-79 years old, dan rata-rata 55 years old. Pada analisis bivariat didapati hubungan bermakna secara statistik antara kesintasan dengan variabel Comorbidity (HR = 2,116, 95% CI: 1,335-3,513, $p < 0,002$), metastasis (HR = 3,802; 95% CI: 1,995-7,249; $p < 0,001$), pengobatan paliatif (HR = 2,108; 95% CI: 1,077-4,125; $p = 0,029$) serta kelompok tanpa pengobatan (HR = 2,924; 95% CI: 1,496-5,716; $p = 0,002$). Analisis multivariat menunjukkan metastasis memberikan risiko kematian terbesar dengan HR = 4,306 (95% CI: 2,125-8,724; $p < 0,001$). HR kelompok paliatif sebesar 2,510 (95% CI: 1,245-5,061; $p = 0,010$) sedangkan kelompok tanpa pengobatan memberikan HR = 2,535 (95% CI: 1,277-5,032; $p = 0,008$). Angka kesintasan 1 years old adalah 14%, dengan median survival 6 bulan.

Simpulan: Kesintasan keseluruhan satu years old pasien kanker pankreas adalah 14%, dengan median survival 6 bulan. Adanya metastasis dan tidak dilakukannya terapi kuratif operasi Whipple pada penderita kanker pankreas di RS Dr. Cipto Mangunkusumo merupakan faktor utama yang berpengaruh negatif terhadap kesintasan 1 years old.

Kata kunci: Kanker pankreas, kesintasan, faktor yang berpengaruh

INTRODUCTION

Pancreatic cancer are the forth highest cancer-related death in US by 2016.^{1,2} Although it accounts for only 3% from all new cancer cases, it estimated would become the second highest cause of cancer-related death in UK at 2030.³ In 2014, 26 cases are found every day in UK.⁴ Incidence in UK are increasing by 6% from 2014 to 2035, nearly 21/100.000 population.⁵

In Asia, including Indonesia, data on incidence and mortality is limited due to unavailable registry data and no health insurance which covered routine screening, early detection, nor prompt treatment. Pancreatic cancer in Asia had low survival rate compared to other cancer, estimated to be 25-30% for 5-years after surgery.^{6,7}

It is difficult to detect pancreatic cancer in early phase due to unspecific findings during routine physical examination.⁸ Unspecific clinical presentation at early phases made it is less preventable, thus moreover lymphatic involvement or metastatic progression are common. More that 80-90% are diagnosed at advanced

stages thus might be inoperable at that time.^{9,10}

Several factors that related to survival rates are histological types, stages at diagnosis, tumor size, therapy modalities, accesibility to healthcare facility, age, gender, and lifestyle.¹¹

Incidence of pancreatic cancer are conversely related to age with median diagnosis in US are 71 years old while in UK are 72 years old. Metastatic rate of pancreatic cancer varies among countries but commonly found higher among women¹² with inconsistent survival rates. It also found higher among black (vs white)^{1,9,13,14} but lowest among Asia population.^{1,5,9,13,14}

Advanced age is accompanied by more morbidity which had direct impact on quality of life. Overall 5-years mortality are 5%, while it contrastly differ between early stage (11%) and metastatic stage (2%).^{10,15} Patients underwent surgical treatment had higher survival rates (27% vs. 7%) compared to no surgical treatment.¹⁵

METHOD

This is a retrospective cohort study using medical records in ward and outpatient clinic data from Cipto Mangunkusumo Hospital from January 2012 until December 2016. Inclusion criteria is ≥ 18 years old with diagnosis of pancreatic cancer. Data were excluded if medical records is incomplete. Diagnosis is made based on radiological examination US or endoscopic ultrasound (EUS)/computed tomography (CT) scan/magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography (MRCP) with or without surgery and histopathologic examination. Age, gender, treatment approach, comorbidities, tumor markers, stages and metastatic status are obtained from the medical records.

Data were analyzed using SPSS 22.0 for Windows. Statistical analysis was using cumulative survival analysis for 1 year after pancreatic cancer diagnosis, present as Kaplan Meier curve. Bivariate and multivariate analysis are using Cox proportional hazard regression model with hazard ratio as main effect measurement. Each predictor with p value < 0.25 in bivariate analysis were included to multivariate analysis. Variables with p value < 0.05 in multivariate analysis are considered correlated to pancreatic cancer mortality.

RESULTS

Subject characteristics are shown in Table 1. From 83 subjects, 52 are male (62.7%) and 68.7% are older than 50 years. Mean and range of subject's age are 55 and 33-79 years old. Mortality after 1 year of observation are 85.5% with one-year survival rate is 14% and median survival time is 6 months.

In bivariate analysis, factors that significantly related to survival rate are metastatic status, comorbidities, and treatment approach. Hazard ratio and confident interval of each variables are shown in Table 2. Male (82.7%) and female (90.3%) subjects did not survive during observation HR = 1.166 (95% CI: 0.724 – 1.879; $p = 0.527$). Mortality among < 50 years are 76.9% while > 50 years are 89.5% (HR = 1,579 (95% CI: 0.950 – 2.683; $p = 0.077$).

Forty-nine study subjects had IKC < 4 , while 31 of 34 subjects with IKC ≥ 4 deceased (91.2%). Subjects who had IKC ≥ 4 had a 2.1 times greater risk of death (HR = 2.166; 95% CI: 1.335-3.513; $p = < 0.002$) compared to the IKC group < 4 .

Pancreatic cancer metastasis occurred in 62 subjects (74.7%). From 21 subject without metastasis, 12 did not survive (57.1%). Of 62 people with metastasis, 59 subject did not survived (95.2%). Patients with

metastatic pancreatic cancer had a 3.8 times greater risk of death than those without metastasis (HR = 3.802; 95% CI: 1.995-7.249; $p \leq 0.001$).

We also investigate the relationship between staging and survival rates. From 5 subjects with stages 1-2. 2 were survive (40%) and 3 did not (60%). Among patients with stages 3-4. we found 10 (12.8%) of them were survived until the end of this study and the rest is not (87.2%). Pancreatic cancer patients who have reached stage 3-4 have a 2.3 times greater risk of mortality (HR = 2.311; 95% CI: 0.723 - 7.385; $p = 0.158$).

To assess the relationship between treatment and pancreatic cancer. we divide subjects into 4 groups: (1) Groups of patients who underwent Whipple surgery; (2) Groups of patients who underwent palliative surgery such as bypass surgery. ERCP with plastic or metal stent placement. EUS BD. or percutaneous transhepatic biliary drainage (PTBD); (3) Groups of patients undergoing chemotherapy treatment; (4) Groups of patients without any therapy. At the end of this study 13 of 18 subject (68.4%) in group 1 did not survived. Of the 30 study subjects in the palliative treatment group. 26 subject (86.7%) did not survive. There were 5 patients undergoing chemotherapy treatment and all of them deceased. twenty seven (93.1%) of subjects without any therapy did not survive. Compared to Whipple surgery. the palliative therapy group had a 2.108 times higher mortality(95% CI: 1.007-4.125). the chemotherapy group had a 1.902 times higher mortality (95% CI: 0.677-5.346). and the group without any treatment had 2.924 times higher mortality (95% CI: 1.496-5.716).

Table 1. Subject baseline characteristics

| Characteristics | n (%) |
|----------------------|-----------|
| Gender | |
| Male | 52 (62.7) |
| Female | 31 (37.3) |
| Age | |
| ≥ 50 years old | 57 (68.7) |
| < 50 years old | 26 (31.3) |
| Ethnic | |
| Javanese | 38 (45.8) |
| Sundanese | 12 (14.5) |
| Betawinese | 13 (15.7) |
| Others | 20 (24.1) |
| Education level | |
| Elementary school | 7 (8.4) |
| Junior high school | 13 (15.7) |
| Senior high school | 41 (49.4) |
| Diploma | 7 (8.4) |
| Bachelor | 13 (15.7) |
| Post-graduate | 2 (2.4) |
| Occupation status | |
| Employed | 48 (57.8) |
| Unemployed | 35 (42.2) |
| Religion | |
| Moslem | 74 (89.2) |
| Christian | 6 (7.2) |
| Hinduism | 2 (2.4) |
| Confucius | 1 (1.2) |
| Marital status | |
| Single | 4 (4.8) |
| Married | 74 (89.2) |
| Divorced | 5 (6.0) |
| Payment status | |
| Government insurance | 81 (97.6) |
| Self paid | 1 (1.2) |
| Corporate insurance | 1 (1.2) |

Table 2. Bivariate analysis of factors related to one year survival of pancreatic cancer

| Variabel | Status | | HR (95% CI) | P |
|-----------------------|---------------|-------------------|----------------------|-------------------|
| | Survive n (%) | Not survive n (%) | | |
| Gender | | | | |
| Male | 9 (17.3) | 43 (82.7) | | |
| Female | 3 (9.7) | 28 (90.3) | 1.166 (0.724-1.879) | 0.527 |
| Age | | | | |
| < 50 years old | 6 (23.1) | 20 (76.9) | | |
| ≥ 50 years old | 6 (10.5) | 51 (89.5) | 1.597 (0.950-2.683) | 0.077 |
| Metastasis | | | | |
| No | 9 (42.9) | 12 (57.1) | | |
| Yes | 3 (4.8) | 59 (95.2) | 3.802 (1.995-7.249) | < 0.001 |
| Comorbidity | | | | |
| < 4 | 9 (18.4) | 40 (81.6) | | |
| ≥ 4 | 3 (8.8) | 31 (91.2) | 2.166 (1.335-3.513) | < 0.002 |
| Stage | | | | |
| 1-2 | 2 (40.0) | 3 (60.0) | | |
| 3-4 | 10 (12.8) | 68 (87.2) | 2.311 (0.723-7.385) | 0.158 |
| Treatment | | | | |
| Curative | 6 (31.6) | 13 (68.4) | | |
| Palliative | 4 (13.3) | 26 (86.7) | 2.108 (1.077-4.125) | 0.029 |
| Chemotherapy | 0 (0.0) | 5 (100) | 1.902 (0.677- 5.346) | 0.222 |
| Without any treatment | 2 (6.9) | 27 (93.1) | 2.924 (1.496- 5.716) | 0.002 |

*HR= hazard ratio; CI= confident interval

Table 3. Multivariate analysis of factors related to one year survival rate (first step)

| Variable | HR | 95% CI | P |
|-------------------|-------|-------------|-------|
| Stage | 1.205 | 0.313-4.636 | 0.786 |
| Treatment | | | |
| Paliative | 2.379 | 1.163-4.869 | 0.018 |
| Chemotherapy | 1.155 | 0.405-3.294 | 0.788 |
| Without treatment | 2.435 | 1.200-4.924 | 0.014 |
| Age | 1.396 | 0.814-2.396 | 0.226 |
| Comorbidity | 1.569 | 0.947-2.601 | 0.081 |
| Metastasis | 3.735 | 1.703-8.192 | 0.001 |

In Table 3. only 2 variables had p < 0.05: treatment and metastatic status. The final model is shown in Table 4.

Table 4. Multivariate analysis of factors related to one year survival rate (final model)

| Variable | HR | 95% CI | p |
|-------------------|-------|---------------|---------|
| Treatment | | | |
| Palliative | 2.510 | 1.245 – 5.061 | 0.010 |
| Chemotherapy | 1.152 | 0.405 – 3.274 | 0.791 |
| Without treatment | 2.535 | 1.277 – 5.032 | 0.008 |
| Metastasis | 4.306 | 2.125 – 8.724 | < 0.001 |

*HR = Hazard Ratio; CI = Confident interval

As seen from Table 4 above, the presence of metastasis gave the greatest risk of death with HR = 4,306 (95% CI: 2.125-8.724; p < 0.001). Without treatment and palliative therapy status provide almost equal risk, HR = 2,535 (95% CI: 1.277-5.032; p = 0.008) and 2,510 (95% CI: 1.245-5.061; p = 0.010), respectively. Median survival rate after one year observations are six months with cumulative survival of 14% (SE 0.04).

DISCUSSION

According to previous studies, the incidence of pancreatic cancer is greater in males than females, except in the 70-79 years old age group which the incidence in females was higher.⁵ This is consistent our findings

in this study which involved 52 men (62.7%) and 31 women (37.3%). This might be due to more Indonesia males that smoke and exposed to various specific chemicals which increase risk for pancreatic cancer.

Most subject are in ≥ 50 years old age group (68.7%) with an average age of 55 years old and age range of 33-79 years old. Previous study reports that the incidence are lowest at 15-49 years old group¹² and increasing conversely with age.⁵ Data in the United States found that the median age of pancreatic cancer patients was 71 years old whereas in UK is 72 years old.¹² This might be due to higher population life expectancy in developed countries that reached 77.5-80 years old.¹⁶ Life expectancy in Indonesia at 2011 according to WHO is 69.55 years old so that the incidence of pancreatic cancer at age > 70 years old is very low.¹⁶

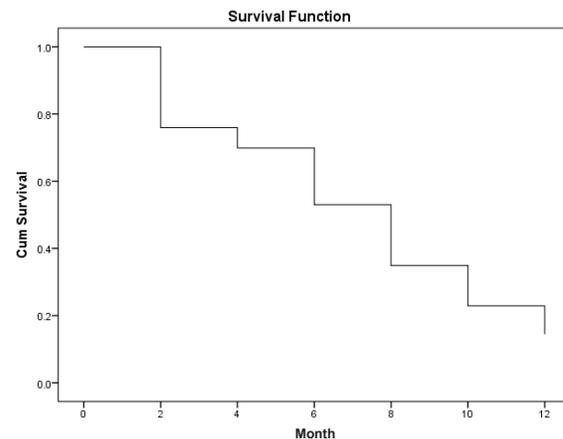


Figure 1. Cumulative survival curve of pancreatic cancer patients

Based on Qiubo Zhang et al, the number of male patients with pancreatic cancer is higher than female (39,200 vs. 26,400) but the mortality rate is quite similar (50.6% in males).¹² A study in Japan also found a higher incidence of pancreatic cancer among men (70%).⁹ In this study, the incidence of pancreatic cancer is higher in male but higher mortality in women with median survival of women is lower (5 months) than male (6 months) (HR = 1.166 (95% CI: 0.724-1.879 p = 0.527), but statistically insignificant. Which factors cause higher mortality among women have not been investigated before. Various studies only report numbers but does not analyze the cause of this phenomenon. The role of hormonal factors also still being studied.

The incidence of pancreatic cancer increases with age while its survival rate decreases by age.⁵ This is likely due to more comorbidities and limited treatment options. In this study, median survival was found similar in < 50 years old and ≥ 50 years old subjects. The prognosis is worse at older age, consistent with previous studies.

Bivariate analysis showed the relationship between comorbidity and one-year survival with HR = 2.166 (95% CI: 1.335-3.513; p = < 0.002) for IKC ≥ 4. The most commonly found comorbidities are hypertension, peripheral vascular disease, diabetes mellitus, chronic liver disease, and chronic kidney disease. Metastatic conditions due to other malignancies were not found in this study. But, subjects with IKC 9, 10, 11, or even 12 shows a poor condition. In the bivariate analysis, IKC ≥ 4 significantly related to mortality, but none in multivariate analysis.

There are 5 subjects in stage 1-2 while the rest are in stage 3-4. As a consequence, no stratification analysis was conducted. This also reflect how difficult early diagnosis of pancreatic cancer, thus it was found in advanced stages. Median survival of stage 1-2 is 11 months while 3-4 is 6 months, with HR = 2.311 in stage 3-4 (95% CI: 0.723-7.385 p = 0.158). This results might be changed if more samples are included in further study.

Metastasis was found in 62 (74.7%) subjects. Previous literature reported that most of pancreatic cancer patients are diagnosed at later stages.^{8,12} Study by Karl et al. reported that metastatic status increase risk of mortality (HR = 2.07; 95% CI: 1.59-2.69; p < 0.0001).¹⁷ Mohammad Al-Haddad et al reported 4 times higher mortality among patients with metastasis (95% CI: 1.90 - 9.52; p < 0.001).¹⁸ This was quite similar to our study with HR = 4.306 (2.125 - 8.724 p ≤ 0.001).

Based on Cancer Net Editorial Board, survival of pancreatic cancer patients reduced from 29% to 15% if metastasis had occur.¹⁵

Multivariate analysis showed that palliative treatment had HR = 2.510 (95% CI: 1.245 – 5.061; p = 0.010) compared to curative treatment, while no therapy had HR = 2.535 (95% CI: 1.277 – 5.032; p = 0.008) and chemotherapy had HR = 1.152 (95% CI: 0.405 – 3.274; p = 0.791). Sixty two patients had metastasis and only 16 patients in stage 3. This high number are likely due to less Whipple surgery compared to palliative treatment. Subjects with chemotherapy was also had insufficient number. With all this limitation, subjects underwent curative treatment had better survival compared to palliative or no therapy groups.

Cummulative survival in this study are 14% with 6 months of median survival. Wolfgang, et al. reported median survival of 8 - 12 months. A previous study also reported a 12 months survival among patients received both surgical and chemotherapy treatment.¹⁹

National cancer data showed that chemotherapy increase overall survival (HR = 0.70; 95% CI: 0.61-0.80 vs. HR = 1.04; 95% CI: 0.93-1.18). According to CONKO 001 study in 368 patients, median survival rate in patients received chemotherapy or not is 22.1 s. 20.2 months while ESPAC 1 study reported 20.1 vs 14.7 months survival (HR = 0.71; 95% CI: 0.55-0.92; p = 0.009).¹⁰ From 955 patients with pancreatic cancer, survival rate is better among patients received chemotherapy compared to surgical only (39.9 vs. 27.8 months; p < 0.001).¹ No literature yet could conclude the survival rate but mostly reported a 5-years survival rate below 5%.¹⁸

Comorbidities are correlated in IKC to pancreatic cancer. In previous studies, factors related to pancreatic cancer mortality are diabetes melitus, smoking, obesity, history of cholecystitis, and cholelithiasis.⁹ As smoking and BMI are an independent risk factors of pancreatic cancer, those variables are not included.

There are several information that could not be analyzed such as address location, education, socioeconomic level, pathologic findings, cancer location, and BMI as those factors might be related to accessibility to advanced cancer care. In this study, survival was measured from patients admission. Ideally, patients should be followed from the first appearance of clinical manifestation. Those data are not obtained due to limited information in medical records data. We also did not analyzed the relationship of each comorbidities, but only dichotomized as IKC

< 4 and \geq 4 based on Charlson index. We also did not analyzed the impact of chemotherapy type and dose to survival rate. Finally, as this study is conducted in one tertiary hospital, the result could not be generalized to Indonesian population.

CONCLUSION

One year survival rate among pancreatic cancer patients are 14% with median survival of 6 months. Metastatic status and not undergo Whipple procedure are statistically significant predictor of mortality. A prospective study with larger sample size is needed in the future to obtained a more reliable information and could be generalized to Indonesia with its multiethnicity.

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