Mortality-related Factors in Patients with Malignant Obstructive Jaundice

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ABSTRAK

Tujuan: *mendapatkan kesintasan dan faktor-faktor yang berhubungan dengan mortalitas pada pasien ikterus obstruktif dengan etiologi maligna.* ***Metode:*** *penelitian kohort retrospektif dan prospektif dilakukan dengan data sekunder pasien ikterus obstruktif yang dirawat di RS. Cipto Mangunkusumo, Jakarta antara Januari 2010–Desember 2013. Faktor-faktor yang dinilai meliputi umur, jenis kelamin, sepsis, hipoalbumin, tingkat bilirubin serum, tingkat CA 19-9 serum, drainase bilier, keganasan non ca ampula Vater, dan komorbid dengan hasil keluaran berupa mortalitas pasien.* ***Hasil:*** *sebanyak 181 dari 402 pasien ikterus obstruktif dengan etiologi maligna memenuhi kriteria penelitian dengan proporsi laki-laki sebesar 58,6 % dengan pasien berumur ≥50 tahun sebesar 57,5%. Analisis multivariat menunjukkan bahwa sepsis, riwayat drainase bilier sebelumnya dan skor komorbid Charlson ≥4 merupakan prediktor independen terhadap mortalitas. Median kesintasan pasien dengan faktor prognosis bermakna adalah 14 hari sedangkan median kesintasan keseluruhan 26 hari. Ambang skor prognostik terbaik didapatkan pada skor ≥2 dengan sensitivitas 68% dan spesifisitas 75%. AUC pada kurva ROC 0.769.* ***Kesimpulan:*** *kesintasan pasien dengan faktor prognosis sepsis, drainase bilier tidak berhasil/tidak ada, dan skor indeks komorbid Charlson ≥4 lebih pendek dibandingkan kesintasan keseluruhan pasien. Skor prognostik ≥2 termasuk dalam risiko tinggi kematian dan kemampuan prediksi mortalitas dari faktor prognosis bermakna adalah 76.9%.*

Kata kunci: *ikterus obstruktif maligna, kesintasan, mortalitas, faktor prognosis, skor prognosis.*

ABSTRACT

Aim: *to obtain survival rate and mortality-related factors of malignant obstructive jaundice patients.* ***Methods:*** *all medical records of obstructive jaundice inpatient at Cipto Mangunkusumo Hospital, Jakarta from January 2010 to December 2013 were reviewed retrospectively. The following factors were analyzed in terms of mortality: age, gender, sepsis, hypoalbumin, serum bilirubin level, serum CA 19-9 level, billiary drainage, non-ampulla Vateri carcinoma, and comorbid factors.* ***Results:*** *total 181 out of 402 patients were enrolled in this study with male proportion was 58.6%, and patients aged 50 years or above was 57.5%. Multivariate analysis showed that only sepsis, unsuccessful or no prior biliary drainage and Charlson comorbid score ≥4 were independent predictors of mortality. Patients with significant prognostic factors had median survival 14 days compared with overall median survival 26 days. Score ≥2 identified as the highest prognostic score threshold with sensitivity 68%, specificity 75%, and AUC on ROC curve 0.769.* ***Conclusion:*** *sepsis, unsuccessful or no prior bilirary drainage, and Charlson comorbid score ≥4 are factors significantly associated with shortened survival in malignant obstructive jaundice patients. Prognostic score ≥2 was determined to classify patients into high risk mortality group. Mortality of patients with those significant prognostic factors can be predicted in 76.9%.*

Keywords: *malignant obstructive jaundice, survival, mortality, prognostic factors, prognostic score.*

INTRODUCTION

Most malignant tumors causing obstructive jaundice have poor prognosis, such as pancreas cancer, cholangiocarcinoma, gall bladder cancer, and etc. At time of diagnosis, the majority of the tumors already present distant metastases. For example, pancreas cancer has very poor prognosis with median survival of 2 to 6 months after stage 4 diagnosis. Data from Cipto Mangunkusumo National General Hospital, Jakarta show an increase in obstructive jaundice with malignant etiology along with an increase in drainage procedures including percutaneous transbiliary drainage (PTBD), endoscopic retrograde cholangio-pancreaticography (ERCP).[1]

There are several available reports on identification of mortality related factors in patients with obstructive jaundice. Age and gender[2], sepsis[3], bilirubin levels[4], CA 19-9[5], albumin levels[6], drainage procedures[7] and comorbid diseases[8] were considered as related factors. Up to date, there are no available limited studies yet in Indonesia to analyze association between mortality related factors and survival rate in obstructive jaundice specifically with malignant etiology.

Mortality of obstructive jaundice depends on the cause of obstruction. Most common cause of obstructive jaundice is different for every population, therefore assessment of any mortality related factors, especially in each population, is necessary. The aim of this study is to find out the 3 months-survival rate, mortality related factors and prognostic scoring in malignant obstructive jaundice patients. The outcome of this study is to optimalize the patients' management to improve survival and quality of life.

METHODS

This study has been approved by The Ethics Committee of the Faculty of Medicine, University of Indonesia, with registry number 525/H2.F1/ETIK/2013. Our institutional database were retrospectively searched for the records of obstructive jaundice inpatients aged 18 years or older with malignant etiology who had been hospitalized in Cipto Mangunkusumo Hospital from January 2010 to February 2014. Seven hundred fifty eight patients were hospitalized in Cipto Mangunkusumo Hospital from January 2010 to February 2014 with 402 among them have malignant etiology. As many as 221 subjects were excluded due to the incomplete data regarding mortality related factors. One hundred eighty one patients were enrolled in this study, following the minimum number of subjects required.

Clinical and Laboratory Parameters

Nine potential predictive factors were studied: age, gender, sepsis, albumin levels, bilirubin levels, CA 19-9 levels, unsuccessful or no history of biliary drainage and Charlson comorbid index score. All malignant tumors found in the ampulla of Vater, pancreas, biliary duct, and liver were included in the study after confirmation through upper gastrointestinal endoscopy, abdominal ultrasonography and/or CT scan and/or MRI and/or cholangiography.

Obstructive jaundice was defined as an elevation in serum bilirubin levels. Initially, an increase in conjugated bilirubin levels occurs without affecting unconjugated bilirubin levels with a finding of mechanical obstruction. Age and gender of the patients were obtained according to patients' identity card. Sepsis was defined according to American College of Chest Physician/Society of Critical Care Medicine 1992 criteria; body temperature >38^{o}C or <36 oC, heart rate >90 beats per minute, respiratory rate >20 breaths per minute or PaCO2 <32 mmHg and leukocyte levels >12.000/mm3 or <4.000/mm3 with evidence of focal infection. Charlson Comorbid Index was used to calculate comorbid score for each patient.

Laboratory parameters include albumin, bilirubin and CA 19-9, were measured on the first day of admission. Albumin levels below 3.0 g/dl was defined as hypoalbuminemia. High bilirubin was defined if bilirubin ≥15 mg/dl. High CA 19-9 levels was defined as levels ≥100 U/ml.

Biliary Drainage

Biliary drainage had been performed through PTBD, ERCP, and/or biliodigestive bypass surgery. Drainage procedure was considered success if a minimal 2 mg/dl bilirubin serum decreased after 2 to 5 days post drainage. Patients were divided into two groups: first group with

history of biliary drainage procedure and the second group with unsuccessful or no history of biliary drainage.

Survival

Follow up for assessment of survival was done by phone calls after the study subjects' death. If the patient was unreachable via phone call, we did a home visit to the patients' registered adress.

Statistical Analysis

All numerical data were presented as mean with standard deviation or median with range. Cumulative three-month survival was measured from the date of diagnosis of obstructive jaundice with malignant etiology and calculated by the methods of Kaplan-Meier. Bivariate and multivariate analyses were performed using Cox Proportional Hazards Regression Model. Each of the predictors was transformed into covariate to mortality outcome in bivariate analysis by considering occurrence time of mortality. Predictors that were deemed of potential importance on the bivariate analysis ($P<0.2$) were included in multivariate analysis of these factors. $P<0.05$ was regarded as significant.

From each significant prognostic factor, a prognostic score was determined from the last regression model. Sensitivity, specificity, positive predictive value and negative predictive value were calculated according to considered relevant cut-off value. Receiver Operating Characteristic (ROC) curve was generated and Area Under Curve (AUC) was calculated using predictive probability from every subject that decided based on last regression model to mortality outcome. All statistical analyses were performed with SPSS for mac version 22.0.

RESULTS

During the period between January 2010 and February 2014, a total of 759 obstructive jaundice patients were hospitalized of whom 402 patients had bile duct obstruction due to malignant etiology. Total 181 patients were enrolled according to inclusion and exclusion criteria related to the completion of data. Among the subjects, 58.6% were men and men to women ratio was 1.42 with majority of all patients were aged 50 years and older. The most common etiological factor of malignant obstructive jaundice was carcinoma of the head of pancreas. There were 24 patients (13.3%) in stage 4 of the disease while 148 patients (81.6%) have insufficient staging data. Detailed characteristics of all patients are summarized in **Table 1**.

Table 1. Subject's characteristics

Variables	Values
Gender (Male), n (%)	106 (58.6)
Age (years), median (range)	52 (18.86)
Age (years), n (%)	
- <50	77 (42.5)
- ≥50	104 (57.5)
Cancer, n (%)	
- Ampulla of vater cancer	31 (17.1)
- Non ampulla of vater cancer :	
- Head of pancreas cancer	101 (55.8)
- Cholangiocarcinoma	35 (19.3)
- Lymphoma	3 (1.7)
- Gall bladder cancer	1 (0.6)
- Hepatocellular carcinoma	8 (4.4)
- Gastric cancer	1 (0.6)
- Metastatic colon cancer	1 (0.6)
- Staging	
- 1: gall bladder cancer	1 (0.6)
- 2: gastric cancer	1 (0.6)
- 3: cholangiocarcinoma, head of pancreas cancer, hepatocellular carcinoma	7 (3.9)
- 4: metastatic colon cancer, cholangiocarcinoma, head of pancreas cancer, hepatocellular carcinoma	24 (13.3)
- Data not available	148 (81.6)

From the laboratory results, most of the subjects have increased serum AST and ALT levels with median of 103.5 IU/L and 66.5 IU/L, respectively. Median value of ureum is 26.4 mg/dL and creatinine is 0.7 mg/dL. Mean of albumin levels is 2.86 g/dL with 61.9% subjects have albumin <3.0 g/dL. There were 68.2% subjects with CA 19-9 levels ≥100 U/mL with overall median of 390.2 U/mL. Baseline bilirubin level ≥15 mg/dL was found in 66.7%. Biliary drainage was performed in all subjects and 64.1% of whom have shown successful result. Charlson

comorbidity index score <4 was seen in majority of subjects (72.4%). Overall 3-month mortality was 55.2% with cumulative survival of 27.7% (SE 4.2%) and median survival of 26 days (SE 2.65 days, 95% CI 20.82 – 31.19). From bivariate analysis, all factors except gender, age and CA 19-9 levels were associated with mortality in malignant obstructive jaundice patients.

Of all the remaining prognostic factors evaluated, only those significantly affecting survival have been listed in **Table 2**. Multivariate analysis demonstrated that sepsis, unsuccessful or no history of biliary drainage and Charlson comorbid index score ≥4 were independent negative prognostic factors.

The overall median survival was 26 days (95% CI 20.82–31.19) and was significantly higher for patients without prognostic factors than with prognostic factors (median 14 days, 95% CI 9.66–18.34) as shown in **Figure 1**. According to biliary drainage procedure, there were slightly different of median survival in patients with palliative surgery and ERCP/PTBD drainage (median 32 days, SE 55.43 and median 30 days, SE 4.3, respectively). Survival improved when palliative drainage was performed after prior ERCP/PTBD with median survival of 450 days, SE 317.91. Shortened median survival was shown in patients with sepsis, unsuccessful or without prior biliary drainage and Charlson comorbid index score ≥4 (17 days SE 1.90, 15 days SE 2.68, 16 days SE 4.37, respectively).

Three of the significant prognostic factors were later then included in the last regression model to determine prognostic score (**Table 3**). Score ≥2 has good sensitivity and specificity with PPV 98.6%. Hosmer-Lemeshow test was done to predict discrimination power of the prognostic score and resulted with P-value of 0.872. Discrimination power of the scoring system in predicting three-month mortality is moderately good with AUC 0.769, 95% CI 0.668–0.871 (**Figure 2**).

Table 2. Multivariate analysis of prognostic factors

Risk factors	HR (95% CI)	p
Sepsis	2.462 (1.552-3.906)	<0.001
Hypoalbuminemia	1.275 (0.808-2.013)	0.297
Non ampulla of Vater cancer	1.622 (0.886-2.967)	0.117
Baseline bilirubin level ≥15 mg/dl	1.604 (0.988-2.603)	0.056
Unsuccessful or no history of biliary drainage	2.476 (1.562-3.923)	<0.001
Charlson comorbid index score ≥4	1.478 (1.117-2.735)	<0.001

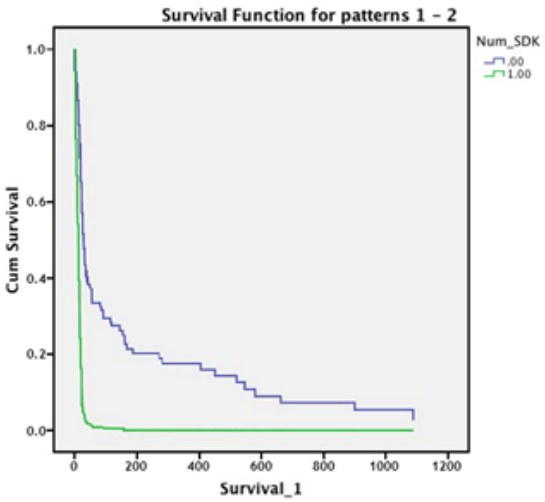

Figure 1. Comparison of survival in malignant obstructive jaundice patients related to significant prognostic factors.

DISCUSSION

In this study, nine factors were studied and three factors were significantly correlated with mortality of malignant obstructive jaundice patients: sepsis, unsuccessful or no history of biliary drainage and Charlson comorbid index score ≥4. Obstructive jaundice occurred almost

Table 3. Multivariable of mortality prognosis factors in malignant obstructive patients

Prognostic factors	coefficient (β)	SE	β/SE	Score	Round up scoring
Sepsis	0,901	0,235	3,83	1,57	2
Unsuccessful or no biliary drainage	0,907	0,235	3,86	1,58	2
Charlson comorbidity index score ≥4	0,558	0,229	2,44	1	1

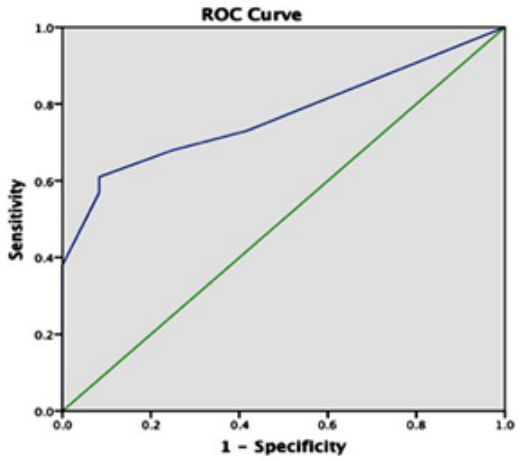

Figure 2. ROC curve of significant prognostic factors to mortality in malignant obstructive jaundice patients.

similarly in both genders with slightly higher in male than female. Majority of the cases were found in patients aged ≥50 years. A study by Moghimi et al.[2] found the male to female ratio was 1.14 and the mean age was 66.58±12.13. In this study, neither gender nor age was statistically correlated with mortality, similar with several other studies.[2,9,10]

Prevalence of obstructive jaundice in both genders depends on the disease etiology. In another study[2], carcinoma of the head of pancreas was commonly found as the cause of obstructive jaundice in males while gall bladder carcinoma more common in females, similar to our study. Different result showed in a study by Chalya et al.[3] found that age was correlated with mortality. Similar result was also found by Pitiakoudis et al.[11]

Albumin was statistically insignificant related to mortality in this study, in contrast to several previous studies.[11-13] Levels of CA 19-9 was also an insignificant factor as shown as other studies.[14,15] In contrast to our result, Ballehaninna et al.[16] found that preoperative serum of CA 19-9 <100 U/mL lead to better survival.

As concluded in prior studies,[2,3,11] sepsis was also significantly correlated with mortality in our study. Jaundice was caused by sepsis and bacterial infection in 20% of cases, as a result of immune response, bacterial products or combination of both. Endotoxemia and release of mediators of inflammation in response to infection were the highlights of cholestasis pathophysiology in sepsis. Inflammatory response and cytokines cascade promote vascular dysfunction through increase in permeability and vasodilatation that result in hypotension and disseminated intravascular coagulation. Those mechanisms lead to cellular hypoxia and lactate acidosis that potentially cause multiple organ dysfunction and death.[12,13]

Biliary drainage was thought as an important step in reducing bilirubin levels and giving more chances for patients to receive additional therapy, including surgery, chemotherapy and focus therapy. Obstructive jaundice damage the tissue due to the release of various inflammatory mediators including oxygen free radicals. A deleterious effect of inflammatory mediators cause damage to hepatic sinusoidal endothelium and liver function. High concentration of bilirubin is also associated with the impaired healing. In our study, unsuccessful biliary drainage was statistically correlated with mortality as found in several studies.[14,15] Contradictory to our studies, Choi et al.[19] found no significant differences with bilirubin decrease and possible complications of the patient as well as in meta analysis of 1826 subjects from 14 studies.[17]

Moreover, we found no significant difference in survival of patients with palliative drainage surgery and patients with ERCP/PTBD procedure. On the other hand, improved survival was shown in patients with prior ERCP/PTBD regardless type of procedure before palliative drainage surgery. Time to drainage since patient was admitted might be considered as a confounding factor that possibly explain the different result concluded in the several studies including ours. Comorbid diseases found to be statistically significant to mortality in our study. Mario et al.[21] with lower score cut off showed similar result. Finally, the mortality rate of malignant obstructive jaundice patients in our study was lower than that of previous studies.[22-24] Different prognostic factors and patients characteristic might play a part in generating different result from each study.

The prognostic score was generated according to last regression model from cox proportional hazards regression by including three significant

prognostic factors. Curve of ROC and AUC showed predictive ability of prognostic factors. We found AUC of 0.769 which means that combining all prognostic factors can predict 76.9% of mortality in malignant obstructive jaundice patients.

In summary, according to our results, sepsis, unsuccessful or no biliary drainage and Charlson comorbid index score ≥4 were all related to mortality in malignant obstructive jaundice patients. Prognostic score ≥2 was considered moderately good in categorizing patients based on the mortality risk. Further research is suggested to analyze other possible factors related to mortality and survival includes prothrombin time, Child Pugh score, disease staging and nutritional status of patients.

CONCLUSION

Sepsis, unsuccessful or no prior bilirary drainage, and Charlson comorbid score ≥4 are factors significantly associated with shortened survival in malignant obstructive jaundice patients. Prognostic score ≥2 was determined to classify patients into high risk mortality group. Mortality with those significant prognostic factors can be predicted in 76,9% of patients with obstructive jaundice.

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