Six-month Survival of Patients with Malignant Distal Biliary Stricture Following Endoscopic Biliary Stent Procedure and Its Associated Factors

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ABSTRAK

Latar belakang: *pasien striktur bilier distal maligna unresectable memerlukan pemasangan stent bilier per endoskopik. Tingkat kesintasan dan faktor-faktor yang memengaruhinya di Indonesia belum diketahui. Tujuan penelitian ini untuk mengetahui kesintasan 6 bulan pasien striktur bilier distal maligna pasca pemasangan stent bilier per endoskopik dan faktor-faktor yang berpengaruh.* ***Metode:*** *penelitian dengan desain kohort retrospektif menggunakan rekam medik pasien striktur bilier distal maligna unresectable, yang meliputi kanker kaput pankreas, ampulla/ papilla Vateri, atau kolangiokarsinoma distal pasca stent bilier per endoskopik, dilakukan di RSUPN-CM pada Juni 2015–Agustus 2017. Kesintasan kumulatif dinyatakan dengan Kurva Kaplan-Meier. Analisis bivariat dan multivariat dilakukan menggunakan regresi Cox terhadap beberapa faktor yaitu kegagalan pemasangan stent, adanya perdarahan, sepsis, komorbid, malnutrisi, dan kadar albumin serum.* ***Hasil:*** *dari total 120 subjek, 85 subjek meninggal 6 bulan pasca stent, dengan proporsi kesintasan 180 hari sebesar 24%, dan median kesintasan 81 hari (IK95% 56–106 hari). Faktor komorbid, sepsis, malnutrisi, dan albumin ≤ 3,0 g/dL memiliki nilai p<0,25 pada analisis bivariat; sedangkan analisis multivariat berikutnya menunjukkan bahwa kadar albumin ≤ 3,0 g/dL memiliki HR 2,73 (IK95% 1,48–5,05; p=0,001).* ***Kesimpulan:*** *kesintasan 6 bulan pasca stent bilier per endoskopik adalah 24% dengan median kesintasan 81 hari. Kadar albumin ≤ 3,0 g/dL memiliki risiko 2,73 kali lebih besar untuk mortalitas 6 bulan.*

Kata kunci: *kesintasan, striktur bilier distal maligna, stent bilier per endoskopik, faktor terkait mortalitas, albumin.*

ABSTRACT

Background: *unresectable malignant distal biliary stricture patients require endoscopic biliary stent placement procedure. The survival rate and its associated factors in Indonesia are unknown. This study aimed to identify 6-month survival of patients with malignant distal biliary stricture following endoscopic biliary stent procedure and its associated factors.* ***Methods:*** *a retrospective cohort study was conducted using medical records of patients with unresectable malignant distal biliary stricture, which involved caput of pancreas, ampulla of Vater or distal cholangiocarcinoma following endoscopic biliary stent procedure between June 2015 and August 2017 at Cipto Mangunkusumo National Central General Hospital. The cumulative survival was defined by using the Kaplan-*

Meier curve. Bivariate and multivariate analyses were performed using Cox regression of some factors including failure of biliary stent insertion, bleeding, sepsis, comorbidities, malnutrition, and serum albumin levels. ***Results:*** *out of total 120 subjects, 85 subjects died within 6 months following the stent procedure with a proportion of 180-day survival of 24% and a median survival of 81 days (CI 95%: 56–106 days). In bivariate analysis, factors of comorbidities, sepsis, malnutrition and albumin levels ≤ 3.0 g/dL had p values of < 0.25; while the subsequent multivariate analysis showed that albumin level of ≤ 3.0 g/dL had HR of 2.73 (CI 95%: 1.48 – 5.05; p = 0.001).* ***Conclusion:*** *the 6-month survival following endoscopic biliary stent procedure is 24% with a median survival of 81 days. Albumin level of ≤ 3.0 g/dL has a 2.73 times greater risk for 6-month mortality rate.*

Keywords: *survival, malignant distal biliary stricture, endoscopic biliary stenting, mortality-related factors, albumin.*

INTRODUCTION

Distal biliary stricture with clinical manifestation of obstructive jaundice can be caused by pancreatobiliary malignancies and the cases are increasing from 48% 1 into 53% 2 at Cipto Mangunkusumo National Central General Hospital compared to previous data a decade ago. The pancreatobiliary malignancies may be primary, such as malignancies of the head of the pancreas (caput of pancreas), ampulla of Vater, distal cholangiocarcinoma, or it may be secondary due to metastatic lesions, for instance.[1,2] Often, the patients are diagnosed with advanced stages, including both unresectable or unoperable patients; therefore, the mortality rate is high. In developing countries, the mortality rate due to pancreatobiliary malignancies ranks fifth following lung, colorectal, breast and prostate cancers.[3] The 5-year survival rate of pancreatobiliary malignancy cases is only 5% or less, with a global median of 3- to 6-month survival, and it is 4.1% in Shanghai with a median survival time of 3.9 months.[4]

Palliative care for biliary drainage may include performing endoscopic biliary stent procedure (ERCP/ EUS-BD).[5,6] Although the procedure is known as the first-line treatment in addition to percutaneous drainage or biliary bypass surgery, but it also has some risks for complications, which are associated with mortality.[2,6] Kurniawan et al found that the 3-month mortality rate for malignant obstructive jaundice cases is 55.2% with overall median survival time of 26 days.[2] However, data on survival of patients with distal biliary stricture due to unresectable malignancy, particularly following palliative care of endoscopic biliary stent procedure has not been available in Indonesia.

The aim of our study was to identify 6-month survival rate of patients with malignant distal biliary stricture following endoscopic biliary stent procedure at PESC Unit of Cipto Mangunkusumo National Central General Hospital in Jakarta, as well as its associated factors. We assumed that some factors may affect the survival rate including comorbidities,[2,7] malnutrition,[7,8] low albumin level,[9-11] bleeding,[12,13] failure at biliary stent placement,[2,13] and sepsis.[2,7,8,14]

METHODS

Our study was a retrospective cohort on adult patients (age >18 years), who had unresectable malignant distal biliary stricture case and underwent endoscopic biliary stent procedure at the Gastrointestinal Endoscopy Center/ *Pusat Endoskopi Saluran Cerna* (PESC), Department of Internal Medicine, Cipto Mangunkusumo Hospital between June 2015 and August 2017.

Data was retrieved using total sampling technique by tracing medical records and electronic health record of the patients consecutively until the minimal limit of sample size was fulfilled, which was 120 subjects. The present study had been approved by Medical Ethic Committee – Faculty of Medicine, University of Indonesia with ethic number of 0298/UN2.F1/ETIK/2018.

The collected data included subject characteristics, which were age, sex, type of malignancies based on diagnostic work-up (histopathology, radiology imaging and

ERCP), history of other diseases for evaluation of comorbidities, sepsis, bleeding, status of successful biliary stent placement and the types, the current albumin level and nutritional status when the procedure was performed including malnutrition screening tools (MST) score and the current body mass index (BMI).

The presence of comorbidities in the subjects was identified based on the total score of Charlson comorbidity index of ≥ 4 as documented on their medical records. Malnutrition was defined as unintentional weight loss or reduced dietary intake with MST score of ≥ 2, and/or the patient was categorized as underweight, i.e. BMI <18.5 kg/m^2. The presence or absence of sepsis was categorized based on diagnosis made on the subjects' medical records at their last hospitalization following biliary stent placement procedure, which was consistent with qSOFA score criteria of ≥ 2 with an evidence of infection.

Hypoalbuminemia was defined as low serum albumin levels in subjects who had been examined on their last hospitalization for having endoscopic biliary stent procedure. The albumin level was categorized low when it was ≤ 3.0 g/dL. Bleeding was defined when there is a clinical evidence of gastrointestinal bleeding or with difference of Hb level of ≥ 2 gr/dL between before and after procedure. Failure of biliary stent placement was defined by unsuccessful cannulation and/or biliary stent placement during ERCP or EUS-BD procedure by a competent operator.

We evaluated outcomes of mortality and the time of death of the observed subjects (time to event), which were determined since the first placement of endoscopic biliary stent. When the subjects was untrackable (lost to follow up) on last observation after the procedure had been performed, the subject was considered as alive on the recorded date in last outpatient medical records and was censored in the survival analysis.

Data analysis was performed using statistic program of SPSS version 23.0 for univariate, bivariate and multivariate analyses. The level of significance used in our study was $\alpha = 0.05$. Variables were considered significant when the p value < 0.05. Survival analysis using the Kaplan-Meier curve was performed, which was followed by Cox proportional hazard regression. The variables were then included into a multivariate model when the p value < 0.25.

RESULTS

Within the period of the study, we found 144 adult patients aged >18 years who fulfilled inclusion criteria. As many as 24 subjects were excluded due to incomplete data in their medical records; therefore, we found 120 subjects with characteristics as shown in **Table 1**.

Table 1. Subject's characteristics

Characteristics	n (%)	
Age		
- < 60 years	73 (60.8)	
- ≥ 60 years	47 (39.2)	
Sex		
- Male	56 (46.7)	
- Female	64 (53.3)	
Histopathology		
- Carcinoma of caput pancreas	34 (28.3)	
- Papilla vater/ periampullar carcinoma	34 (28.3)	
- Distal cholangiocarcinoma	23 (19.2)	
- Inconclusive/ other lession	29 (24.2)	
Stent		
- Successful	111 (92.5)	
- Plastic stent	80 (72.1)	
- Metal stent	31 (27.9)	
- Failed	9 (7.5)	
Sepsis		
- Yes	28 (23.3)	
- No	92 (76.7)	
Bleeding		
- Yes	20 (16.7)	
- No	100 (83.3)	
Comorbidities		
- Present	59 (49.2)	
- Absent	61 (50.8)	
Malnutrition		
- Yes	79 (65.8)	
- No	41 (34.2)	
Albumin		
- > 3.0 g/dL	28 (23.3)	
- ≤ 3.0 g/dL	92 (76.7)	
Outcome	6 months	1 year
- Alive	35 (29.2)	22 (18,3)
- Dead	85 (70.8)	98 (81,7)

The proportion of survival in patients with malignant distal biliary stricture following endoscopic biliary stent procedure based on observation of day 30, 60, 90, 180 and 360 was 58%, 46%, 38%, 24% and 6%, respectively as can be seen in **Table 2**; therefore, we found that the proportion of 3 month and 6 month mortality rate following the procedure was 62% and 76%, respectively. By the Kaplan-Meier curve in **Figure 1**, showed that median survival time (which was the time when 50% of study subjects survived) was 81 days, with a range between 56-106 days after the biliary stent placement procedure had been done.

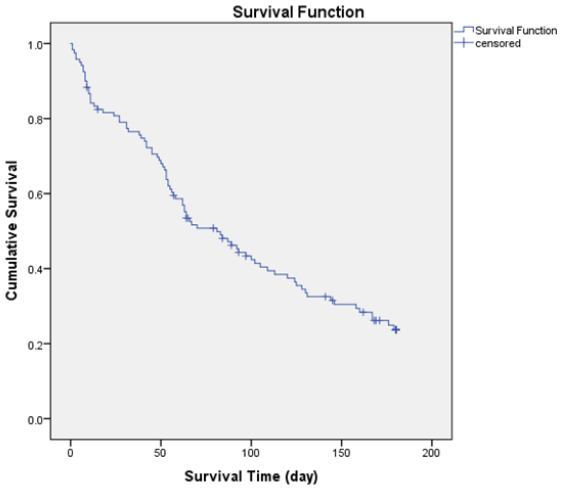

Figure 1. The Kaplan-Meier curve on 6-month survival of patients with malignant distal biliary stricture following endoscopic biliary stent procedure.

Table 2. Proportion of survival in patients with malignant distal biliary stricture following endoscopic biliary stent procedure

Survival at Day	Cumulative Proportion of Subjects Alive (%)
30	58.0
60	46.0
90	38.0
180	24.0
360	6.0

Bivariate analysis, which is presented in **Table 3**, was performed to evaluate factors that affect the survival of subjects with malignant distal biliary stricture following endoscopic stent procedure. The analysis was done using Cox regression analysis. The degree of association was presented in the form of hazard ratio (HR). Four variables, which were included as candidates in the multivariate analysis using Cox Proportional Hazard Model (**Table 4**), were variables with p value < 0.25 in the bivariate analysis, which were sepsis, the presence of

Table 3. Bivariate analysis on factors affecting 6-month survival in patients with malignant distal biliary stricture following endoscopic biliary stent procedure.

Variables	Alive, n(%)	Dead, n(%)	HR (95% CI)	p value
Stent				
- Failed	2 (22.2)	7 (77.8)	0.7 (0.3 – 1.6)	0.414
- Successful	33 (29.7)	78 (70.2)		
Sepsis				
- Yes	4 (14.3)	24 (85.7)	1.6 (1.0 – 2.7)	0.035
- No	31 (33.7)	61 (66.3)		
Bleeding				
- Yes	6 (30.0)	14 (70.0)	1.2 (0.7 – 2.1)	0.592
- No	29 (29.0)	71 (71.0)		
Comorbidities				
- Present	14 (23.7)	45 (76.3)	1.4 (0.9 – 2.1)	0.119
- Absent	21 (34.4)	40 (65.6)		
Malnutrition				
- Yes	18 (22.8)	61 (77.2)	1.8 (1.1 – 2.9)	0.017
- No	17 (41.5)	24 (58.5)		
Albumin				
- ≤ 3.0 g/dL	19 (20.7)	73 (79.3)	2.7 (1.5 – 5.0)	0.001
- > 3.0 g/dL	16 (57.1)	12 (42.8)		

Table 4. Multivariate analysis on factors affecting 6 month survival in patients with malignant distal biliary stricture following endoscopic biliary stent procedure

Steps	Variables	HR (95%CI)	p value
1st	Albumin ≤ 3.0 g/dL	2.22 (1.13 – 4.37)	0.021
	Malnutrition	1.31 (0.77 – 2.22)	0.314
	Comorbidities	1.28 (0.81 – 2.03)	0.292
	Sepsis	1.32 (0.79 – 2.19)	0.287
2nd	Albumin ≤ 3.0 g/dL	2.56 (1.38 – 4.75)	0.003
	Comorbidities	1.22 (0.78 – 1.92)	0.383
	Sepsis	1.36 (0.82 – 2.25)	0.232
3rd	Albumin ≤ 3.0 g/dL	2.58 (1.39 – 4.79)	0.003
	Sepsis	1.46 (0.91 – 2.36)	0.116
4th	Albumin ≤ 3.0 g/dL	2.73 (1.48 – 5.05)	0.001

comorbidities, the presence of malnutrition and albumin level of ≤ 3.0 g/dL. At the end of multivariate analysis, we found a significant variable ($p<0.05$) that affected survival, which was serum albumin level of ≤3.0 g/dL.

Subjects with albumin level of 3.0 g/dL or less had a risk of death as great as 2.73 times (95% CI: 1.48 – 5.05) compared to subjects with albumin level > 3.0 g/dL. It was statistically significant with p value of 0.001. Meanwhile, other variables, which were comorbidities, malnutrition and sepsis did not affect the subjects' survival.

DISCUSSION

In the present study, out of 111 subjects who had successful placement of biliary stent procedure mostly were subjects with plastic stent, that were 80 (72.1%) subjects and the other 31 (27.9%) subjects had metal stent. Median cumulative survival of subjects between both groups of biliary stent type was relatively very different, which was 66 days (95%CI: 38 – 93 days) for subjects with plastic stents and 160 days (95%CI: 53 – 267 days) for subjects with metal stent.

The 3-month cumulative survival in a study conducted by Kurniawan et al.[2] on patients with malignant obstructive jaundice at Cipto Mangunkusumo Hospital between 2010 and 2014 was 27.7% with median survival time of 26 days (95%CI: 20.8–31.2). Such difference may occur since the sample population in Kurniawan et al study also included all patients with pancreatobiliary malignancies that caused obstructive jaundice along with all kinds of treatment, both surgical and non-surgical treatment (endoscopic or percutaneous); while the population in our study was more homogenous, i.e. only unresectable pancreatobiliary malignancy cases located at the distal part of the biliary duct were included as the indication for performing endoscopic biliary stent procedure.

Another study conducted by Saudale et al found that the one-year cumulative survival rate in patients with pancreatic cancer at Cipto Mangunkusumo Hospital between 2012 and 2016 was 14% with median survival time of 6 months, which also means that the proportion of 6-month cumulative survival was 50% subjects.[15] Their results are different from our results that found the proportion of 6-month survival of 24% with median survival time of 81 days. The difference may occur since in the study[15] is more specific and was only conducted in a population of pancreatic cancer patients with all kinds of care, either curative, palliative care or even without treatment. While in our study, we included all kinds of histopathological causes of malignant distal biliary stricture, not only the pancreatic cancer, but with homogenous treatment, i.e. only endoscopic biliary stent procedure as the biliary drainage.

In the bivariate analysis of our study, we found that subjects who experienced sepsis had 1.6 times greater risk of death within 6 months following endoscopic biliary stent procedure

(95% CI: 1.0 – 2.7) and it was statistically significant on survival (p=0.035). However, when it was followed with multivariate analysis, sepsis became not significant (p=0.116). The results are different from those in Chalya et al study in 2006 to 2010 that found sepsis as one of predictor factors for mortality in patients with obstructive jaundice (p<0.001).[14] Similar to that, a study by Moghimi et al also support the results that sepsis is one of main predictors for mortality rate in hospitalized patients with odds ratio of 7.123 (95%CI: 4.78–13.54; p<0.001).[8] Another study by Kurniawan et al found sepsis as an independent prognostic factor with HR of 2.46 (95%CI: 1.55–3.91; p<0.001) in addition to other evaluated factors, i.e. hypoalbuminemia, non-ampulla Vater malignancies, initial bilirubin level of ≥15 mg/dL, unsuccessful/ no biliary drainage and Charlson comorbidity index score of 4 or more.[2]

Failure at endoscopic biliary placement had 0.7 times greater risk of death within 6 months following the procedure (95% CI: 0.3–1.6) based on bivariate analysis and it did not show statistically significant correlation to survival (p=0.414); therefore, it was not followed by multivariate analysis. Biliary drainage in the malignancy cases was performed as an essential palliative therapy as it could alleviate clinical symptoms caused by hyperbilirubinemia; therefore, it enabled physical improvement and quality of life of the patient.[6] With advances in endoscopic technique, ERCP with biliary stent placement becomes main choice of treatment for malignant distal biliary stricture cases. When CBD cannulation is difficult to perform due to the obstructing tumor mass, the biliary stent can be placed using EUS-BD.[5,13] Our study did not differentiate the proportion of how the procedure of endoscopic biliary stent placement was performed, whether by ERCP or EUS-BD. Paik et al reported that there was no significant survival between ERCP vs. EUS-BD for biliary stent placement as primary palliative treatment in malignant obstructive jaundice, with overall median survival time in ERCP group was 178 days compared to 144 days in the EUS-BD group (p=0.92).[16]

The presence of comorbidities, which was evaluated with Charlson comorbidity index score of ≥4, had 1.4 times greater risk of death within six months following endoscopic biliary stent procedure (95% CI 0.9–2.1) compared to subjects with score < 4 (p = 0.119). When it was continued with multivariate analysis, the comorbidities variable did not have a strong effect on 6-month survival and the power of this variable in our study was relatively low (31.4%). Nakai Y, et al.[17] suggested that comorbidities have more roles as prognostic factors in patients with advanced stage of pancreatic cancer. Though there are differences in capacity of predicting mortality using the index for cancer with a relatively long life expectancy (such as breast cancer or prostate cancer) compared to cancer with low life expectancy (lung cancer or pancreatic cancer), the Charlson comorbidity index has been widely used in various studies that evaluate the correlation between comorbidities and mortality or with treatment success.[18]

Based on bivariate analysis on the bleeding variable, we found that subjects with bleeding had mortality risk within 180 days following endoscopic biliary stent as many as 1.2 times (95%CI: 0.7–2.1). However, the presence or absence of bleeding did not have statistically significant correlation with subject's survival (p > 0.592); therefore, it was not continued into multivariate analysis (p>0.25). Bleeding with clinical evidence and signs of a decrease of hemoglobin level of more than 2 g/dL or there was a need for blood product transfusion were found as complications of ERCP procedure performed at Cipto Mangunkusumo National Central General Hospital in 3 out of 54 patients (5.5%).[12]

Although the rate of bleeding is relatively small, but with the presence of malignant lesion in biliary tract, particularly at distal area, the risk of difficult cannulation is also higher.[13] Hepatopancreatobiliar malignant lesion may cause hemostatic disorders, which are associated with impaired synthesis of clotting factors in the liver. The more difficult the cannulation procedure to be performed, the greater the risk of biliary trauma and bleeding.[13]

Subjects with malnutrition had 1.8 times risk of death within 6 months following endoscopic

biliary stent procedure (95% CI=1.1–2.9) and had statistically significant correlation with subject survival (p=0.017).

A study by Prat et al[7] suggested that the size of tumor and weight loss can also be predictors of survival. In patients with carcinoma of caput pancreas, 80-90% of them will experience a significant weight loss at the time the diagnosis is made.[7] However, the factor is not consistent as prognostic factor. Body weight does not exactly describe nutritional status of patients with cancer since there is extracellular fluid and edema. A more meticulous evaluation on nutritional status will increase the accuracy of the evaluation as in a study conducted by Falconer et al that used albumin data.[7] It is consistent with the results of multivariate analysis of our study, which found that malnutrition did not have a strong prognostic correlation on subject's survival with the biggest p value (p=0.314) when it was compared to other variables.

Albumin is an acute phase protein and its level decreases during inflammation, trauma and injury. Albumin level can not reflect an adequate nutritional intake of the patients. Moreover, hypoalbuminemia is highly associated with outcomes of mortality and poor morbidities such as post-gastrointestinal surgery infection.[19] Based on multivariate analysis in our study, the factor that affected subject survival the most was low albumin level of ≤ 3.0 g/dL. Subjects in such group had 2.73 times greater risk of mortality (95%CI: 1.48 – 5.05) compared to those in the group with albumin level of >3.0 g/dL, and it was statistically significant (p=0.001). It is similar to Park et al study[20], which demonstrated that patients with advanced stage of cholangiocarcinoma (unresectable) who had albumin level of >3.0 g/dL had better prognosis than patients with serum albumin level of ≤ 3.0 g/dL. Akirov et al[21] reported that hypoalbuminemia at the time of hospital admission correlated with the further lower serum albumin level before hospital discharge or on patients' mortality with risk of > 70%. Normalization of albumin level before the patients are discharged from the hospital is associated with reduced risk of death as much as 51%.

The Benefits and Limitations of Study

The present study is the first study conducted to evaluate survival following palliative endoscopic biliary stent procedure for unresectable malignant distal biliary stricture cases at Cipto Mangunkusumo Hospital in Jakarta. Using cohort design, we could identify the proportion, mortality time, median survival time and the associated factors. After we evaluate the power of survival analysis in this study to measure the effect of variables on the survival of the subject during 6 months of observation, we obtained one variable i.e hypoalbuminemia (serum albumin level ≤ 3.0 g/dL) that has excellent power (99.6%). The limitation of the present study is retrospective design as it was based on medical record data; therefore, the variables of sepsis, comorbidities and nutritional status could not be explored further. Moreover, it is difficult to evaluate the non-clinical issues that could affect services for the patients such as the speed of referral system. Our study was conducted only in a single hospital, which is the highest referral national hospital in Indonesia; therefore, the results may be less representative for similar patients in other hospitals of various settings.

CONCLUSION

As many as 24% patients with malignant distal biliary stricture at Cipto Mangunkusumo Hospital survive within a period of 6 months following endoscopic biliary stent procedure with median survival time of 81 days. Factors affecting 6-month survival in patients with malignant distal biliary stricture following endoscopic biliary stent procedure are albumin level of ≤ 3.0 mg/dL with 2.73 times greater risk for mortality incidence. The variable has an excellent power of study (99.6%).

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