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Original Article

# *Efficacy of Biliary Stent Drainage and Factors Associated with Complications in Endoscopic Palliative Treatment of Patients with Hilar Cholangiocarcinoma*

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***Abstract***

***Introduction:*** **Various types of stent drainage have been used for symptom alleviation in patients with unresectable hilar cholangiocarcinoma. However, its efficacy and factors associated with morbidity and mortality after the operation are unclear.**

***Methods:*** **We carried out a retrospective cohort study of 100 unresectable hilar cholangiocarcinoma patients treated with endoscopic biliary drainage between January 2008 and December 2009. We aimed to identify complications, jaundice resolution rate, stent patency time, and patient's survival time and to evaluate factors associated with patients' morbidity and mortality.**

***Results:*** **Plastic stents and self-expanding metallic stents (SEMS) were inserted in 12 patients and 88 patients respectively. Successful drainage was achieved in 70% of cases. Cholangitis occurred in 26% and 21 patients died within the first 30 days. Late complications occurred in 24 cases. The median patency times for plastic stent and SEMS were 57 days and 74 days respectively. The median survival times for patients with plastic stent and SEMS were 57 and 83 days respectively. Univariate analysis showed that successful drainage and albumin level less than 2 mg % were highly associated with the presence of cholangitis (P = 0.000 and P = 0.008 respectively) and associated with 30-day mortality rate (P = 0.00 and P = 0.012 respectively). After confirmation of the nine tested variables with the stent patency time and survival time using the Kaplan Mier and log rank test successful drainage and albumin level were associated with patency time and patients' survival times.**

***Conclusion:*** **Incidence of morbidity was found to be relatively low. However, more than half died within 90 days. Albumin level and successful drainage were the significant factors related with patients' morbidity and mortality.**

***Key words:*** **biliary stent, endoscopic biliary drainage, hilar cholangiocarcinoma, obstructive jaundice**

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## Introduction

Hilar cholangiocarcinoma (HC) is a common cause of malignant biliary obstruction in Asia.[1] HC has an extremely poor prognosis with a 5-year survival rate less than 10%.[2,3] Almost all of the patients with HC were asymptomatic until they were in advanced stage. Hence, less than 20% of patients were subjected to curative resection.[4-6] HC is usually classified according to Bismuth classification which is useful for decision making in relation to the resectability of tumor as patients who undergo complete tumor resection with negative resection margins have a better long-term survival.[7,8] However, the majority of patients have incurable disease at the time of presentation[9] and these patients are usually offered with palliative drainage management.[7] Currently biliary drainage through surgical, percutaneous or endoscopic approaches is the mainstay for palliative treatment of malignant obstructive jaundice. The advantages of biliary drainage are not only to relieve jaundice and pruritus but also to relieve associated anorexia, poor bowel movement, abnormal sleep pattern, poor social function, bad mental health, and other conditions that contribute to poor quality of life.[10,11]

Endoscopic stent insertion is the practical biliary drainage in many countries. There are two types of stents with individual advantages. The plastic stent is less expensive. However, it has a short patency time that last only a few months.[12,13] The advantage of self expanding metallic stent (SEMS) with an almost three-fold larger diameter after full expansion is to offer a longer patency time than a plastic stent.[12-14] The average median patency time of SEMS for malignant common bile duct obstruction ranges from 3 to 10 months.[14,15] However, many series have reported the patency time of SEMS for malignant hilar obstruction to be shorter (less than six months).[3,16]

In our study, we aimed to determine the outcomes in term of patency time, survival time as well as complications after placement of stents in patients with hilar cholangiocarcinoma. Moreover, we also analyzed factors that might influence the complications as well as the patency and survival times.

## Materials and Methods

A retrospective cohort study was carried out to determine outcomes of the placement of plastic stent and SEMS in patients with unresectable hilar cholangiocarcinoma and to find the correlation with patency and survival time and complications related to cholangitis and pancreatitis. All patients diagnosed of unresectable hilar cholangiocarcinoma with jaundice between January 2008 and December 2009 at the Khon Kaen Hospital were recruited into the present study. All participants underwent endoscopic retrograde cholangiopancreatography (ERCP). Every patient received midazolam for sedation. Prior to the procedure, antibiotic (either ciprofloxacin or ceftriaxone) was given intravenously and continuation was decided by the endoscopist. A therapeutic duodenoscope with a 4.2-mm accessory channel (TJF 150®; Olympus Optical Co., Tokyo, Japan) was used for stent insertion. Different types and lengths of plastic stents (100mm × 10 Fr, Plastic biliary stent; Boston Scientific) and SEMS (80 mm × 10 mm, 100 mm × 10 mm, Wallstent; Taewoong medical, Niti-s biliary uncoverd stent) were used. Cholangiogram was obtained by retrograde injection technique to avoid unnecessary injection into the undrainable lobes. The stent deployment technique was similar to those described elsewhere.[16] Blood chemistry parameters were assessed at admission time and one month after the operation. The patients were followed up at the Out Patient Department every three months.

Outcomes regarding the placement of stents for symptomatic alleviation in patients with hilar cholangiocarcinoma in relation to successful drainage, early and late complications, patency time and thirty-day mortality were examined. Successful drainage was defined as a decrease in bilirubin level to lower than 75% of pre-treatment value within one month. Early and late complications were defined as those occurring within 30 days and after 30 days of stent placement respectively. Cholangitis was defined as fever that developed without other discernible causes and persisted longer than 24 hours after ERCP. Pancreatitis was diagnosed when serum amylase levels rose to more than three times of the normal limit with notable persistent abdominal pain for more than 24 hours post-procedurally. Thirty-day mortality was defined as death occurred within 30 days of the first attempt of stent insertion. Stent patency time was defined as the period between the time of stent insertion until the study endpoint (stent occlusion or death; stent occlusion was defined as recurrence of jaundice,

increase in bilirubin level and late cholangitis). Survival time was defined as the time from stent insertion until death from any cause.

All variables were collected from the medical records during the admission and visit at Out-Patient Department at Khon Kaen Hospital on to a record form. The form was tested and approved by the expert physicians. Data in regard to the patients' date of death were sought through Department of Birth and Death Registry, Khon Kaen Municipality. All data were recorded into design spread sheet and put into the software computer. They were then verified for the correctness and were cleaned before the analysis. Statistical analysis was performed using statistic software package. For categorical data, number and percentage were used to summarize the findings. For inferential statistics, either chi-square or exact test was used where appropriate. For numerical data, they were tested for normal distribution using the Kolmogorov-Smirnov test. For normally distributed values, they were expressed using mean and standard deviation. For those with non-normally distributed values, they were described using median and interquartile range. Cumulative rates of stent patency and survival in each group were calculated by the Kaplan-Meier method using the log-rank chi-squared test. All statistical significances were defined as P-value < 0.05.

## Results

During the 2-year study period, 108 patients with unresectable hilar cholangiocarcinoma were admitted for elective ERCP. One hundred patients had undergone successful stent insertion and included in this study. There were 73 men and 27 women with average age of 61.4 years old (Table 1). Most of them were in Type I of Bismuth Classification. Plastic stents were inserted in 12 patients and SEMS were inserted in 88 patients. Successful drainage was achieved in 70%. Early complications occurred in 34%. Twenty one patients died within the first 30 days. Late complications occurred in 24 cases.

Regarding 24 cases with late complications, eight patients had cholangitis and were treated with appropriate antibiotics, three cases were diagnosed with complicated cholecystitis and underwent cholecystectomy. Those with cholangitis and complicated cholecystitis had clinical improvement after medical treatment. Stent occlusions occurred in 13 patients and were managed by insertion of plastic stents through the SEMS in six patients, insertion an additional SEMS in two patients, cleaning of the metallic stent by flushing and balloon sweeping in three patients and percutaneous transhepatic biliary drainage (PTBD) in two patients. The mean stent patency time in plastic stent and SEMS was 107.3 and 132.8 days, respectively and their median stent patency time was 57 and 74 days, respectively. The mean survival times of plastic stent and SEMS were 143.8 and 159.7 days, respectively and their median survival times were 57 and 83 days, respectively. Four patients were alive at the end of this study.

From the univariate analysis, successful drainage and albumin level less than 2 mg% were found highly

**Table 1** Characteristics of the participants

| | N (%)* |
|---|---|
| Mean age: Years (SD) | 61.8 (9.4) |
| Male: N (%) | 73 |
| Bismuth classification of cholangiocarcinoma: N (%) | |
| I | 34 |
| II | 25 |
| III | 24 |
| IV | 17 |
| Type of stent: N (%) | |
| Plastic | 12 |
| Metallic | 88 |
| Mean total bilirubin before ERCP: mg% (SD) | 19.1 (9.2) |
| Underlying diseases: N (%) | |
| Diabetes mellitus | 13 |
| Hypertension | 9 |
| Renal insufficiency | 2 |
| Others | 6 |
| Preoperative cholangitis: N (%) | 13 |
| Preoperative albumin: mg (%) (SD) | 2.2 (0.67) |
| Early complications : N (%) | |
| Cholangitis | 26 |
| Pancreatitis | 8 |
| Late complications : N (%) | 24 (30.4) |
| Successful drainage : N (%) | 70 (70) |
| 30 Days mortality : N (%) | 21 |
| Median patency time : Days (IQR) | 73.5 (33.5-169.2) |
| Median patency time of plastic stent | 57 (17-158 ) |
| Median patency of metallic stent | 74 (34-180.5) |
| Median survival time: Days (IQR) | 82 (35-208.5) |
| Median survival time of plastic stent | 57(19-330) |
| Median survival time of metallic stent | 83 (35-206) |

*Number in cells are N (%) excepts stated otherwise

**Table 2** Univariate analysis of factors associated with complication and 30 days mortality

| Variable | Cholangitis | | | Pancreatitis | | | Early Complication* | | | All type of Complication** | | | 30 Days Mortality | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Y | N | P-value | Y | N | P-value | Y | N | P-value | Y | N | P-value | Y | N | P-value |
| Age | | | 0.927 | | | 0.052 | | | 0.35 | | | 0.33 | | | 0.824 |
| < 45 | 1 (3.8) | 2 (2.7) | | 1 (12.5) | 2 (2.2) | | 2 (5.9) | 1 (1.5) | | 2 (3.9) | 1 (2) | | 1 (4.8) | 2 (2.5) | |
| 45-60 | 9 (34.6) | 28 (37.8) | | 5 (62.5) | 32 (34.8) | | 14 (41.2) | 23 (34.8) | | 22 (43.1) | 15 (30.6) | | 7 (33.3) | 30 (38) | |
| > 60 | 16 (61.5) | 44 (59.5) | | 2 (25) | 58 (63) | | 18 (52.9) | 42 (63.6) | | 27 (52.9) | 33 (67.3) | | 13 (61.9) | 47 (59.5) | |
| Sex | | | 0.15 | | | 0.206 | | | 0.575 | | | 0.729 | | | 0.356 |
| M | 22 (84.6) | 51 (68.9) | | 4 (50) | 69 (75) | | 26 (76.5) | 47 (71.2) | | 38 (74.5) | 35 (71.4) | | 17 (81.0) | 56 (70.9) | |
| F | 4 (15.4) | 23 (31.1) | | 4 (50) | 23 (25) | | 8 (23.5) | 19 (28.8) | | 13 (25.5) | 14 (28.6) | | 4 (19.0) | 23 (29.1) | |
| Bismuth classification | | | 0.537 | | | 0.987 | | | 0.7 | | | 0.243 | | | 0.106 |
| I | 6 (23.1) | 28 (37.8) | | 3 (37.5) | 31 (33.7) | | 9 (26.5) | 25 (37.9) | | 14 (27.5) | 20 (40.8) | | 3 (14.3) | 31 (39.2) | |
| II | 7 (26.9) | 18 (24.3) | | 2 (25) | 23 (25) | | 9 (26.5) | 16 (24.2) | | 16 (31.4) | 9 (18.4) | | (23.8) | 20 (25.3) | |
| III | 7 (26.9) | 17 (23) | | 2 (25) | 22 (23.9) | | 9 (26.5) | 15 (22.7) | | 14 (27.5) | 10 (20.4) | | 7 (33.3) | 17 (21.5) | |
| IV | 6 (23.1) | 11 (14.9) | | 1 (12.5) | 16 (17.4) | | 7 (20.6) | 10 (15.2) | | 7 (13.7) | 10 (20.4) | | 6 (28.6) | 11 (13.9) | |
| Type of Stent | | | 0.726 | | | 1 | | | 0.746 | | | 0.491 | | | 0.712 |
| Plastic | 2 (7.7) | 10 (13.5) | | 1 (12.5) | 11 (12) | | 3 (8.8) | 9 (13.6) | | 5 (9.8) | 7 (14.3) | | 3 (14.3) | 9 (11.4) | |
| Metalic | 24 (92.3) | 64 (86.5) | | 7 (87.5) | 81 (88) | | 31 (91.2) | 57 (86.4) | | 46 (90.2) | 42 (85.7) | | 18 (85.7) | 70 (88.6) | |
| Underlying diseases | | | 0.6 | | | 1 | | | 0.575 | | | 0.729 | | | 0.711 |
| Yes | 6 (23.1) | 21 (28.4) | | 2 (25) | 25 (27.2) | | 8 (23.5) | 19 (28.8) | | 13 (25.5) | 14 (28.6) | | 5 (23.8) | 22 (27.8) | |
| No | 20 (76.9) | 53 (71.6) | | 6 (75) | 67 (72.8) | | 26 (76.5) | 47 (71.2) | | 38 (74.5) | 35 (71.4) | | 16 (76.2) | 57 (72.2) | |
| Pre-op cholangitis | | | 0.314 | | | 1 | | | 0.356 | | | 0.415 | | | 0.464 |
| Yes | 5 (19.2) | 8 (10.8) | | 1 (12.5) | 12 (13) | | 6 (17.6) | 7 (10.6) | | 8 (15.7) | 5 (10.2) | | 4 (19.0) | 9 (11.4) | |
| No | 21 (80.8) | 66 (89.2) | | (87.5) | 80 (87) | | 28 (82.4) | 59 (89.4) | | 43 (84.3) | 44 (89.8) | | 17 (81.0) | 70 (88.6) | |
| Successful Drainage | | | 0*** | | | 0.101 | | | 0.002*** | | | 0.04*** | | | 0*** |
| Yes | 9 (34.6) | 61 (82.4) | | 8 (100) | 62 (67.4) | | 17 (50) | 53 (80.3) | | 31 (60.8) | 39 (79.6) | | 0 (0) | 70 (88.6) | |
| No | 17 (65.4) | 13 (17.6) | | 0 (0) | 30 (32.6) | | 17 (50) | 13 (19.7) | | 20 (39.2) | 10 (20.4) | | 21 (100) | 9 (11.4) | |
| White blood cell (cell /mm$^3$) | | | 0.064 | | | 0.583 | | | 0.264 | | | 0.478 | | | 0.817 |
| < 10,000 | 7 (26.9) | 38 (51.4) | | 5 (62.5) | 40 (43.5) | | 12 (35.3) | 33 (50) | | 21 (41.2) | 24 (49) | | 9 (42.9) | 36 (45.6) | |
| 10,000-15,000 | 11 (42.3) | 25 (33.8) | | 2 (25) | 34 (37) | | 13 (38.2) | 23 (34.8) | | 18 (35.3) | 18 (36.7) | | 7 (33.3) | 29 (36.7) | |
| > 15,000 | 8 (30.8) | 11 (14.9) | | 1 (12.5) | 18 (19.6) | | 9 (26.5) | 10 (15.2) | | 12 (23.5) | 7 (14.3) | | 5 (23.8) | 14 (17.70) | |
| Albumin (mg%) | | | 0.008*** | | | 0.063 | | | 0.201 | | | 0.680 | | | 0.012*** |
| < 2 | 18 (69.2) | 29 (39.2) | | 1 (12.5) | 46 (50) | | 19 (55.9) | 28 (42.4) | | 25 (49) | 22 (44.9) | | 15 (71.4) | 32 (40.5) | |
| > 2 | 8 (30.8) | 45 (60.8) | | 7 (87.5) | 46 (50) | | 15 (44.1) | 38 (57.6) | | 26 (51) | 27 (55.1) | | 6 (28.6) | 47 (59.5) | |

*Early complication included cholangitis and pancreatitis, **All type of complication included early complication and late complication, ***Significant, P≤0.05

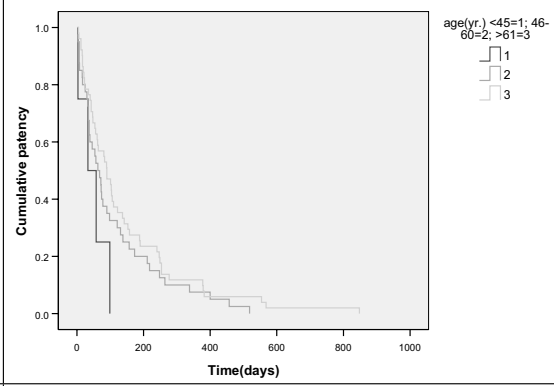
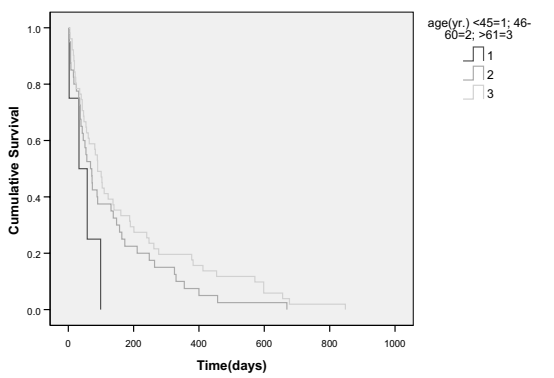
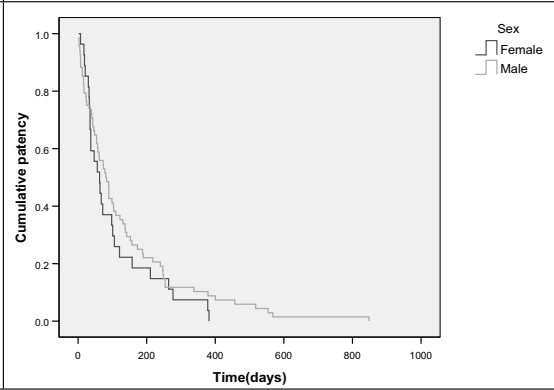
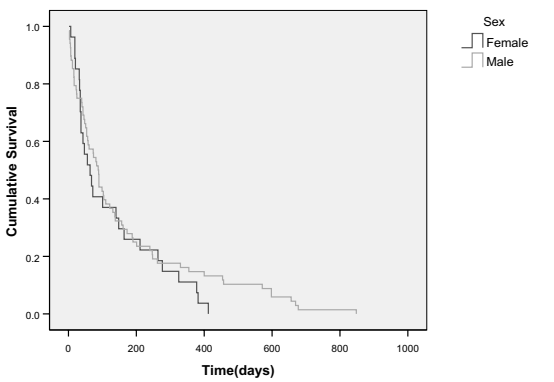
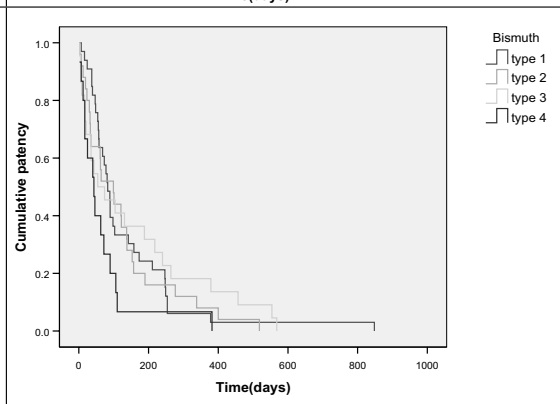
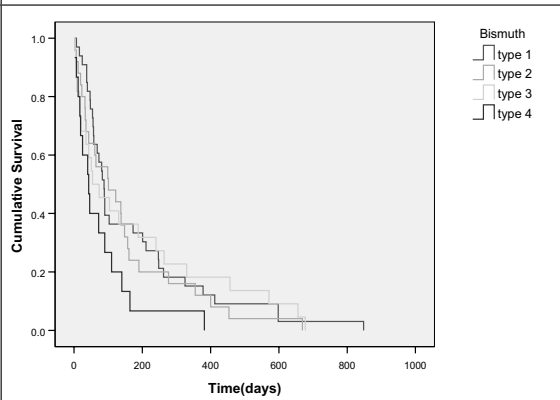
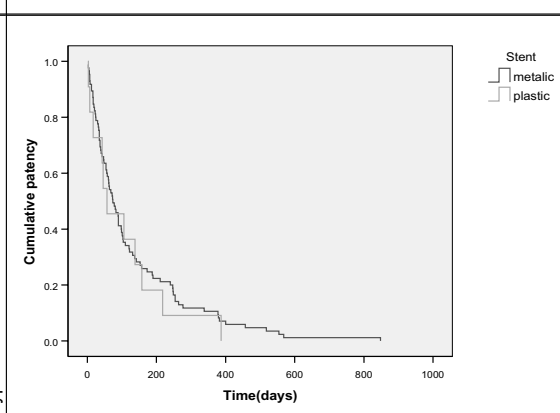
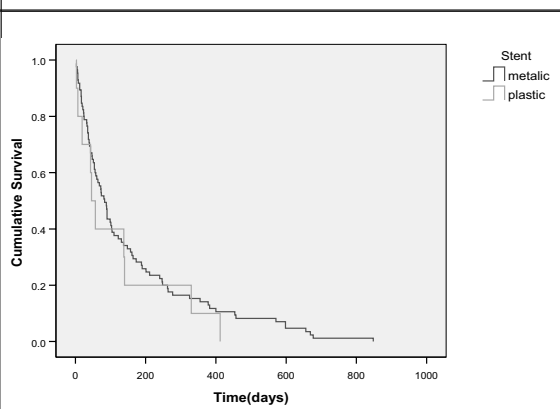
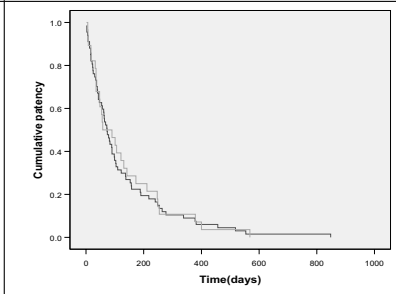
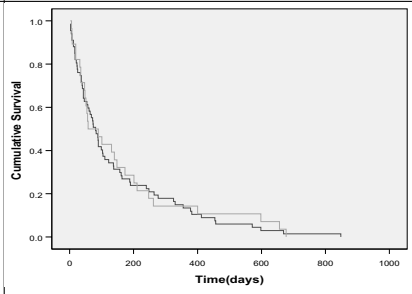
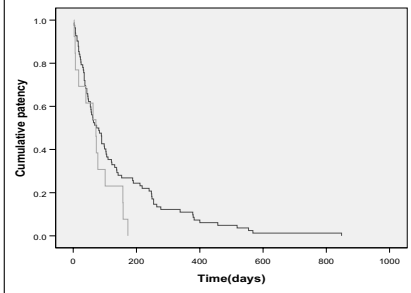
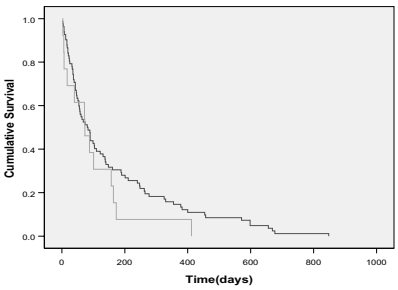
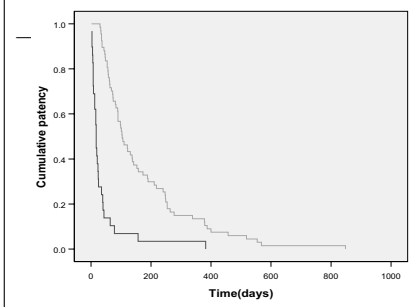
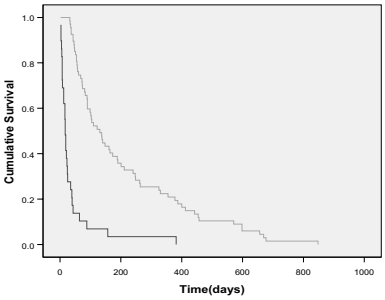
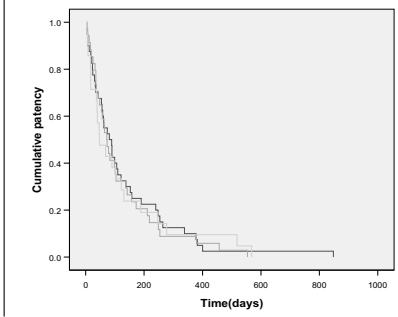
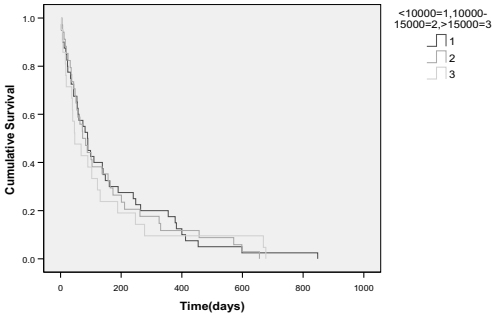
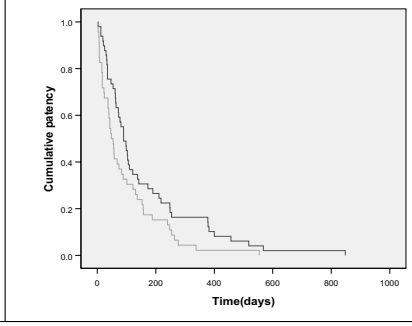
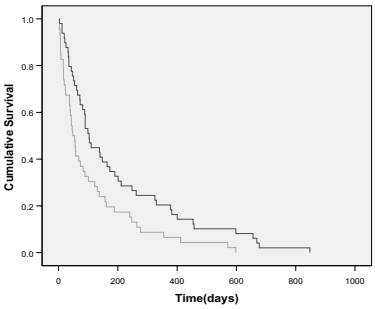
| | Patency time | P value | Survival time | P value |
|---|---|---|---|---|
| Age |  | 0.205 |  | 0.129 |
| Sex |  | 0.306 |  | 0.425 |
| Bismuth Classification |  | 0.155 |  | 0.147 |
| Type of Stent |  | 0.622 |  | 0.686 |

**Figure 1** Kaplan-Meier plot of factors associated with cumulative stent patency time and cumulative survival time

| | Patency time | P-value | Survival time | P-value |
|---|---|---|---|---|
| Underlying diseases |  | 0.986 |  | 0.891 |
| Pre -op cholangitis |  | 0.095 |  | 0.208 |
| Successful Drainage |  | 0.000<br>* |  | 0.000<br>* |
| White blood cell (cell/mm$^3$) |  | 0.916 |  | 0.835 |
| Albumin |  | 0.012<br>* |  | 0.005<br>* |

* $P < 0.05$

**Figure 1 (cont.)** Kaplan-Meier plot of factors associated with cumulative stent patency time and cumulative survival time

associated with presence of cholangitis (P = 0.00 and P = 0.008 respectively) whereas age, sex, Bismuth classification, type of stent, underlying diseases, pre-ERCP cholangitis, white blood cell count showed no significant correlation with this complication (Table 2). This pattern of correlation was observed for other complications as well as early complications, all type of complications and thirty days mortality in which only successful drainage was the only significant factor predicting complications (P = 0.002, P = 0.04 and P = 0.00, respectively). Moreover, albumin was not associated with early complications and all type of complications but it was associated with 30-day mortality (P = 0.012). After confirmation of the nine tested variables with the stent patency time and survival time using the Kaplan-Meier and log rank test, two factors that showed significant correlation were the successful drainage and albumin level (Figure1).

## Dicussion

The majority of patients underwent ERCP by insertion of SEMS. The median patency time for plastic stents was 57 days and 74 days for that of SEMS. Regarding the median survival time, it was 57 days in plastic stent and 83 days in SEMS. Early complications were found in 34 cases; 26 cases had cholangitis and eight cases had pancreatitis. Late complications were found in 24 cases; eight cases had late cholangitis, three cases had cholecystitis and stent were occluded in 13 cases. The only predictor for mortality, patency time and complication (both early and late) was the successful drainage while level of serum albumin lower than 2 mg% on the admission was significant predictor for 30-day mortality, patency time and survival time.

The present study was the largest to our knowledge that explore factors determining the outcomes of treatment in term of stent patency time, survival time and complication exclusively for hilar cholangiocarcinoma. However, there were some limitations i.e. some data were missing as this was a retrospective cohort study. Nonetheless, nearly 90% of the information was retrievable. Moreover, we did not investigate the outcomes regarding each type of the cancer using Bismuth classification. Furthermore, plastic stents were account for only 12% of cases. Direct comparison between the outcomes of using metallic versus plastic stents might be inappropriate. Success rate for the palliation of cholestasis by SEMS has been reported to be 69-97%[3,18] similar to the success rate of biliary palliation in our study (70%). Reduction of the complication and mortality is the key goal in improving outcomes of patients undergoing stenting for malignant hilar obstruction. Factors associated with adverse outcome have been explored in this study. Successful drainage and decreasing serum albumin were both significantly associated with complication and 30 days mortality from the univariate analysis and also significantly associated with stent patency time and survival time. This concurs with previous studies that showed that the palliation of biliary stasis importantly determines survival time in patients with HC.[19,20] Depression of albumin is central to the nutritional deficiency and cachexia that typifies terminal hepatopancreaticobiliary malignancy, and it has previously been shown to correlate with poor outcome in other series.[21,22]

In comparison with other studies, SEMS patency time and patient survival time in our study appeared to be shorter than the others regardless of the obstruction level.[16,17] It is speculated that all patients in our study were in advanced hilar cholangiocarcinoma while other studies included every cause and stage of hilar obstruction. With the short survival time of our patients, the question arises as to what type of stent should be used for hilar cholangiocarcinoma, the cost-effectiveness of SEMS is an important consideration. A recent systematic review demonstrated that SEMS had a better patency time than plastic stent; as early as four months after insertion SEMS was associated with an ICER of $1,820 per ERCP.[23] This meant that repeat ERCP for plastic stent occlusion costing higher than $1,820 can diminish the benefit of plastic stent insertion. So, the patients whose survival time was longer than four months should have undergone SEMS insertion whereas functionally poor status patients deemed to have a shorter prospect for survival are consigned to receive plastic stents.

In the present study, the reason for poorer performance of plastic stents in HC may be due to the characteristics of the plastic stent itself as it has a number of theoretical disadvantages including rigidity, limited malleability to the tortuous intrahepatic ductal system, increased propensity to migrate, and inability to drain secondary branch ducts. In addition to this, bacterial contamination of secondary branch ducts

blocked by the side walls of plastic stents may result in a segmental cholangitis. In contrast, SEMS offer several theoretical advantages in hilar tumors. Their small introductory caliber facilitates placement and flexibility allows a more natural and stable conformation to the hilar anatomy. The open mesh design allows secondary branch duct drainage, and imbedding of the mesh into the duct wall may limit biofilm formation. The primary disadvantage of SEMS is their substantial cost which can be 10 to 15 times higher than that of plastic stents.[24]

In our study, there are no procedure-related complications pertaining to bleeding and perforation, and the early post ERCP cholangitis and pancreatitis is comparable to other study.[3,25] Good endoscopic technique is paramount to a further reduction in the risk of cholangitis in patients with hilar obstruction. Injection of contrast into obstructed segment was deliberately limited to the distal end of the main biliary tract, and manipulation of ducts that would not be drained was avoided. A minimum volume of contrast was injected and only into the duct to be drained. A new technique known as "contrast-free" is one that uses a guidewire to traverse the stricture and perform balloon dilatation without injection of either contrast or air. Singh et al. reported a successful endoscopic biliary drainage without post ERCP cholangitis by using this technique in their 18 Bismuth type II hilar block patients.[26] At the present time, the benefit of this technique still awaits results from further studies.

In conclusion, endoscopic biliary drainage is technically feasible and safe with acceptable rate of complication in palliative treatment of patients with HC. SEMS seems to have longer patency time and survival time than plastic stent. Plastic stent, however, might be appropriate for those with relatively short life expectancy. The present study indicated that once biliary obstruction and low albumin level have been corrected, longer survival might be expected in advanced HC. However, randomized controlled trials comparing SEMS and plastic stents, as well as the analysis in term of cost effectiveness should be conducted for better understanding of the efficacy of stents and factors associated with adverse outcome.

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