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ORIGINAL ARTICLE

Risk factors of early dysfunction after switching from plastic to metal stents in malignant extrahepatic biliary obstruction

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Abstract

Background: Patients diagnosed with extrahepatic malignant biliary obstruction (MBO) often initially undergo endoscopic retrograde biliary drainage with a plastic stent (PS). Self-expandable metallic stents (SEMSs) have been shown to yield better outcomes than PS. This study aimed to identify predictors of early SEMS dysfunction in MBO patients who initially received PS and subsequently underwent SEMS placement.

Methods: We retrospectively analyzed patients who received their first SEMS insertion following prior PS placement for distal extrahepatic MBO between January 2015 and December 2021. We also analyzed the possible risk factors for early SEMS dysfunction defined as occurring within 90 days.

Results: Fifty-six patients who received their first SEMS for distal extrahepatic MBO were identified. The rate of early SEMS dysfunction was 30.1%. The main causes of early SEMS dysfunction were nonspecific cholangitis (35.3%) and stent clogging (35.3%). Multivariate logistic regression analysis identified two independent predictors of early SEMS dysfunction: (a) a history of a short PS patency (<60 days), and (b) post-endoscopic retrograde cholangiopancreatography (ERCP) cholangitis following SEMS placement. The odds ratio (OR) for (a) was 10.77 (95% confidence interval [CI] 2.54 to 45.66, $p = 0.001$), and for (b) was (OR) 6.59 (CI 1.00–43.43, $p = 0.050$).

Conclusion: Two risk factors associated with early SEMS dysfunction in patients with extrahepatic MBO are short PS patency (<60 days) before SEMS insertion and the development of post-ERCP cholangitis following SEMS placement.

Keywords: Biliary tract diseases; Cholestasis; Endoscopic retrograde; Extrahepatic; Self-expandable metallic stents

Lay Summary: For patients with extrahepatic malignant biliary obstruction, endoscopic retrograde cholangiopancreatography (ERCP)-guided stenting helps drain obstructed bile ducts. Self-expandable metallic stents (SEMS) generally perform better than plastic stents, especially in patients with a life expectancy greater than three months. However, a review of the literature shows that early SEMS dysfunction—defined as SEMS dysfunction within 90 days—affects 22.5–31% of cases, leading to treatment delays, reduced quality of life, and a higher risk of cholangitis. This retrospective study examined patients who switched from plastic to metal stents. We found that SEMS were more likely to fail early if the plastic stent lasted less than 60 days or if patients developed post-ERCP cholangitis after SEMS placement. These results highlight the need for proper timing when switching to SEMS and strict infection control to improve patient outcomes.

1. INTRODUCTION

For patients experiencing extrahepatic malignant biliary obstruction (MBO), the use of endoscopic retrograde cholangiopancreatography (ERCP)-guided biliary stenting is indicated for palliative biliary drainage[1] or for use before surgical resection.[2] The self-expandable metallic stent (SEMS) provides better outcomes compared with the plastic stent (PS) in terms of prolonged stent patency, reduced intervention rates, and fewer adverse events in patients with a life expectancy exceeding 3 months.[3–7] However, the incidence rate of SEMS dysfunction within 3 months ranges from 22.5% to 31%.[8,9] Recurrent biliary obstruction (RBO) due to SEMS dysfunction would either delay chemotherapy or surgical intervention, or worsen a patient's quality of life, possibly causing life-threatening complications

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such as cholangitis.[9] Identifying risk factors for early SEMS dysfunction is crucial, and preventive measures such as close monitoring or shorter intervals for stent replacement may help prevent RBO in high-risk patients.

In certain countries, biliary SEMS may not be covered by insurance programs, leading many MBO patients to undergo initial biliary drainage with PS. The risk factors for early SEMS dysfunction in patients who have undergone SEMS placement following initial PS placement remain unknown. This study specifically aimed to identify predictors of early SEMS dysfunction in distal extrahepatic MBO patients who underwent SEMS placement after initial PS placement.

2. METHODS

2.1. Study population

We conducted a retrospective study at Taichung Veterans General Hospital, enrolling patients with distal extrahepatic MBO, which is defined as MBO below the liver hilum, who underwent their first ERCP-guided SEMS insertion following prior PS placement between January 2015 and December 2021. Patients were followed up until March 2022. The diagnosis of MBO was based on pathological and/or typical radiological findings. Exclusion criteria were (1) concurrent intrahepatic obstruction; (2) obstruction extending to the confluence of the left and right hepatic ducts; (3) use of a SEMS as the initial drainage method; and (4) loss of follow-up within 3 months after SEMS placement. This study received approval from the Institutional Review Board of Taichung Veterans General Hospital (CE22198B) and was conducted in compliance with the ethical guidelines outlined in the Declaration of Helsinki.

2.2. Data collection

We reviewed patients' electronic medical records, along with sonography results, computed tomography (CT)/ magnetic resonance imaging (MRI) images, and ERCP data. Data collected included age, gender, and laboratory findings. These findings encompassed serum white blood cells (WBC), differential counts, C-reactive protein (CRP), total bilirubin (TB), aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT) levels. We also collected data on the etiology of stricture (primary vs metastatic), the TNM stage of cancer, anticancer therapy (including chemotherapy, radiotherapy, and immunotherapy the patients were undergoing after SEMS insertion), and their Eastern Cooperative Oncology Group (ECOG) score. We also documented prior biliary drainage procedures, the duration of patency of any previous PS before SEMS insertion, the length of the bile duct stricture, and any evidence of duodenal invasion based on endoscopy and imaging reports. Furthermore, we used the Gastric Outlet Obstruction Scoring System (GOOSS), which assigns a point score based on each patient's level of oral intake. A score of 0 indicated no oral intake tolerance, 1 indicated tolerance of liquids only, 2 allowed a soft diet, while 3 signified tolerance of a low-residue or full diet. This scoring system allowed us to objectively determine the patient's ability to eat.[10] The selection of stent length and type (uncovered, partially covered, or fully covered SEMS) was determined by experienced endoscopists. Additionally, we collected information regarding the duration of follow-up after SEMS placement, post-ERCP complications, and the underlying causes of SEMS dysfunction.

2.3. Definition

SEMS dysfunction was defined as meeting at least two of the following three criteria: (a) Ultrasound revealing new dilatation of the intrahepatic or extrahepatic bile ducts; (b) TB ≥2 mg/dL (34.2 μmol/L) with an increase ≥1 mg/dL (17.1 μmol/L) when compared to the value after initial successful drainage, or an elevation of ALP >2 times the upper limit of normal values with an increase of at least 30 U/L; (c) Presence of signs indicative of cholangitis (fever and leukocytosis or CRP elevation).[11] The causes of SEMS dysfunction were identified through imaging studies such as CT/MRI or findings from an endoscopy. These causes included stent migration or occlusion, which could have resulted from factors such as stent clogging, tumor ingrowth, or tumor overgrowth. The specific reasons for stent occlusion were determined by analyzing endoscopic observations and conducting biopsies during the reintervention process. Other cases of cholangitis that improved solely by antibiotic treatment, without requiring any additional interventions such as ERCP or other biliary drainage procedures, were classified as nonspecific cholangitis. This category encompassed conditions such as nonocclusive cholangitis or other cholangitis cases which had not been definitively determined.

Post-ERCP cholangitis was diagnosed as postoperative fever caused by the biliary system. The diagnostic criteria were based on the Tokyo Guidelines 2018.[12] Patients typically presented with signs of systemic inflammation, such as fever or chills, or had laboratory data indicating an inflammatory response and cholestasis, as well as imaging evidence of biliary dilation, strictures, stones, or stents. The definition of post-ERCP pancreatitis followed the ASGE Guidelines 2017, using the consensus definition and classification proposed by Cotton et al. in 1991.[13] ERCP-related pneumonia was defined as a fever (temperature >38°C, often with chills) within 72 hours after ERCP, accompanied by imaging evidence of pneumonia.[14]

We defined a PS patency of <60 days as short PS patency based on previous research findings. A randomized controlled study in Austria reported a stent patency of 96 days for their PS group.[15] Similarly, a study in Japan on patients with pancreatic head cancer found a median time to stent malfunction of 110 days for their PS group.[16] Additionally, PS patency in cases of distal obstruction has been reported to last between 4 and 6 months. Depending on whether patients underwent chemotherapy or radiation therapy, the median patency of PSs ranged from 38 to 133 days.[17] Based on a review of the literature, we consider PS patency of <60 days to be short and a potential risk factor affecting SEMS patency.

2.4. Endpoint

The primary endpoint of our study was to analyze the associated risk factors for early SEMS dysfunction. Additionally, we conducted an analysis to identify the causes of early SEMS dysfunction, measure the duration of SEMS patency, and evaluate any adverse events associated with ERCP. SEMS patency was defined as the period between the initial placement of the SEMS and the occurrence of SEMS dysfunction. In cases where there was no biliary obstruction, the patency period coincided with the patient's survival duration.

If the patient passed away during follow-up, we analyzed the cause of mortality. We also analyzed the associations between SEMS dysfunction and patient mortality. The cause of mortality was divided into two categories. One category was mortality related to stent-associated cholangitis, which was defined as the presence of an indwelling biliary stent, elevation of serum bilirubin, and at least two of the following: (a) bacteremia, (b) pus seen on ERCP or PTC, (c) fever, or (d) leukocytosis.[18] The other category was non-cholangitis-related mortality, which included disease progression without signs of infection or infections other than cholangitis.

Table 1

Baseline characteristics and outcomes of patients who received a SEMS for extrahepatic malignant biliary obstruction

	Patients with an SEMS (n = 56)
Age, y	72.5 (59.2-82.0)
Male, n (%)	32 (57.1)
Gallbladder in situ, n (%)	50 (89.3)
ECOG performance status, n (%)	
0	0 (0)
1	33 (58.9)
2	18 (32.1)
3	4 (7.1)
4	1 (1.8)
Initial laboratory results	
WBC (/μL)	7580 (6095-9132.5)
Neutrophil (%)	71.1 (60.5-80.1)
CRP (mg/dL)	3.7 (1.5-15.0)
AST (U/L)	32.0 (20-55)
ALT (U/L)	30.0 (15-75)
ALP(U/L)	221.0 (116-437)
GGT (U/L)	378 (123.5-528.8)
Presence of biliary stones or sludge, n (%)	22 (39.3)
Malignancy, n (%)	
Pancreatic cancer	42 (75.0)
Ampullary cancer	8 (14.2)
CCA	1 (1.8)
Gallbladder cancer	2 (3.6)
Metastatic periampullary cancer[a]	3 (5.4)
Tumor stage, n (%)	
I	4 (7.1)
II	12 (21.4)
III	8 (14.2)
IV	32 (57.1)
Cancer treatment, n (%)[b]	32 (57.1)
Chemotherapy	29
Concurrent chemoradiotherapy	2
Immunotherapy	1
Tumor response to treatment, n (%)	
Partial response	2 (6.2)
Stable disease	10 (31.3)
Progressive disease	20 (62.5)
Duodenal invasion, GOOSS score, n (%)	20 (35.7)
1	4 (7.14)
2	6 (10.71)
3	10 (17.86)
External biliary drainage, n (%)[c]	18 (32.1)
Resultant location of biliary stenosis, n (%)	
Distal bile duct	52 (92.9)
Perihilar bile duct	4 (7.1)
Length of stricture, cm	2.3 (1.7-2.7)
Type of SEMS, n (%)	
Uncovered	9 (16.1)
Partially covered	43 (76.8)
Fully covered	4 (7.1)
SEMS length, n (%)	
5 cm	5 (8.9)
6 cm	30 (53.6)
7 cm	14 (25.0)
8 cm	6 (10.7)
10 cm	1 (1.8)
ERCP-related complications, n (%)	14
Cholangitis	8 (14.3)
Pancreatitis	4 (7.1)
Pneumonia	2 (3.6)
SEMS patency, d	94.0 (44.7-243.7)
SEMS dysfunction (all), n (%)	28 (50.0)
Nonspecific cholangitis	6 (21.4)
Migration	5 (17.9)
Clogging	11 (39.3)
Tumor ingrowth	4 (14.3)
Tumor overgrowth	1 (3.6)
Liver abscess	1 (3.6)
Early SEMS dysfunction (<90 d), n (%)	17 (30.1)
Nonspecific cholangitis	6 (35.3)
Migration	1 (5.9)
Clogging	6 (35.3)
Tumor ingrowth	2 (11.8)
Tumor overgrowth	1 (5.9)
Liver abscess	1 (5.9)
History of PS patency <60 d, n (%)	23 (41.1)
PS length, n (%)	
4 cm	1 (1.8)
5 cm	10 (17.9)
7 cm	33 (58.9)
8 cm	1 (1.8)
9 cm	5 (8.9)
11 cm	2 (3.5)
PS diameter, n (%)	
7 Fr	4 (7.1)
8.5 Fr	5 (8.9)
9 Fr	1 (1.8)
10 Fr	41 (73.2)

Continuous variables are expressed as a median (25%-75% interquartile ranges).

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; CCA = cholangiocarcinoma; CRP = C-reactive protein; ECOG = Eastern Cooperative Oncology Group; GOOSS = Gastric Outlet Obstruction Scoring System; ERCP = endoscopic retrograde cholangiopancreatography; GGT = gamma-glutamyl transferase; SEMS = self-expandable metal stent; TB = total bilirubin; WBC = white blood cell count.

[a]Esophagus cancer, colon cancer, pancreatic neuroendocrine tumors.

[b]Including chemotherapy, radiation therapy, concurrent chemoradiotherapy according to the oncologist and radiation oncologist.

[c]Percutaneous transhepatic cholangiography drainage/percutaneous transhepatic gallbladder drainage before SEMS placement.

2.5. Statistical analyses

Categorical variables are presented as number (percentage) and analyzed using the Chi-square test or Fisher's exact test. Continuous variables are presented as the median (interquartile range) and analyzed using the Mann-Whitney *U* test. Predictors of early SEMS dysfunction were evaluated through logistic regression analysis, with the results expressed as odds ratios (ORs) along with 95% confidence intervals. We utilized the Kaplan-Meier technique to generate cumulative SEMS dysfunction plots and patient survival curves. The threshold for statistical significance was set at $p < 0.05$. Factors with a p value <0.1 in univariate analysis were included in multivariate analysis. For data analysis, we employed SPSS (Statistical Package for the Social Sciences, Version 25.0, Armonk, NY).

3. RESULTS

We analyzed 56 consecutive patients who underwent their first SEMS placement for extrahepatic MBO. In this cohort, 18 patients (32%) had external biliary drainage, specifically percutaneous transhepatic cholangiography drainage (PTCD) or

percutaneous transhepatic gallbladder drainage (PTGBD). Of these, 10 had external biliary drainage performed by a local hospital or had endoscopic retrograde biliary drainage (ERBD) in combination with external biliary drainage prior to being referred to a medical center for ERBD and further cancer treatment. The remaining eight patients were brought to the emergency department for biliary tract infection-related sepsis, where the emergency physicians consulted interventional radiologists for urgent placement of external drainage tubes. Additionally, 22 patients (39.3%) had biliary stones or sludge before SEMS placement. Most patients (n = 52, 92.9%) had an obstruction level below the cystic duct convergence. Furthermore, duodenal invasion was observed in 20 patients (36%). Pancreatic cancer constituted most cases (n = 40, 71%). Most malignant cases were classified as TNM stage III and IV (n = 40, 71%). Anticancer therapy was administered to 32 patients (57%), with 29 individuals receiving chemotherapy, two undergoing concurrent chemoradiotherapy, and one receiving immunotherapy. Ten patients had stable disease, while 20 experienced disease progression. Only two achieved a partial response. Out of the 56 patients, 23 (41.1%) had a history of a shorter PS patency, which was defined as requiring a PS exchange due to RBO or cholangitis within 60 days of the previous PS insertion. In total, 43 patients (76.8%) received a partially covered SEMS, four (7.1%) received a fully covered SEMS, and nine (16.1%) received an uncovered SEMS. The median levels of WBC, CRP, TB, and ALP before the procedure were 7580/μL, 3.7 mg/dL, 1.01 mg/dL, and 221 IU/dL, respectively. The median duration from PS insertion to SEMS insertion was 39.5 days, while the median follow-up time was 141 days. The median length of the PS was 7 cm, and a French size of 10 Most of the PSs were either 7 cm long (58.9%) or 5 cm long (17.8%), with the majority having a French size of 10 (73.2%). The number of prior biliary PS placements was 1 (n = 52, 92.9%), with the remaining patients having had 2. Detailed patient characteristics are summarized in Table 1.

Throughout the follow-up period, SEMS dysfunction was observed in 28 of 56 patients (50%), with 17 (30.1%) experiencing early dysfunction. The median time to dysfunction was 94 days (interquartile range: 44.7-243.7). The causes of both early and all SEMS dysfunction are outlined in Table 1. Major contributors to early SEMS dysfunction included nonspecific cholangitis (35.3%), clogging (35.3%), and tumor ingrowth (11.8%). For overall SEMS dysfunction, the primary causes were clogging (39.3%), nonspecific cholangitis (21.4%), and migration (17.9%). Adverse events occurred in 14 patients (25%), including cases of cholangitis (n = 8), pancreatitis (n = 4), and pneumonia (n = 2).

We compared data between the early SEMS dysfunction group with the non-early dysfunction group, as presented in Table 2. During the follow-up period, 34 patients (60.7%) passed away. Notably, stent-associated cholangitis-related mortality was higher in the early SEMS dysfunction group (77.8%, n = 7) when compared to the non-early dysfunction group (28%, n = 7, $p = 0.009$). Other causes of death included disease progression without any infection signs (n = 5), gastrointestinal bleeding (n = 2), cardiovascular diseases (n = 3), pneumonia (n = 7), and other sources of infection (urosepsis, catheter-related infections, peritonitis; n = 3). The cumulative survival is shown in Fig. 1. Additionally, we analyzed the previous patency of PSs, revealing that PS patency was <60 days in 25.6% (n = 10) of the non-early SEMS dysfunction group and 76.5% (n = 13) of the early SEMS dysfunction group, which is statistically significant ($p = 0.001$). We used the Chi-square test to analyze the relationship between PS patency and stent length or diameter, finding no significant differences ($p = 0.363$ and $p = 0.208$, respectively, data not shown). Similarly, there was no significant difference in stent length or diameter for early SEMS dysfunction ($p = 0.920$ and $p = 0.871$, Table 2). The median survival was 153 days for the early SEMS dysfunction group and 132 days for the non-early dysfunction group. However, this difference in survival was not statistically significant (log-rank test, $p = 0.839$). A summary of the results is presented in Table 2.

Table 3 presents the possible risk factors associated with early SEMS dysfunction. These include host factors (serologic data, hemogram, performance status, presence of biliary stones or sludge), tumor factors (cause of malignancy, tumor stage, tumor response to anticancer treatment, and location of biliary stenosis), and stent factors (type of SEMS). Univariate analyses demonstrated that post-ERCP cholangitis following SEMS placement, as well as a history of shorter PS patency were both significantly associated with a higher risk of early SEMS dysfunction (all $p < 0.050$). Multivariate logistic regression analyses further established that a history of shorter PS patency and post-ERCP cholangitis after SEMS placement independently predicted early SEMS dysfunction (OR, 10.77 [CI] 2.54-45.66, $p = 0.001$ and OR, 6.59 [CI] 1.00-43.43, $p = 0.050$, respectively). Kaplan-Meier analysis revealed that patients with a history of a short PS patency (<60 days) also experienced shorter SEMS patency compared to patients without a history of a short PS patency (Fig. 2, log-rank test, $p = 0.005$). A similar trend was also observed in the post-ERCP cholangitis group, where SEMS patency was significantly shorter compared to patients without post-ERCP cholangitis (Fig. 3, log-rank test, $p < 0.001$).

4. DISCUSSION

The recommendation for using a SEMS in patients having a life expectancy exceeding 3 months is based upon considerations of cost-effectiveness and the duration until RBO.[15,19] However, in clinical practice, SEMS dysfunction can occur within 3 months. The available literature reports an early SEMS dysfunction rate of 31%,[8] with the rate of early stent obstruction being between 13.4%[20] and 22.5%.[9] In our single-center study involving 56 patients with distal extrahepatic MBO, we observed an early SEMS dysfunction rate of 30.1%. Additionally, we noted that patients experiencing early SEMS dysfunction were at a higher risk of stent-associated cholangitis-related mortality. Identifying any risk factors which may lead to early SEMS dysfunction before transitioning from PS to SEMS is of paramount importance. In our study, we identified two risk factors for early SEMS dysfunction: a history of a short PS patency before SEMS placement and the development of post-ERCP cholangitis following SEMS placement.

Factors contributing to a shorter PS patency included an increase in bilirubin levels from the baseline and biliary tract infections. Similar risk factors for a reduced stent patency have been reported, including elevated initial bilirubin levels before ERCP,[21] as well as cholangitis before SEMS insertion in cases of malignancy-related hilar obstruction.[22,23] An inadequate ALP/GGT or bilirubin decline could indicate a slow-moving bile flow.[24] Reduced bile flow promotes the adherence of proteins and bacteria to the inner layer of the stent, leading to sludge formation, and consequently higher risks of clogging.[25] Nevertheless, whether jaundice and/or infection are the causes of a short patency of PS or the results of stent obstruction still requires further rigorous experimental analysis. In our study, the baseline serologic data and hemogram did not significantly exceed normal values. This may be because these patients had already undergone endoscopic papillotomy, biliary PS placement, or even external biliary drainage. Therefore, despite the presence of biliary tract infection, the values did not differ significantly, and thus there was no statistically significant difference.

Table 2

Patients who suffered SEMS early dysfunction vs those who did not

Characteristics	Non-early dysfunction (n = 39)	Early dysfunction (n = 17)	*p*
Age, y	76 (60-82)	71 (57-76.5)	0.209
Male, n (%)	22 (56.4)	10 (58.8)	1.000
Gallbladder in situ, n (%)	34 (87.2)	16 (94.1)	0.402
ECOG performance status, n (%)			0.424
0	0	0	
1	23 (59.0)	10 (58.8)	
2	11 (28.2)	7 (41.2)	
3	4 (10.3)	0 (0)	
4	1 (2.6)	0 (0)	
Initial laboratory results			
WBC (/μL)	7770 (6240-9540)	7080 (5340-8170)	0.258
Neutrophil (%)	70 (60.3-79.2)	72.9 (61.1-82.2)	0.354
CRP (mg/dL)	8.01 (0.9-15.0)	2.88 (1.88-17.79)	0.905
TB (mg/dL)	0.8 (0.4-3.2)	2.2 (0.6-3.2)	0.139
AST (U/L)	31.0 (20.0-52.0)	40.5 (20.2-76.3)	0.500
ALT (U/L)	29.0 (15.0-62.8)	30.0 (13.0-92.0)	0.750
ALP (U/L)	219.0 (115.0-437.0)	237.5 (127.2-418.8)	0.745
GGT (U/L)	263 (77-540)	495	1.000
Presence of biliary stones or sludge, n (%)	13 (33.3)	9 (52.9)	0.167
Malignancy, n (%)			0.700
Pancreatic cancer	28 (71.8)	14 (82.4)	
Ampullary cancer	7 (17.9)	1 (5.9)	
CCA	1 (2.6)	0 (0)	
Gallbladder cancer	1 (2.6)	1 (5.9)	
Metastatic periampullary cancer[a]	2 (5.1)	1 (5.9)	
Tumor stage, n (%)			0.573
I	2 (5.1)	2 (11.8)	
II	10 (25.6)	2 (11.8)	
III	5 (12.8)	3 (17.6)	
IV	22 (56.4)	10 (58.8)	
Cancer treatment, n (%)[b]	22 (56.4)	10 (58.8)	1.000
Chemotherapy	21 (53.8)	10 (58.8)	
Immunotherapy	1 (2.6)	0	
Tumor response to treatment, n (%)			0.592
Partial response	2 (9.1)	0 (0)	
Stable disease	7 (31.8)	3 (30)	
Progressive disease	13 (59.1)	7 (70)	
External biliary drainage, n (%)[c]	12 (30.8)	6 (35.3)	0.982
Resultant location of biliary stenosis, n (%)			0.577
Below cystic duct convergence	37 (94.9)	15 (88.2)	
Above cystic duct convergence	2 (5.1)	2 (11.8)	
Duodenal invasion, n (%)[d]	13 (33.3)	7 (41.2)	0.795
1	3 (7.7)	1 (5.9)	
2	4 (10.3)	2 (11.8)	
3	6 (15.4)	4 (23.5)	
Length of stricture, cm	2.5 (1.7-2.8)	2.1 (1.6-2.7)	0.454
Type of SEMS, n (%)			0.641
Uncovered	6 (15.4)	3 (17.7)	
Partially covered	31 (79.5)	12 (70.6)	
Fully covered	2 (5.1)	2 (11.8)	
SEMS length, n (%)			0.705
5 cm	4 (10.3)	1 (5.9)	
6 cm	22 (56.4)	8 (47.1)	
7 cm	9 (23.1)	5 (29.4)	
8 cm	3 (7.7)	3 (17.6)	
10 cm	1 (2.6)	0 (0)	
SEMS patency, d	131.0 (72-280)	50.0 (20.5-115)	
Overall survival, d[e]	132.0 (72-308)	153.0 (98.5-276.5)	0.839
Stent-associated cholangitis-related mortality, n (%)	7 (28)	7 (77.8)	0.009
Post-ERCP complications, n (%)	6 (15.4)	5 (47.1)	0.086
Cholangitis	3 (10.3)	5 (29.4)	0.047

(Continued)

Table 2

Continued.

Characteristics	Non-early dysfunction (n = 39)	Early dysfunction (n = 17)	*p*
Pancreatitis	2 (5.1)	2 (5.9)	0.577
Pneumonia	1 (2.6)	1 (5.9)	0.519
History of PS patency <60 d, n (%)[f]	10 (25.6)	13 (76.5)	0.001
PS length, n (%)			0.920
4 cm	1 (2.8)	0	
5 cm	7 (19.4)	3 (18.8)	
7 cm	23 (63.9)	10 (62.5)	
8 cm	1 (2.8)	0	
9 cm	3 (8.3)	2 (12.5)	
11cm	1 (2.8)	1 (6.3)	
PS diameter, n (%)			0.871
7 Fr	3 (8.6)	1 (6.3)	
8.5 Fr	3 (8.6)	2 (12.5)	
9 Fr	1 (2.9)	0	
10 Fr	28 (80)	13 (81.3)	

Continuous variables are expressed as a median (25%-75% interquartile ranges).

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; CCA = cholangiocarcinoma; CRP = C-reactive protein; ECOG = Eastern Cooperative Oncology Group; ERCP = endoscopic retrograde cholangiopancreatography; GGT = Gamma-glutamyl transferase; PS = plastic stent; SEMS = self-expandable metal stent; TB = total bilirubin; UA = univariate analysis; WBC = white blood cell count.

[a]Esophagus cancer, colon cancer, pancreatic neuroendocrine tumors.

[b]Including chemotherapy and immunotherapy at the time after SEMS insertion according to the oncologist.

[c]Percutaneous transhepatic cholangiography drainage/percutaneous transhepatic gallbladder drainage before SEMS placement.

[d]Gastric Outlet Obstruction Scoring System.

[e]Median survival time according to the Kaplan-Meier method.

[f]Due to new-onset obstructive jaundice or biliary tract infection.

Post-ERCP cholangitis may cause elevated serum bilirubin levels, while increased viscosity from hyperbilirubinemia can impede an adequate flow of bile, thus inducing early SEMS dysfunction.[26] Cholangitis also releases inflammatory substances, causing sludge and bile stasis. The bacterial colonization leads to biofilm formation, subsequently causing stent occlusion.[25]

Another significant cause of early stent dysfunction is non-occlusion cholangitis, which impacts patient outcomes, including delays in scheduling cancer and is associated with a 14% mortality rate within 30 days of occurrence.[27] One study evaluating the long-term risk of cholangitis in patients with a SEMS for MBO reported a 13% cholangitis incident rate within 3 months and a 40% rate within a year.[27] Yamakawa *et al.*[28] reported that

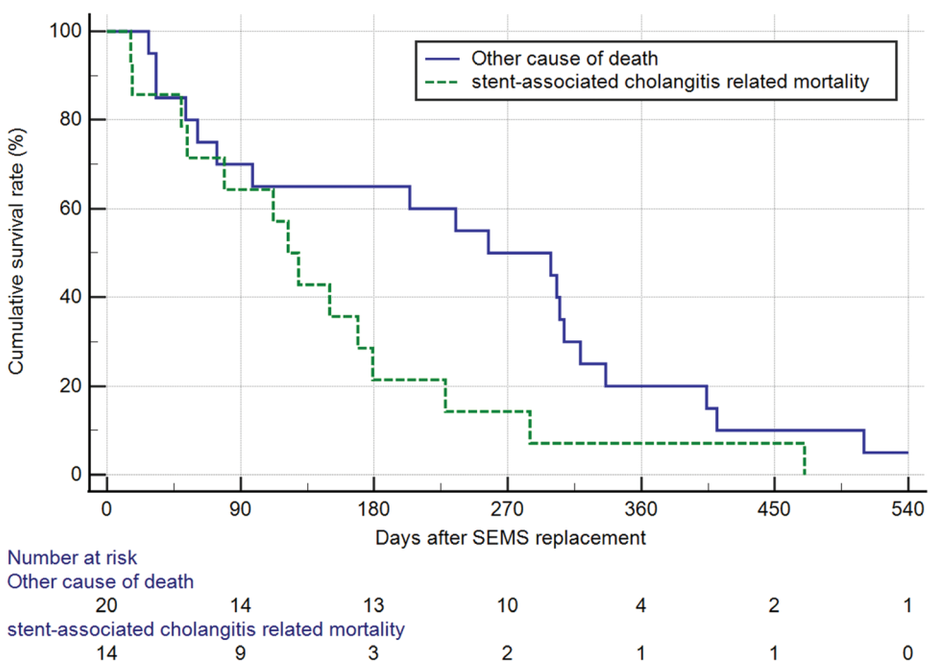

Fig. 1 The cumulative survival rate for stent-associated cholangitis-related mortality vs other causes of death, estimated through use of the Kaplan-Meier method. SEMS = self-expandable metallic stent.

Table 3

Multivariable regression analysis model for self-expandable metal stent early dysfunction

	Univariable model		Multivariable model	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age, y	0.98 (0.94-1.02)	0.345		
Male vs female	1.10 (0.35-3.50)	0.867		
ECOG				
1 (reference)	-			
2	1.46 (0.44-4.88)	0.535		
3	NE[a]	NE		
4	NE	NE		
Initial laboratory results				
WBC	1.00 (1.00-1.00)	0.244		
Neutrophil	1.02 (0.97-1.06)	0.467		
CRP	0.99 (0.83-1.18)	0.929		
TB	1.09 (0.92-1.28)	0.336		
AST	1.01 (0.99-1.02)	0.264		
ALT	1.00 (1.00-1.01)	0.285		
ALP	1.00 (1.00-1.00)	0.671		
Presence of biliary stones or sludge	2.25 (0.70-7.19)	0.171		
Malignancy				
Pancreatic cancer (reference)	-			
Ampullary cancer	0.29 (0.03-2.56)	0.262		
CCA	NE	NE		
Gallbladder cancer	2.00 (0.12-34.4)	0.633		
Metastatic periampullary cancer[b]	1.00 (0.08-12.0)	1.000		
Tumor stage				
I (reference)	-			
II	0.20 (0.02-2.39)	0.203		
III	0.60 (0.05-6.79)	0.680		
IV	0.45 (0.06-3.70)	0.461		
Cancer treatment[b]	1.10 (0.35-3.50)	0.867		
Tumor response to treatment				
Stable disease (reference)	-			
Progressive disease	1.26 (0.25-6.45)	0.784		
Partial response	NE	NE		
External biliary drainage[c]	1.23 (0.37-4.09)	0.739		
Resultant location of biliary stenosis				
Below cystic duct (reference)	-			
Above cystic duct convergence	2.47 (0.32-19.2)	0.388		
Duodenal invasion	1.40 (0.43-4.52)	0.574		
1 (reference)	-			
2	1.50 (0.09-25.39)	0.779		
3	2.00 (0.15-26.73)	0.600		
Length of stricture	0.75(0.38-1.50)	0.421		
Type of SEMS				
UC vs covered	0.85 (0.19-3.88)	0.83		
Post-ERCP cholangitis	5.00 (1.04-24.11)	0.045	6.59 (1.00-43.43)	0.050
History of PS patency <60 d	9.42 (2.48-35.68)	0.001	10.77 (2.54-45.66)	0.001

ALP = alkaline phosphatase; ALT = alanine transaminase; AST = aspartate transaminase; CCA, cholangiocarcinoma; GGT, gamma-glutamyl transferase; CRP = C reactive protein; ECOG = Eastern Cooperative Oncology Group; ERCP = endoscopic retrograde cholangiopancreatography; NE = not estimable; OR = odds ratio; PS = plastic stent; SEMS = self-expandable metal stent; TB = total bilirubin; UC = uncovered SEMS; WBC = white blood cell count.

[a]NE due to zero events in the comparison group or insufficient sample size to calculate reliable estimates.

[b]Including chemotherapy, radiation therapy, concurrent chemoradiotherapy according to the oncologist and radiation oncologist.

[c]Percutaneous transhepatic cholangiography drainage/percutaneous trans-hepatic gallbladder drainage before SEMS placement.

non-occlusion cholangitis occurs frequently in patients with distal MBO, affecting one's long-term prognosis. The cumulative incidence rate of non-occlusion cholangitis was 30% at 100 days, and 66.3% at 365 days. Duodenobiliary reflux due to duodenal invasion is thought to be the major cause.[28]

Previous studies have also reported that duodenal invasion is a significant risk factor for early dysfunction of a biliary SEMS. The major causes of SEMS dysfunction include food impaction and non-occlusion cholangitis, rather than tumor ingrowth or overgrowth,[8] a finding which is similar to our study. Reflux of gastric and duodenal contents through SEMS placed across the papilla of Vater is a common phenomenon but does not necessarily cause cholangitis, the reflux empties through the SEMS as easily as it enters.[29] Both Hamada *et al.*[8] and Kwon and Lehman[25] concluded that during duodenal invasion, the inner pressure of the duodenum may be increased by the narrowing of the duodenum or by reduced peristalsis, causing food residue or duodenal juice to ascend into the SEMS causing the formation

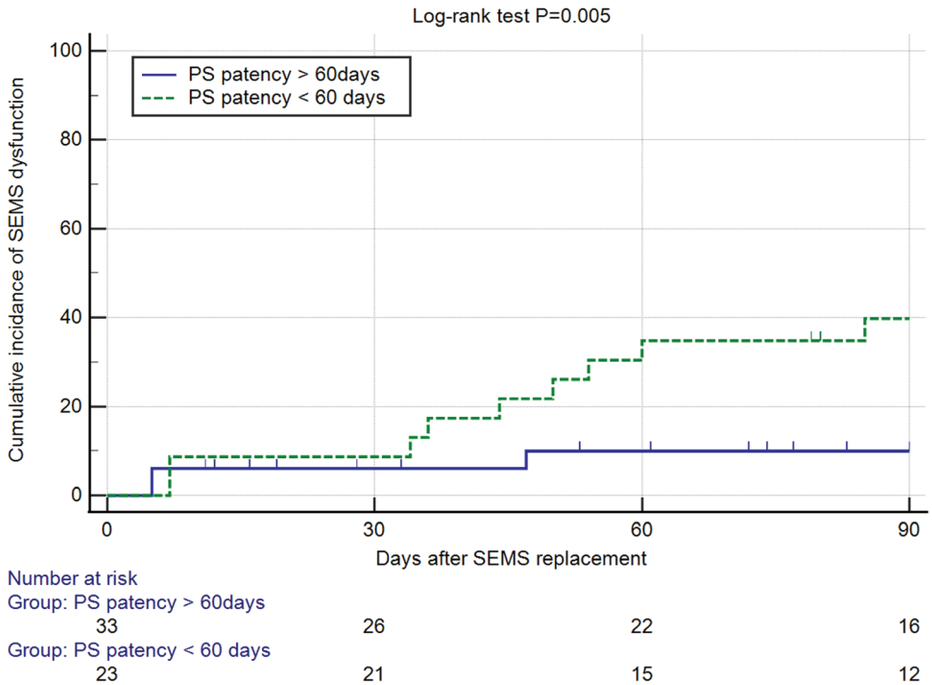

Fig. 2 Kaplan-Meier estimates of SEMS dysfunction between patients with a history of a short PS patency (<60 d) and longer plastic stents patency. PS = plastic stent; SEMS = self-expandable metallic stent.

of a bacterial biofilm and sludge in the bile duct, and thus leading to stent occlusion or cholangitis. These findings highlight the complex interplay of factors that which can contribute to SEMS dysfunction in patients with duodenal invasion. In our study, all patients underwent SEMS insertion across the ampulla of Vater. Moreover, the diagnosis of duodenal invasion was primarily based upon endoscopic examination rather than any pathologic findings. It is important to note that most of our patients exhibited a good tolerance to oral intake, with scores between 2 and 3 on the gastric outlet obstruction scoring system, indicating

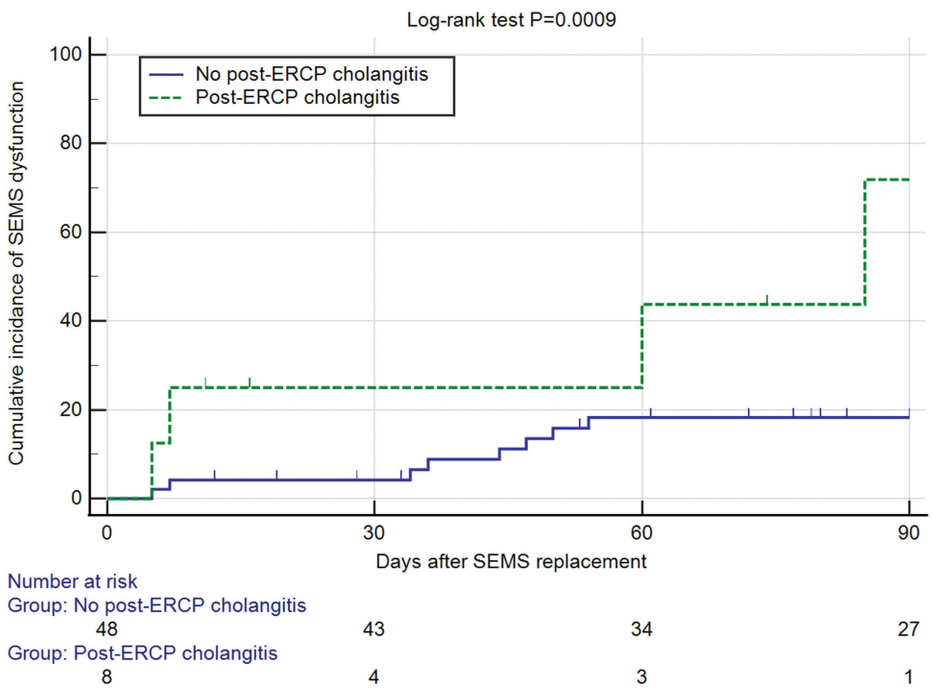

Fig. 3 Kaplan-Meier estimates of SEMS dysfunction between patients with post-ERCP cholangitis and those without post-ERCP cholangitis. ERCP = endoscopic retrograde cholangiopancreatography; SEMS = self-expandable metallic stent.

reasonable peristalsis function.[10] Given these findings, our study did not identify duodenal invasion as a significant risk factor for SEMS dysfunction.

We also analyzed the response to anticancer treatment to SEMS patency duration. Studies performed regarding the risk model of stent patency in SEMSs show that the chemotherapy group had significantly more cases of normalized bilirubin levels than the supportive care group.[30] This may explain why chemotherapy after biliary stent insertion leads to longer durations of stent patency and improved survival rates.[9,30] However, certain studies have presented a contrary view, indicating a higher percentage of occlusion in patients undergoing chemotherapy after stent insertion.[31] Other retrospective data suggest that chemo(radio) therapy does not reduce biliary stent patency.[32] Two earlier Japanese studies support our findings, as they found that there was no effect of chemotherapy on metal stent patency.[33,34] In our study, we found that anticancer therapy did not affect SEMS patency, possibly due to the treatment response not meeting expectations as well as a high disease progression rate of 62.5%.

According to the ESGE guidelines, the current recommendation is to use a SEMS for preoperative biliary drainage or palliative drainage of extrahepatic MBO. For early-stage cancer that is operable, surgery is advised unless there is cholangitis, severe symptomatic jaundice, a delay in surgery, or the need for preneoadjuvant chemotherapy in jaundiced patients. For advanced-stage patients, a SEMS is preferred for biliary drainage.[2] However, in Taiwan, the National Health Insurance plan does not cover metal stents, so the decision to use a SEMS depends on various factors, such as cost, the patient's general condition, and decisions made by ERCP specialists. In our cohort, there were 16 patients (28.5%) diagnosed with early-stage cancer (stage I or II); most of whom chose palliative treatment rather than surgery due to old age or multimorbidity. These patients later switched to a SEMS after experiencing recurring cholangitis. In contrast, 40 patients (71.3%) who were classified as either stage III or IV, most agreed to switch to the more expensive SEMS after tissue confirmation and upon the recommendation of a gastroenterologist. Still, 13 advanced-stage patients finally switched to a SEMS only after multiple episodes of biliary infection or repeated PS replacements. The median time for all patients to switch from a PS to a SEMS was 49 days. For patients with stage I cancer, the median time was 106.5 days, compared to 59.5 days for stage II, 50 days for stage III, and 46.5 days for stage IV (Supplemental Table, http://links.lww.com/JCMA/A321). Given the cost-effectiveness and technical challenges associated with SEMS intervention, we believe many other countries may face similar situations where health insurance does not cover metal stents. By analyzing the population, identifying the risk factors causing early SEMS dysfunction is a discussion extremely worthy of further consideration.

Our finding, that the history of a short PS patency is a risk factor surrounding early SEMS dysfunction, is an extremely valuable discovery. It implies that if early PS dysfunction occurs, transitioning to a SEMS may not necessarily lead to an improvement in stent patency. While this finding suggests that the factors contributing to early SEMS dysfunction may already be present before SEMS deployment, our study has also made an effort to investigate various local and systemic factors that which may increase the likelihood of SEMS occlusion and/or non-occlusive cholangitis. We conducted analyses involving initial serologic data and hemogram tests, tumor response to treatment after SEMS insertion, length of the malignant stricture, resultant location of biliary stenosis, length and diameter of the previous PS, types of SEMS, including whether they were covered or uncovered, and the presence of biliary stones, sludge or external drainage tubes (Tables 2 and 3). However, we did not identify any other risk factors for early SEMS dysfunction in our study. It is evident that further research is still necessary in order to gain a more precise understanding of the factors that predispose SEMSs to early dysfunction.

There are several limitations to our study that should be acknowledged. First, it is a retrospective study with a relatively small patient population conducted at a single center. Additionally, the retrospective data collected is prone to bias, while the non-randomized design has resulted in imbalances in patient characteristics. To confirm our findings and address these limitations, larger-scale multicenter studies that which incorporate more comprehensive patient information are still required.

In conclusion, our study has identified a prior history of short PS patency before transitioning to SEMS as well as the development of post-ERCP cholangitis following SEMS placement as two significant risk factors regarding early SEMS dysfunction in patients with extrahepatic MBO who had switched from a PS to a SEMS. Based on our findings, we recommend that clinicians carefully assess the cause of PS dysfunction and determine the optimal timing for transitioning to a SEMS. These assessments include evaluating whether any risk factors can be corrected, such as controlling a biliary infection before switching to a SEMS. Additionally, we emphasize our finding that patients having with a history of a short PS patency may require frequent stent reinterventions even after transitioning to a SEMS. These patients with risk factors may require more frequent follow-ups after SEMS placement. Given the cost-effectiveness and technical challenges associated with SEMS reintervention, the strategy of regularly changing PS may be considered as an alternative option.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A321.

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