Efficacy and safety of covered versus uncovered self-expandable metal stents for the palliative treatment of malignant distal biliary stricture: A long-term retrospective study

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Abstract. Both covered self-expandable metal stents (CSEMSs) and uncovered self-expandable metal stents (USEMSs) have been tried in the palliation of malignant distal biliary strictures by means of endoscopic retrograde cholangiopancreatography (ERCP); however, the comparison of efficacy and safety between them remains contested. To the best of our knowledge, no similar studies have assessed this in the Chinese population. In the present study, the clinical and endoscopic data of 238 patients (CSEMSs, n=55; USEMSs, n=183) with malignant distal biliary strictures from 2014 to 2019 were collected. The efficacy indicated by mean stent patency, stent patency rate, mean patient survival time and survival rate, and the safety indicated by adverse events after CSEMS or USEMS placement were retrospectively analyzed and compared. The mean stent patency time was significantly longer in the CSEMSs group than that in the USEMSs group (262.8±195.3 days vs. 169.5±155.7 days, P=0.002). The mean patient survival time was significantly longer in the CSEMSs group than that in the USEMSs group (273.9±197.6 days vs. 184.9±167.6 days, P=0.003). The stent patency rate and patient survival rate were significantly higher in the CSEMSs group than those in the USEMSs group at 6 and 12 months, but not at 1 and 3 months. There was no significant difference in stent dysfunction and adverse events between the two groups, although post-ERCP pancreatitis (PEP) occurred more frequently in the CSEMSs group than in the USEMSs group (18.1% vs. 8.8%, P=0.049). In conclusion, CSEMSs were better than USEMSs for malignant distal biliary strictures in terms of stent patency time and patient survival time as well as stent patency rate and patient survival rate in the long term (>6 months). Adverse events in the two groups occurred at a similar rate, although the incidence of PEP was higher in the CSEMSs group.

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Introduction

The most common causes of malignant biliary stricture (MBS) are the primary pancreaticobiliary tumors and other local tumors (such as gallbladder cancer and liver metastatic cancer) that compress the bile duct (1). Patients with MBS often have no obvious symptoms or signs in the early stage of the disease and typically have unexplained jaundice or manifestations of cholangitis such as abdominal pain and fever in the advanced stage (2). When MBS is diagnosed, several patients are in the advanced stage and may have lost the opportunity for surgery. Certain patients that need surgical treatment may also be inoperable due to old age and/or poor conditions. As a result, the 5-year survival rate of MBS patients is <5% (3). At present, endoscopic placement of bile duct stents is the first choice for palliative treatment of unresectable MBS and is also recommended to relieve biliary obstruction for patients who plan to undergo surgery but have cholangitis prior to surgery (4,5).

Currently, available bile duct stents include plastic stents (PSs) and self-expandable metal stents (SEMSs). The latter can be subdivided into uncovered self-expandable metal stents (USEMSs) and covered self-expandable metal stents (CSEMSs). PSs are composed of polyethylene, polyurethane, or Teflon, whereas SEMSs are made of various metal alloys that are constructed to achieve adequate radial expandable force without sacrificing flexibility and conformability to the duct (6). To better counteract tumor in growth in USEMSs, CSEMSs were developed by placing a thin nonporous membrane on the inside of the metal mesh (5,7). Studies have shown that SEMSs have the advantages of longer stent patency and lower stent obstruction rates over PSs in the palliative treatment of patients with MBS that cannot be surgically

resected (7). However, the efficacy and safety of CSEMSs vs. USEMSs in the treatment of MBS have not been clarified. There is still controversy in the selection of stents, and most choices are made based on the preference and experiences of endoscopists. Furthermore, to the best of our knowledge, no similar studies have been reported in the Chinese population. In the present study, the efficacy and safety of USEMSs and CSEMSs in the palliative treatment of malignant common bile duct strictures were compared as a 5-year retrospective study from the Chinese population in order to provide a reference for endoscopic physicians to choose the appropriate stent.

Patients and methods

Patient selection. The study was designed as a single-center retrospective study that collected data from all patients with a clinical diagnosis of distal MBS who underwent SEM placement for the first time at The First Affiliated Hospital of Nanchang University (Nanchang, China) between November 2014 and March 2019. All the patients with distal MBS involved in this research did not undergo surgery after stent placement due to the advanced nature of the tumor, old age, or poor conditions. Exclusion criteria included: i) <18 years old; ii) metastatic enlarged lymph node compression in the bile duct; iii) placement of partially covered SEMs (PC-SEMSs) in the bile duct; and iv) benign stricture confirmed by a final diagnosis (Fig. 1). The indications for CSEMS placement included distal biliary strictures and the patient intention for stent removal or replacement if the old one was obstructed. The contraindications for CSEMS placement were hilar biliary strictures. The indications for USEMS placement included malignant biliary strictures and patient intention to not remove the stent. The contraindications for USEMS placement were benign biliary strictures. All patients involved in this study provided informed consent for future research when they underwent endoscopic retrograde cholangiopancreatography (ERCP). The study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (approval number, IIT2019036) and was performed in accordance with the ethical standards described in the 1964 Declaration of Helsinki and its later amendments (8). All included cases were recorded in the Human Genetic Resources Center of the First Affiliated Hospital of Nanchang University.

Patient characteristics. General information on the patients was collected, including sex, age, tumor type, tumor staging, and laboratory test results (routine blood tests and liver function tests) within 1 week prior to and following stent placement. There were 33 males (60.0%) and 22 females (40.0%) in the CSEMS group, and 94 males (51.4%) and 89 females (48.6%) in the USEMS group, with no significant difference in sex between the two groups (P=0.260). The age of all patients ranged from 25 to 93 years old. The age (mean ± standard deviation) of the patients in the CSEMS and USEMS groups was 71.47±12.22 and 70.10±10.92 years old, respectively, with no significant difference in age between the two groups (P=0.192). The presence of the gallbladder, and whether antibiotics were used before stent placement was also recorded. Procedure-related data included pre-cut before stent placement, endoscopic sphincterotomy, pancreatic duct stent placement and biliary stent specifications. Post-ERCP surgical operation and radiotherapy or chemotherapy after stent placement were also recorded. Adverse events were recorded including biliary infection, post-ERCP pancreatitis (PEP), hyperamylasemia, bleeding, and perforation, as well as procedure-related mortality.

Outcome variables and end events. The primary outcomes included the average stent patency time, stent patency rate, and incidence of adverse events. The secondary outcomes included average patient survival time, survival rate, and liver function. The end point of this study was stent dysfunction or patient death during follow-up.

Stent placement. All ERCP procedures were performed by experienced endoscopic physicians (each performing >200 ERCP procedures per year). All patients underwent ERCP after anesthesia with propofol. The diameter of SEMSs was 10 mm, and SEMSs with different lengths (50, 60, 70 or 80 mm) were selected according to the location and length of the biliary stricture. The proximal end of the stent was placed at least 10 mm beyond the stricture, and the distal end was placed at least 10 mm outside the duodenal papilla. Both CSEMSs and USEMSs were WallFlex™ biliary self-expandable metal stents produced by Boston Scientific Corporation.

Event definition. Distal biliary stricture was defined as a stricture of the distal half of the extrahepatic bile duct (9). The diagnostic criteria for MBS were malignant signs confirmed by cytological examination, endoscopic biopsy, surgical specimens, or other pathological examinations. For patients who could not be diagnosed by the above-mentioned pathological examinations, or patients who refused or could not complete the examinations, the stricture was regarded as MBS if the patients demonstrated malignant progression after 1 year of follow-up (10,11). Stent patency was assessed as the period from stent insertion to stent dysfunction or patient death. Survival time was defined as the overall survival time, from stent insertion to death. Survival rate was defined as the percentage of patients alive as a product of the starting number of patients. Stent dysfunction was diagnosed when the patient developed signs of cholangitis (fever, tenderness on the right upper quadrant, and/or ≥2-fold elevation of the total serum bilirubin above the baseline level following stent placement) (12). Technical success was defined as the successful placement of the stent across the stricture according to appropriate radiographic positioning with bile or contrast outflow (13).

Statistical analysis. All analyses were performed using SPSS version 25.0 (IBM Corp.). A Student's t-test was used for the comparison of continuous variables. A χ^2 test or Fisher's exact test was used for comparison of categorical variables. Mixed ANOVA followed by Bonferroni/Sidak's test was used for multiple comparisons. The cumulative stent patency rate and patient survival rate were analyzed using Kaplan-Meier curves. If the Kaplan-Meier curves of the two groups did not cross each other, a log-rank test was performed. Otherwise, the two-stage procedure was performed. If the log-rank test gave a significant result, then the entire two-stage procedure was halted and it was concluded that the Kaplan-Meier curves

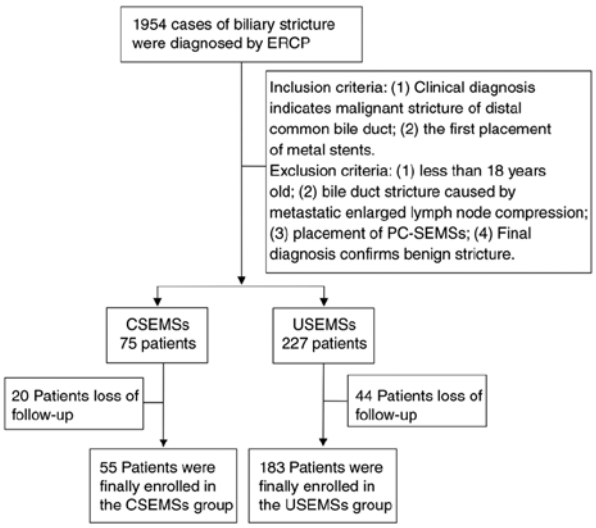

Figure 1. Flow diagram of patient enrollment. CSEMSs, covered self-expandable metal stents; USEMS, uncovered SEMSs; PC-SEMSs, partially covered SEMSs; ERCP, endoscopic retrograde cholangiopancreatography.

of the two groups were significantly different. Otherwise, the stage-II test was performed, which was designed specifically for detecting the crossing difference between the two hazard rate functions and has the property that its test statistic was independent of the log-rank test statistic. P<0.05 was considered to indicate a statistically significant difference.

Results

General patient information. A total of 238 patients who underwent SEMS placement with ERCP were included in the study (55 in the CSEMSs group and 183 in the USEMSs group). The primary reason for the large difference in the numbers between the two groups was hospital procurement. USEMSs were introduced into The First Affiliated Hospital of Nanchang University in 2014, whereas CSEMSs were not introduced until 2016, thus USEMSs were the only choice of SEMSs for patients prior to 2016. All the patients that accepted SEMSs were included in this retrospective study, such that the number of USEMS patients was ~3x larger than that of the CSEMSs patients. Elderly patients >70 years old were predominant in both groups and the age distribution between the two groups did not differ significantly (P=0.192). Regarding the causes of MBS, there were 27 cases (49.1%) of pancreatic cancer, 15 (27.3%) of cholangiocarcinoma, 1 (1.8%) of gallbladder cancer, 8 (14.5%) of duodenal papillary cancer, and 4 (7.3%) of others in the CSEMSs group and 76 (41.6%), 74 (40.4%), 9 (4.9%), 13 (7.1%) and 11 (6.0%), respectively, in the USEMSs group. There was no significant difference in the cause distribution of MBS between the two groups (P>0.05), no difference in the tumor staging between the two groups (P>0.05), and the technical success rate of stent placement in both groups was 100%. The number of patients who underwent cholecystectomy prior to stent placement was 6 (10.9%) in the CSEMSs group and 14 (7.7%) in the USEMSs group, with no significant difference (P=0.418). Antibiotics use prior to stenting was more frequently used in the CSEMSs group (n=13, 23.6%) than in the USEMSs group (n=20, 10.9%) (P=0.017). In terms of ERCP-related procedures, no significant difference was seen in the pre-cut, endoscopic sphincterotomy, and pancreatic duct stent placement between the two groups (P>0.05). In terms of stent length, biliary stents 60 mm in length were more commonly used in the CSEMSs group (n=41, 74.5%) than in the USEMSs group (n=76, 41.5%) (P<0.001). No patients underwent surgical operations after stent placement in either group and there was no significant difference with regard to radiotherapy or chemotherapy after stent placement between the two groups (P=0.458) (Table I).

Laboratory results. There was no significant difference in liver function between the CSEMSs and USEMSs groups both prior to and following the placement of SEMSs (P>0.05). The levels of serum bilirubin, aminotransferase, γ-glutamyl transferase (γ-GT), and other parameters. after SEMS placement were significantly lower than those prior to SEMSs placement in both groups (P<0.05). The amylase levels after ERCP were significantly higher than that before ERCP in both groups (P<0.05) (Table II).

Stent patency and patient survival. The overall stent dysfunction (caused by stent obstruction or stent migration) rates in the CSEMSs group and the USEMSs group within the follow-up period were 20.0 and 18.6% respectively, with no significant differences between the two groups. The stent patency time of the CSEMSs group (262.8±195.3 days) was significantly longer than that of the USEMSs group (169.5±155.7 days) (P=0.002). The stent patency rates at 1, 3, 6 and 12 months after stent placement were 90.9, 74.5, 56.4 and 29.1%, respectively, in the CSEMSs group, and 89.6, 62.3, 33.9 and 12.0%, respectively, in the USEMSs group. The stent patency rates of the two groups did not differ significantly 1 and 3 months after stent placement (P>0.05), but the stent patency rates of the CSEMSs group at 6 and 12 months were significantly higher than those of the USEMSs group (P<0.05). The patient survival time of the CSEMSs group (273.9±197.6 days) was significantly longer than that of the USEMSs group (184.9±167.6 days) (P=0.003). Patient survival rates at 1, 3, 6 and 12 months were 94.5, 76.4, 58.2 and 34.5%, respectively, in the CSEMSs group and 90.7, 65.6, 37.2 and 13.7%, respectively, in the USEMSs group. No significant difference in survival rates was observed between the two groups at 1 and 3 months after stent placement (P>0.05), but the survival rates of the CSEMSs group at 6 and 12 months were significantly higher than those of the USEMSs group (P<0.05) (Table III). It was noted that 5 patients with stage I tumors from the USEMSs group lived for a longer period of time (>600 days after stent placement) than all the patients from the CSEMSs group although there was no significant difference between the two groups in the ratios of all the stages of tumors. The Kaplan-Meier curve showed that the cumulative stent patency rate of the CSEMSs group was higher than that of the USEMSs group (P=0.003) (Fig. 2A) and the cumulative patient survival rate of the CSEMSs group was significantly higher than that of the USEMSs group (P=0.009) (Fig. 2B).

Adverse events. The total incidence of postoperative adverse events in the CSEMSs group and the USEMSs group was 25.5 and 19.7%, respectively, with no significant difference (P=0.356). The incidence of PEP in the CSEMSs group (18.1%)

Table I. Patient characteristics.

Patient characteristics	CSEMSs	USEMSs	P-value
Number of patients, n	55	183	
Sex, n (%)			0.260
Male	33 (60.0)	94 (51.4)	
Female	22 (40.0)	89 (48.6)	
Age, years			
Mean ± SD	71.47±12.22	70.10±10.92	0.192
<50	4 (7.3)	9 (4.9)	0.504
50-60	7 (12.7)	25 (13.7)	0.859
61-70	12 (21.8)	50 (27.3)	0.415
>70	32 (58.2)	99 (54.1)	0.593
Causes of strictures, n (%)			
Pancreatic cancer	27 (49.1)	76 (41.6)	0.321
Cholangiocarcinoma	15 (27.3)	74 (40.4)	0.077
Gallbladder cancer	1 (1.8)	9 (4.9)	0.461
Duodenal papillary carcinoma	8 (14.5)	13 (7.1)	0.104
Others	4 (7.3)	11 (6.0)	0.754
Tumor staging, n (%)			
I	23 (41.8)	79 (43.2)	0.859
II	5 (9.1)	20 (10.9)	0.697
III	6 (10.9)	21 (11.5)	0.908
IV	21 (38.2)	63 (34.4)	0.609
Technical success, n (%)	55 (100)	183 (100)	1.000
Cholecystectomy before ERCP, n (%)	6 (10.9)	14 (7.7)	0.418
Antibiotics use before stent placement, n (%)	13 (23.6)	20 (10.9)	0.017[a]
Pre-cut before stent placement, n (%)	10 (18.2)	24 (13.1)	0.346
Endoscopic sphincterotomy, n (%)	20 (36.4)	54 (29.5)	0.335
Pancreatic duct stent placement, n (%)	16 (29.1)	39 (21.3)	0.230
Size of SEMSs in mm[c]			
10x50	Unavailable	6 (3.3)	-
10x60	41 (74.5)	76 (41.5)	<0.001[b]
10x70	Unavailable	33 (18.0)	-
10x80	14 (25.5)	68 (37.2)	0.109
Post-ERCP surgical operation, n (%)	0	0	-
Radiotherapy or chemotherapy after stent placement, n (%)	7 (12.7)	17 (9.3)	0.458

[a]P<0.05, [b]P<0.001. CSEMSs, covered self-expandable metal stents; USEMSs, uncovered self-expandable metal stents; SEMSs, self-expandable metal stents; ERCP, endoscopic retrograde cholangiopancreatography.

was higher than that in the USEMSs group (8.8%) (P=0.049). Some of the patients in both groups had hyperamylasemia or pancreatitis after ERCP, but not before ERCP. Thus, amylase levels after ERCP in these patients were significantly higher than those before ERCP, which further raised the average amylase levels of all the patients following ERCP in both groups. Therefore, both post-ERCP pancreatitis and post-ERCP hyperamylasemia were the cause of the increase in amylase levels after ERCP. There was no significant difference in the incidence of biliary infection, hyperamylasemia, bleeding, or perforation between the two groups (P>0.05). There was no procedure-related death in the CSEMSs group; however, 3 patients died in the USEMSs group, of which 1 patient died of bleeding after ERCP, and 2 died of severe biliary infection. There was no significant difference in procedure-related mortality between the two groups (P=1.000) (Table IV).

Discussion

Endoscopic placement of stents such as SEMSs and PSs can effectively relieve symptoms such as fever, jaundice, itchiness, and dyspepsia, amongst others, in patients with MBS and improve their quality of life (6). Endoscopic stent placement has become the first choice for the palliative treatment of

Table II. Liver function parameters (mean ± SD) prior to and following stent placement.

Parameter	Time	CSEMSs	USEMSs	P1[a]	P2[b]	P3[c]
TBIL, μmol/l	Pre-ERCP	212.6±139.1	226.9±127.2	<0.001[a]	0.209	0.431
	Post-ERCP	172.9±119.8	196.4±106.1			
	P_4[d]	0.021[e]	<0.001[f]			
DBIL, μmol/l	Pre-ERCP	164.1±103.6	173.9±97.5	<0.001[e]	0.545	0.241
	Post-ERCP	127.7±87.6	146.0±78.2			
	P_4[d]	0.040[e]	<0.001[f]			
ALT, U/l	Pre-ERCP	109.4±83.0	127.9±92.6	<0.001[a]	0.597	0.181
	Post-ERCP	80.1±68.4	86.6±52.3			
	P_4[d]	0.044[e]	<0.001[f]			
AST, U/l	Pre-ERCP	105.1±68.8	121.1±77.3	<0.001[a]	0.341	0.200
	Post-ERCP	77.8±85.3	87.5±67.2			
	P_4[d]	0.030[e]	<0.001[f]			
ALP, U/l	Pre-ERCP	525.7±314.2	574.7±341.9	0.071	0.890	0.211
	Post-ERCP	474.9±305.0	515.5±259.9			
	P_4[d]	0.356	0.061			
γ-GT, U/l	Pre-ERCP	569.2±483.8	510.1±309.8	0.001[e]	0.493	0.329
	Post-ERCP	440.5±358.5	425.9±261.2			
	P_4[d]	0.032[e]	0.005[g]			
Amylase, U/l	Pre-ERCP	79.8±80.8	121.3±417.9	<0.001[a]	0.183	0.800
	Post-ERCP	296.1±427.2	232.5±381.5			
	P_4[d]	0.001[f]	0.005[g]			

P-values for [a]Integrated comparison between pre-ERCP and post-ERCP in the two groups; [b]interaction effect between the group factor (in the CSEMSs group or the USEMSs group) and the time factor (pre-ERCP or post-ERCP); [c]comparison between the two groups for both pre-ERCP and post-ERCP; and [d]paired comparisons between pre-ERCP and post-ERCP in each group. [e]P≤0.05; [f]P≤0.001; [g]P≤0.01. TBIL, total bilirubin; DBIL, direct bilirubin; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; ALP, alkaline phosphatase; γ-GT, γ-glutamyl transferase; ERCP, endoscopic retrograde cholangiopancreatography.

patients with MBS in which the tumor cannot be resected by surgery, and it is also the primary method of preoperative biliary drainage for patients with cholangitis (14). The disadvantage of PSs is that re-obstruction occurs earlier. PSs usually need to be replaced in ~3 months. Otherwise, fatal cholangitis may occur (15). It has been reported that SEMSs have a longer patency time, lower stent occlusion rate, fewer adverse events, and requires fewer interventions than PSs (15). As a result, SEMSs exhibit improved cost-effectiveness and are currently widely used, especially for patients whose expected survival time is >3 months (9).

In recent years, the endoscopic stent placement technique has improved significantly. Recently, studies have demonstrated that the technical success rate of endoscopic stenting is close to 100% (15-17). The results of the present study showed that the technical success rates in both the CSEMSs group and the USEMSs group were 100%. The demographic characteristics of the patients indicated that there seemed to be more male patients in both the CSEMSs group and the USMESs group than the female patients, but there was no significant difference in sex distribution between the two groups. The majority of patients in both groups were elderly patients, most of whom were >70 years old, but there was no significant difference in the age distribution between the two groups. Etiological analysis of MBS indicated that pancreatic cancer and cholangiocarcinoma were predominant, but there was no significant difference in the etiology composition and tumor staging between the two groups. In addition, there was no significant difference in cholecystectomy before ERCP between the two groups. In terms of ERCP-related techniques, there was no significant difference in pre-cut, endoscopic sphincterotomy, and pancreatic duct stent placement. Interestingly, it was noticed that antibiotics were more frequently used prior to ERCP in the CSEMSs group than in the USEMSs group, likely due to the possibility that endoscopic physicians tended to use CSEMSs for patients with severe infections based on their experience, and clinicians were more likely to use antibiotics for patients with severe infections. It was also found that biliary stents 60 mm in length were more often used than 80 mm in the CSEMSs group but not in the USEMSs group and biliary stents 60mm in length were more often used in the CSEMS group than in the USEMS group. We hypothesize that the possible reason for this might be that all the cases included in the present study were distal bile duct strictures and when CSEMSs were used, endoscopists preferred shorter stents for relieving bile duct obstructions in the CSEMSs group to minimize the blockade of the cystic duct as longer CSEMSs for distal biliary strictures have a higher risk of blocking the cystic duct by the covering membrane of CSEMSs. Liver function tests indicated that there was a significant decrease in

Table III. Comparison of stent patency time (rate) and patient survival time (rate).

Parameter	CSEMSs	USEMSs	P-value
Stent dysfunction, n (%)	11 (20.0)	34 (18.6)	0.813
Stent obstruction	10 (90.9)	34 (100)	0.548
Stent migration	1 (9.1)	0 (0.0)	0.548
Stent patency time, days[a]	262.8±195.3	169.5±155.7	0.002[b]
Stent patency rate, %			
1 month	90.9	89.6	0.780
3 months	74.5	62.3	0.095
6 months	56.4	33.9	0.003[b]
12 months	29.1	12.0	0.002[b]
Patient survival time, days[a]	273.9±197.6	184.9±167.6	0.003[b]
Patient survival rate, %			
1 month	94.5	90.7	0.579
3 months	76.4	65.6	0.132
6 months	58.2	37.2	0.006[b]
12 months	34.5	13.7	<0.001[c]

[a]Data are presented as mean ± SD. [b]P<0.01, [c]P<0.001.

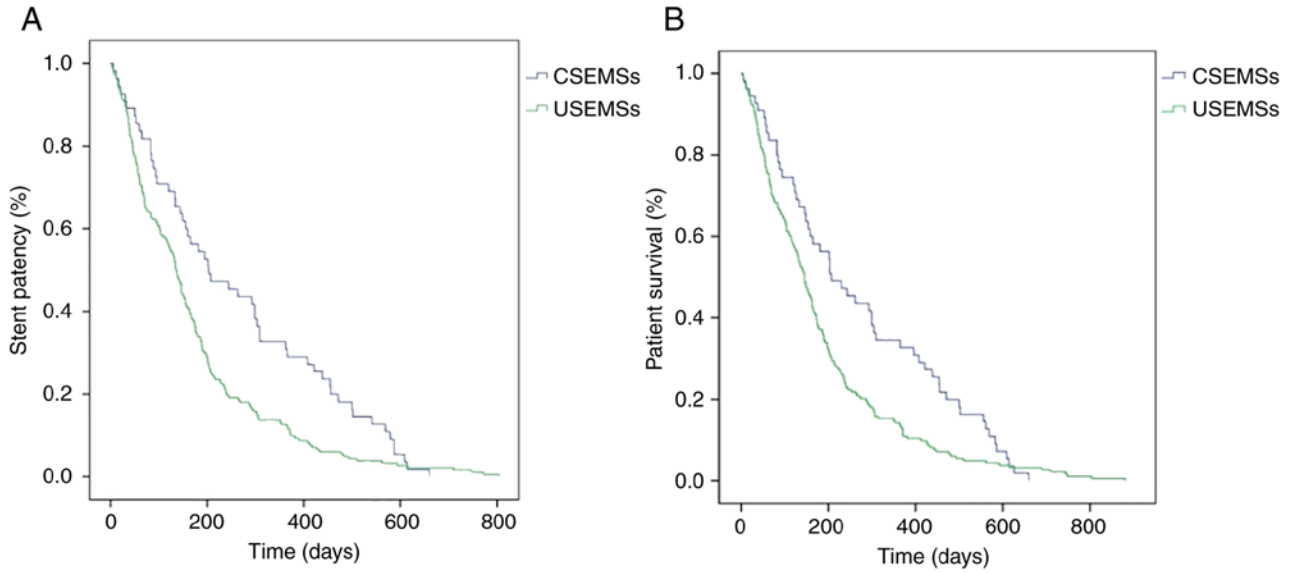

Figure 2. Cumulative stent patency rate and cumulative survival rate of the patients. (A) The cumulative stent patency rate of the CSEMSs group was significantly higher than that of the USEMSs group (P=0.003). (B) The cumulative survival rate of the CSEMSs group was significantly higher than that of the USEMSs group (P=0.009). CSEMSs, covered self-expandable metal stents; USEMS, uncovered SEMSs.

serum bilirubin, transaminase, and γ-GT in both the CSEMSs group and the USEMSs group after the placement of SEMSs, indicating that both stents could significantly improve the liver function of patients in the short term. In addition, there was no significant difference between the two groups in the liver function tests before or after ERCP, indicating that CSEMSs and USEMSs played an equivalent role in improving liver function in the short term. It was also noted that post-ERCP serum amylase in both groups was significantly higher than that before ERCP, possibly because certain patients in both groups had PEP or post-ERCP hyperamylasemia. Hence, amylase levels after ERCP in these cases were significantly higher than those before ERCP, which further raised the average amylase level after ERCP in both groups.

It is still contested whether to use CSEMSs or USEMSs in the palliative treatment of patients with MBS. The comparison of the efficacy and safety of CSEMSs and USEMSs remains uncertain, and the results of several studies differed. Certain studies showed that the patency time of the stents in the CSEMSs group was significantly longer than that in the USEMSs group (18,19), and the patency rate of the stents in the CSEMSs group was also significantly higher (20). However, several studies have also shown that there is no difference in the stent patency time and stent patency rate between the two

Table IV. Adverse events following stent placement.

Adverse events	CSEMSs, n (%)	USEMSs, n (%)	P-value
Total	14 (25.5)	36 (19.7)	0.356
Biliary infection	2 (3.7)	7 (3.8)	>0.999
Post-ERCP pancreatitis	10 (18.1)	16 (8.8)	0.049[a]
Hyperamylasemia	2 (3.7)	12 (6.6)	0.531
Bleeding	0 (0.0)	1 (0.5)	>0.999
Perforation	0 (0.0)	0 (0.0)	-
Procedure-related mortality	0 (0)	3 (1.6)	>0.999

[a]P<0.05. ERCP, endoscopic retrograde cholangiopancreatography.

groups for the treatment of MBS (13,21-25). In fact, a recent randomized multicenter study by Conio *et al* (26) showed the opposite result to the aforementioned studies. Conio *et al* (26) found that the median stent patency time of the USEMSs group was significantly longer than that of the CSEMSs group (541 days vs. 240 days), but there was no significant difference in the stent patency rate. The reason for the above inconsistent results may lie in differences in study design, patient selection criteria, stent materials and structures, and the experience of endoscopists. The present study showed that although there was no significant difference in the overall stent dysfunction rate between the two groups within the follow-up period, the average stent patency time of the CSEMSs group was significantly longer than that of the USEMSs group (262.8±195.3 days vs. 169.5±155.7 days). In terms of the stent patency rate, there was no significant difference between the two groups at 1 and 3 months after stent placement, but the stent patency rate of the CSEMSs group at 6 and 12 months was significantly higher than that of the USEMSs group. This indicates that CSEMSs are superior to USEMSs in terms of stent patency time and long-term patency rate.

Regarding the prognosis of the patients, most of the previous studies revealed that there was no significant difference in survival time between the CSEMSs group and the USEMSs group (13,18,20). However, a meta-analysis showed that patients in the CSEMSs group had longer survival times than those in the USEMSs group (19). The results of the present study showed that the survival time and the cumulative 1-year survival rate of patients in the CSEMSs group were better than those in the USEMSs group. Further analysis in the present study showed that there was no significant difference in the survival rate between the two groups at 1 and 3 months after stent placement, but the survival rate of the CSEMSs group was significantly higher than that of the USEMSs group at 6 and 12 months, which demonstrated that the long-term survival rate of patients in the CSEMSs group was higher than that in the USEMSs group. The survival time and survival rate for inoperable patients may be affected by tumor staging and chemotherapy after stent placement. In this study, it was demonstrated that there was no significant difference in tumor staging or chemotherapy between the two groups (Table I). Therefore, it was considered that the reason why the CSEMS group had a longer survival time and higher survival rate may be due to the longer stent patency time and higher patency rate. This is because the covering membrane in CSEMSs prevents tumor growth across the stents so CSEMSs may be obstructed slower and obstructive cholangitis may occur later than USEMSs. A recent randomized control trial (RCT) conducted by Seo *et al* (27) showed that during the new adjuvant therapy for patients with bile duct obstruction caused by pancreatic cancer, the cumulative 1-year survival rates of patients in the CSEMSs group and the USEMSs group were 60.2 and 56.8%, respectively, with no significant difference. However, in the present study, the cumulative 1-year survival rates of both groups were notably lower than that reported by Seo *et al*. A possible reason for this difference may lie in the fact that fewer patients in the present study accepted radiotherapy or chemotherapy after stent placement. It was noted that overall survival time/rate was used in the present study rather than disease-free survival time/rate as no patients in the present study were actually disease-free prior to death. Furthermore, there were two reasons stent-dysfunction-free survival was not used either: Firstly, the stent-dysfunction-free survival time had the same period as stent patency time according to the definition of stent patency in the present study design, thus there was no need to show dysfunction-free survival; secondly, overall survival was used to demonstrate that the possible reason why the CSEMS group had a longer survival time and higher survival rate may be the longer stent patency time and higher patency rate as the patient overall survival time and survival rate for inoperable patients may have been affected by stent patency as well as tumor staging and chemotherapy; however, there were no significant differences in tumor staging and chemotherapy between the two groups.

A retrospective study showed that the incidence of total post-ERCP adverse events in the CSEMSs group and the USEMSs group was 22.8 and 15.9%, respectively (17). Similarly, our study showed that the incidence of post-ERCP adverse events in the CSEMSs group and the USEMSs group was 25.5 and 19.7%, respectively, with no significant difference. However, in the present study, it was found that the incidence of PEP in the CSEMSs group was higher than that in the USEMSs group (18.1% vs. 8.8%). The cause of higher PEP in the CSEMSs group may be the obstruction of pancreatic duct drainage by the covering membrane of CSEMSs. In addition, the present study showed no significant difference in post-ERCP biliary duct infection and hyperamylasemia

between the two groups. There were no cases of bleeding in the CSEMSs group and 1 case in the USEMSs group, with no significant difference in bleeding between the two groups. In the present study, there were no perforation complications in either group, which may be due to the experience of the endoscopic physicians and the small sample size in this study. In addition, all the patients in the present study exhibited jaundice and impaired liver function, and certain patients even had poor blood coagulation function, so only a few patients underwent endoscopic sphincterotomy during ERCP, which might be another reason for the lack of perforation adverse events.

Partially covered self-expandable metal stents (PC-SEMSs) were not included in the present study according to the study design. However, previous studies demonstrated the application value of PC-SEMSs, although these have also been contested. A study by Kim *et al* (13) showed that compared to uncovered SEMSs, PC-SEMSs did not prolong stent patency in unresectable malignant distal biliary obstruction. Stent migration was more frequent with PC-SEMSs; however, tumor ingrowth was less frequent with PC-SEMSs compared to uncovered SEMSs. Conversely, a study by Yokota *et al* (17) showed that PC-SEMSs with a proximal uncovered flared end had a longer patency than uncovered and fully covered SEMSs by preventing tumor ingrowth and stent migration.

Previous studies determined the diagnosis of malignant bile duct stricture by pathology or by patients' clinical manifestations, laboratory data, and abdominal imaging such as CT and MRCP (12,13,15-38). However, benign and malignant biliary strictures often have similar clinical manifestations and imaging characteristics at the early stage, so it is difficult to distinguish them only by clinical and imaging data. Furthermore, the differential diagnostic yield by ERCP is limited even by means of the SpyGlass choledochoscope (10). Finally, some patients with indeterminate bile duct strictures were inoperable or reluctant to accept surgery due to old age and/or poor conditions. As a result, whether the indeterminate biliary stricture is benign or malignant might not be clarified during hospitalization. In this situation, the follow-up was extremely important for the differential diagnosis. It is recommended that the benign bile duct stricture be considered if no malignant progression is observed by imaging or ERCP during follow-up for at least 6 months. Otherwise, a malignant bile duct stricture should be diagnosed (9). One year of follow-up in the present study was performed for patients with indeterminate biliary stricture unless they died, to maximize the reliability of the diagnosis of malignant bile duct strictures. To sum up, the patients with malignant bile duct strictures were enrolled based on pathology or by follow-up according to the international consensus to ensure the reliability of diagnosis, and this inclusion criterion was not mentioned by previous studies. This is one innovation and advantage of the present study compared with previous studies.

However, the present study has some limitations. It was a single-center and retrospective study, so there were inevitable shortcomings. Firstly, the choice of stent type was based on the preference of endoscopists, and there may be a selection bias. Secondly, the prognosis of patients with advanced stage or tumor metastasis was poor, such that died soon after stent placement. As a result, their follow-up time was short, which may have affected the long-term evaluation of stent function and stent-related adverse events. Thirdly, patients receiving PC-SEMSs were excluded, thus, it was not possible to compare all the different types of SEMSs as palliative treatments of malignant bile duct strictures. Additional multicenter RCTs are required for further confirmation of the findings of the present study. Finally, the number of patients who received USEMSs was ~3x larger than that of the CSEMSs patients in the present study given the hospital procurement criteria, which may have biased the results.

In conclusion, the present study showed that CSEMSs were better than USEMSs for malignant distal biliary strictures in terms of stent patency time and patient survival time as well as stent patency rate and patient survival rate in the long term (>6 months). Adverse events in the two groups occurred at a similar rate, although the incidence of PEP was higher in the CSEMSs group.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LZ collected and analyzed the data, and drafted the manuscript. ZW, ZH, XY, ZY and RC participated in the follow-up of the patients, and the collection and analysis of the data. YC designed the study, supervised the project and reviewed the final manuscript. LZ, ZW, ZH, XY, ZY, RC and YC confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University (approval number, IIT2019036) and was performed in accordance with the ethical standards described in the 1964 Declaration of Helsinki and its later amendments. All included cases were recorded in the Human Genetic Resources Center of the First

Affiliated Hospital of Nanchang University. Informed consent was obtained from all subjects involved in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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