Communication from the ASGE Standards of Practice Committee

GUIDELINE

ASGE American Society for Gastrointestinal Endoscopy

American Society for Gastrointestinal Endoscopy guideline on management of post–liver transplant biliary strictures: summary and recommendations

Prepared by: ASGE STANDARDS OF PRACTICE COMMITTEE

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This clinical practice guideline from the American Society for Gastrointestinal Endoscopy provides an evidence-based approach for strategies to manage biliary strictures in liver transplant recipients. This document was developed using the Grading of Recommendations Assessment, Development and Evaluation framework. The guideline addresses the role of ERCP versus percutaneous transhepatic biliary drainage and covered self-expandable metal stents (cSEMSs) versus multiple plastic stents for therapy of post-transplant strictures, use of MRCP for diagnosing post-transplant biliary strictures, and administration of antibiotics versus no antibiotics during ERCP. In patients with post-transplant biliary strictures, we suggest ERCP as the initial intervention and cSEMSs as the preferred stent for extrahepatic strictures. In patients with unclear diagnoses or intermediate probability of a stricture, we suggest MRCP as the diagnostic modality. We suggest that antibiotics should be administered during ERCP when biliary drainage cannot be ensured. (Gastrointest Endosc 2023;97:607-14.)

This guideline document was prepared by the Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy using the best available scientific evidence and considering a multitude of variables including but not limited to adverse events, patients' values, and cost implications. The purpose of these guidelines is to provide the best practice recommendations that may help standardize patient care, improve patient outcomes, and reduce variability in practice.

We recognize that clinical decision-making is complex. Guidelines, therefore, are not a substitute for a clinician's judgment. Such judgements may, at times, seem contradictory to our guidance because of many factors that are impossible to fully consider by guideline developers. Any clinical decisions should be based on the clinician's experience, local expertise, resource availability, and patient values and preferences.

This document is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating for, mandating, or discouraging any particular treatment. Our guidelines should not be used in support of medical complaints, legal proceedings, and/or litigation, because they were not designed for this purpose.

Bile duct strictures are a common adverse outcome of liver transplantation and are associated with significant morbidity. These strictures, and the associated cholangiopathy, can lead to a variety of adverse outcomes ranging from asymptomatic elevation in liver-associated enzymes to hospitalization, cholangitis, allograft rejection, and allograft failure.[1,2] These post-transplant biliary strictures can often be diagnosed based on a varying combination of elevated liver enzymes, conjugated hyperbi lirubinemia, and biliary dilation on imaging.[3,4]

The treatment of post-transplant biliary strictures often requires serial therapeutic interventions including stricture dilation and stent placement.[5] ERCP and various interventional radiology–guided biliary procedures have been used to manage post-transplant strictures. Such therapies are selected based on a host of patient-specific factors including the location and type of stricture,[6] type of allograft, availability of technical expertise, and time from transplant. Because liver transplant recipients are immunosuppressed, there is a perceived risk of infectious adverse events (AEs) associated with ERCP.[7] Hence, managing post–liver transplant biliary strictures requires a multidisciplinary, evidence-based approach. The aim of this guideline

was to provide evidence-based recommendations for facilitating the management of liver transplant recipients with biliary strictures.

METHODS

This document was prepared by the Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy (ASGE) and was conceptualized and conducted according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[8] Evidence was presented to a panel of experts representing various stakeholders including transplant surgery, transplant hepatology, and gastroenterology. A patient advocate was also included. All panel members were required to disclose potential financial and intellectual conflicts of interest, which were addressed according to ASGE policies. In developing these recommendations, we took into consideration the certainty in the evidence, benefits and harms of different management options, feasibility, patient values and preferences, resources utilization, cost-effectiveness, and health equity. The final wording of the recommendations including direction and strength were approved by all members of the panel and the ASGE governing board. Stronger recommendations are stated as "we recommend," whereas conditional recommendations are indicated by "we suggest" based on the GRADE framework. Further details of the methodology used for this guideline including systematic reviews, evidence profile, and results from all meta-analyses, are presented separately in the methodology article accompanying this guideline in the current edition of *Gastrointestinal Endoscopy*.[9]

This guideline addressed the following clinical questions using the GRADE format:

1. In liver transplant recipients with a biliary stricture, should ERCP be used compared with percutaneous transhepatic biliary drainage (PTBD) as the initial therapy of choice for management of biliary strictures?
2. In patients with post-transplant biliary strictures, should covered self-expandable metal stents (cSEMSs) be used compared with multiple plastic stents (MPSs) as the initial therapy of choice for management of biliary strictures?
3. In liver transplant recipients with suspected biliary stricture, should MRCP be considered the preferred diagnostic modality?
4. In patients with post–liver transplant biliary strictures without cholangitis undergoing elective ERCP, should antibiotics be administered or not administered to reduce risk of infections?

SUMMARY OF RECOMMENDATIONS

Details of our literature search, data analyses, pooled-effects estimates, evidence profiles, forest plots, and panel deliberation for each outcome can be found in the methodology and technical review document. A summary of our final recommendations for management of patients with post–liver transplant biliary strictures is listed in Table 1.

Question 1: In liver transplant recipients with a biliary stricture, should ERCP be used compared with PTBD as the initial therapy of choice for management of biliary strictures?

Recommendation 1: In liver transplant recipients with a biliary stricture, the ASGE suggests ERCP over PTBD as initial therapy for management of strictures. (*Conditional recommendation, very low quality of evidence*.)

Summary of evidence

For this question, we performed a systematic review of studies comparing ERCP and PTBD with or without cholangioplasty as the initial intervention for liver transplant recipients with biliary strictures. Patients undergoing ERCP or PTBD as salvage procedures were excluded, as were patients with an altered foregut anatomy like Roux-en-Y hepaticojejunostomy. Four full-text studies meeting selection criteria that directly compared ERCP and PTBD were reviewed.[2,10-12] All studies were retrospective in design, and only 1 study was a multicenter nationwide study.[2] In aggregate, 432 procedures were analyzed, of which 275 were ERCP and 157 were PTBD as the initial therapy for post–liver transplant biliary strictures. Outcomes of interest were technical success, incidence of readmission after the procedure, allograft failure, infection, and a composite of AEs.

For the outcome of allograft rejection, a single multicenter, retrospective study used the Nationwide Readmissions Database and assessed the risk of allograft rejection in hospitalized post–liver transplant patients.[2] On multivariate analysis, the adjusted odds of failure of liver allograft were 8.47 greater for PTBD as compared with ERCP (95% confidence interval [CI], 1.47-48.6; $P = .017$). In addition to a higher risk of allograft rejection, PTBD was also associated with longer hospitalization (odds ratio [OR], 14.4; 95% CI, 3.7-25.1; $P = .008$), higher disposition to a nursing home (OR, 2.72; 95% CI, 1.08-6.87; $P = .03$), and higher overall cost.[2]

One study reported fewer number of procedures with ERCP than PTBD ($2.5 \pm .9$ vs $6.1 \pm .4$, $P < .01$).[11] Among patients undergoing PTBD, the study reported an average of $3.0 \pm .4$ additional procedures were performed because of external catheter problems such as leakage (14.9%), retraction of the catheter (29.8%), decreased drainage (43.2%), cholangitis (6.6%), and other (5.5%). The total duration of the intervention for successful treatment was $5.3 \pm .8$ months for ERCP and $6.5 \pm .7$ months for PTBD ($P = .31$).[11] There was no difference in technical success (relative risk, 1.28; 95% CI, .27-2.33; $P = .42$;

TABLE 1. Summary of recommendations

Recommendation	Best practice advice	Strength of recommendation	Quality of evidence
In liver transplant recipients with a biliary stricture, the ASGE suggests ERCP over PTBD as initial therapy for management of strictures.	ERCP preferred if it is difficult for caregivers to manage percutaneous drains/catheters, risk of dislodgement of percutaneous drains/catheters, presence of multiple intrahepatic strictures in different hepatic lobes, and lack of significant biliary dilation to facilitate percutaneous drainage. PTBD preferred if difficult endoscopic biliary access because of various reasons including altered anatomy or increased risk of adverse events from anesthesia	Conditional recommendation	Very low
In liver transplant recipients with biliary strictures, the ASGE suggests covered self-expandable metal stents should be used instead of multiple plastic stents for initial therapy of extrahepatic biliary strictures.	Covered metal stents are most often used for extrahepatic biliary strictures, typically at the anastomosis. Cholangiographic findings, such as intrahepatic biliary strictures or anastomotic strictures just below the bifurcation, may preclude the use of covered metal stents.	Conditional recommendation	Low to moderate
In liver transplant recipients with suspected biliary stricture(s), the ASGE suggests use of MRCP as a diagnostic test.	MRCP is an acceptable diagnostic test for detecting post-transplant strictures. Individual clinical scenarios should dictate the utility of MRCP. In patients with a high pretest probability for a biliary stricture or cholangitis, proceeding directly to ERCP without a diagnostic MRCP is prudent	Conditional recommendation	Moderate to high
In patients with post–liver transplant biliary strictures undergoing elective ERCP in whom complete biliary drainage is technically challenging to achieve (ischemic cholangiopathy, multiple strictures, failure of stenting), the ASGE suggests administration of periprocedural antibiotics over no antibiotics to reduce incidence of infectious adverse events.	An individualized approach for administering antibiotics based on each patient's unique biliary anatomy and clinical condition is prudent. Patients with inadequate drainage of the biliary tree because of strictures may benefit from preprocedural antibiotics. Otherwise, use of antibiotics should be discussed with the patient and transplant team before ERCP.	Conditional recommendation	Very low

ASGE, American Society for Gastrointestinal Endoscopy; *PTBD*, percutaneous transhepatic biliary drainage.

$I^2 = 53.4\%$), composite of AEs (relative risk, 1.12; 95% CI, .62-2.0; $P = .7$; $I^2 = 0\%$), adjusted odds of inpatient mortality (OR, 1.47; 95% CI, .15-14.6; $P = .74$), nonelective 30-day readmission (OR, .98; 95% CI, .45-2.07; $P = .97$),[2] or the total duration of therapy for successful treatment (5.3 ± .8 months for ERCP vs 6.5 ± .7 months for PTBD, $P = .31$).

We did not find studies directly comparing costs or cost-effectiveness of ERCP or PTBD. One study restricted to hospitalized patients reported the overall cost of hospitalization as $179,179.3 ± $123,386.6 for patients undergoing inpatient ERCPs versus $257,058.7 ± $201,423.3 for PTBD ($P < .01$).[2] The panel discussed that cost of both procedures may be comparable based on a host of extrinsic factors. Additionally, there were no studies on patient preferences on this topic. However, the patient advocate favored ERCP to avoid external drains and consequent discomfort, cosmetic disfigurement, risk of dislodgement, and need for specialized care.

Overall, the panel considered that the above evidence favors ERCP as the initial therapy of choice. The finding of higher allograft rejection in PTBD on multivariable analysis was discussed. Additionally, management of external drains can be very challenging for patients when discharged home. The panel recognized the risk of selection bias inherent in retrospective studies that were analyzed in formulating this recommendation. Further studies on this topic are needed and could change the strength of recommendation from conditional to strong. The panel recognized some scenarios in which 1 modality may be preferred over the other:

- ERCP may be especially preferred in the following circumstances: difficulty for caregivers to manage percutaneous drains/catheters, risk of dislodgement of percutaneous drains/catheters, presence of multiple intrahepatic strictures in different hepatic lobes requiring multiple drains/stents, and lack of significant biliary dilation to facilitate percutaneous drainage.
- PTBD may be preferred among the following patients: difficult endoscopic biliary access because of various reasons including altered foregut anatomy or an increased risk of AEs from anesthesia.

Question 2: In patients with post-transplant biliary strictures, should cSEMSs be used compared with MPSs as the initial therapy of choice for management of biliary strictures?

Recommendation 2: In liver transplant recipients with biliary strictures, the ASGE suggests cSEMSs should be used instead of MPSs for initial therapy of extrahepatic biliary strictures. (*Conditional recommendation, low to moderate quality of evidence*.)

Summary of evidence

We performed a systematic review that was restricted to studies assessing outcomes comparing use of cSEMSs with MPSs as the first-line therapy for liver transplant recipients with post-transplant strictures. Notably, only those studies in which patients could undergo either treatment irrespective of foregut anatomy were included. We identified 4 multicenter randomized controlled trials (RCTs) and several meta-analyses. A decision was made to use the existing published analyses from Visconti et al.[13] In aggregate, 205 patients were analyzed within the 4 RCTs of which 103 underwent cSEMS placement and 102 underwent MPS placement as the initial therapy for post–liver transplant biliary strictures.[14-17] Follow-up was for at least 1 year for each of the studies, except for Kaffes et al,[14] where the mean follow-up was at least 1 year. Although not always specifically noted, strictures were anastomotic in location (duct to duct) and did not involve the intrahepatic ducts.

Based on 4 RCTs,[14-17] there was no difference in rates of stricture resolution between cSEMSs and MPSs (pooled risk difference, .01; 95% CI, –.08 to .10; I^2 = 12%). Notably, plastic stents were exchanged through the point of resolution, whereas metal stents were removed after a defined period of 3 to 6 months, regardless of cholangiogram interpretation. Stricture recurrence was assessed in 181 patients in the 4 RCTs. There was no significant difference in stricture recurrence between the groups (pooled risk difference, .13; 95% CI, –.03 to .28; I^2 = 52%). Additionally, cSEMSs were associated with fewer procedures (average of about 2 fewer procedures when using cSEMSs [mean difference, –1.86; 95% CI, –3.12 to –.06; I^2 = 97%]) and fewer days required to achieve resolution (mean difference, –105.07; 95% CI, –202.38 to –7.76; I^2 = 95%). Two RCTs involving 112 patients evaluated the overall number of stents used for stricture management. Both reported fewer stents per patient with cSEMSs compared with MPSs, with a mean difference of –10.63 (95% CI, –20.82 to –.44).

The most common AE was stent migration, with no significant difference between SEMSs and MPSs on meta-analysis of 84 patients. Notably, stent migration was considered only a procedural finding rather than an AE if the stent was recovered on schedule and the stricture resolved. There has been indirect evidence that cSEMSs can be associated with post-ERCP pancreatitis.[18] However, this was not reported in any of the RCTs.

We did not identify any studies that assessed the cost-effectiveness of cSEMSs compared to MPSs. Two RCTs, however, compared the total cost between treatment strategies that included facility fees, thereby incorporating the expense of the devices deployed.[14,16] Mean treatment cost with cSEMSs was less than that with MPSs ($8288 vs $19,580, respectively; $P < .01$). The patient advocate stressed that fewer procedures and lower number of days with stents in place are relevant outcomes to patients.

Several factors influence the type and number of stents used during ERCP: duration to liver transplant, stricture distance from both the bifurcation and the ampulla, length of common bile duct, stent availability, risk of pancreatitis with metal stents, and local expertise. Endoscopists must factor all the above in their final decision. Overall, the panel considered that the above evidence is slightly in favor of SEMSs as the stent of choice assuming the available SEMS is long enough to bridge the stricture. This was a conditional recommendation with a low to moderate quality of evidence. The panel recognized the following salient points:

- Stricture location was not delineated in the 4 RCTs. However, the panel noted that cholangiographic findings during the procedure, such as intrahepatic biliary strictures or anastomotic strictures just below the bifurcation,[6] may obviate the use of cSEMSs. Moreover, no clear strategy was evaluated to guide positioning across or upstream of the biliary orifice.

Data on patient values and mortality were limited. The panel believed patients would favor cSEMSs considering that fewer procedures were needed and their lower cost.

Question 3: In liver transplant recipients with suspected biliary stricture, should MRCP be considered the preferred diagnostic modality?

Recommendation 3: In liver transplant recipients with suspected biliary stricture, the ASGE suggests use of MRCP as a diagnostic test. (*Conditional recommendation, moderate to high quality of evidence*.)

Summary of evidence

We performed a systematic review restricted to studies assessing the performance of MRCP in predicting biliary strictures in post–liver transplant patients using ERCP as the criterion standard. We identified 21 studies that met the inclusion and exclusion criteria, 13 of which were retrospective[4,19-31] and 8 prospective.[32-39] We compared pooled sensitivity, specificity, positive and negative predictive values, and accuracy of MRCP compared with ERCP for post-transplant biliary stricture by meta-analyses.

For assessing sensitivity and specificity, 20 studies were found to have sufficient data for meta-analyses, involving an aggregate of 758 patients.[4,19,21-36,38,39] MRCP correctly

diagnosed post-transplant biliary strictures with a pooled sensitivity of 94.9% (95% CI, 92.4-96.6; I^2 = 32.8%) and a pooled specificity of 90.3% (95% CI, 84.7-94.0; I^2 = 87.8%).

Sixteen studies were found to have sufficient data for meta-analyses to evaluate positive predictive value, involving an aggregate of 584 patients.[4,19,21,22,24-28,31,32,34,36-39] Of those with strictures on ERCP, MRCP correctly diagnosed biliary strictures at a rate of 90.6% (95% CI, 85.6-93.9; I^2 = 64.4%).

Fourteen studies were found to have sufficient data for meta-analyses to evaluate negative predictive value, involving an aggregate of 505 patients.[4,19,22,24-27,31,32,34,36-39] Of those without strictures found on ERCP, MRCP was consistent at a rate of 93.7% (95% CI, 86.2-97.2; I^2 = 81.2%.) For assessing accuracy, 13 studies with 508 patients were found to have sufficient data for meta-analyses.[19,21,22,25-28,32,33,36,38,39] MRCP was found to have a pooled accuracy of 92.4% (95% CI, 89.0-94.6; I^2 = 24.1%).

Therefore, in a population of 1000 patients with a pretest probability of 50% for biliary stricture, MRCP will correctly identify 452 patients as having no stricture and 475 patients as having strictures. MRCP will incorrectly identify 48 patients as having strictures (false positives) and will miss only 25 patients who had strictures (false negatives).

None of the studies assessed the risk of MRCP. However, the overall risk was deemed to be low by the panel, especially compared with ERCP, which is associated with significant risk of AEs. No studies assessed the cost or cost-effectiveness of MRCP in this patient population, and there were no data on patient values and preferences. Our patient advocate expressed minimal concern about undergoing MRCP in this setting, although MRCP may be challenging in a subset of patients with magnetic resonance imaging–incompatible metallic implants or claustrophobia.

Overall, the panel considered that the above evidence was in favor of MRCP as an acceptable diagnostic test for detecting post-transplant strictures. Individual clinical scenarios should dictate the utility of MRCP. In patients with a high pretest probability for a biliary stricture, proceeding directly to ERCP without a diagnostic MRCP would be prudent. This was a conditional recommendation with moderate to high quality of evidence.

Question 4: In patients with post–liver transplant biliary strictures without cholangitis undergoing elective ERCP, should antibiotics be administered or not administered to reduce risk of infections?

Recommendation 4: In patients with post–liver transplant biliary strictures undergoing elective ERCP in whom complete biliary drainage is technically challenging to achieve (ischemic cholangiopathy, multiple strictures, failure of stenting), the ASGE suggests administration of periprocedural antibiotics over no antibiotics to reduce incidence of infectious AEs. (*Conditional recommendation, very low quality of evidence*.)

Summary of evidence

We conducted a systematic review of publications that compared the outcomes in liver transplant recipients with biliary strictures undergoing elective ERCP who received antibiotics with those who did not receive antibiotics. Notably, patients with cholangitis were not assessed because there are clear guidelines that recommend administration of antibiotics.[40]

Only 2 retrospective, single-center studies from the United States met the selection criteria.[41,42] One study assessed the risk of infections and impact of antibiotics over time. Data regarding liver transplant recipients undergoing ERCP were limited to a subgroup analysis.[41] The second study directly compared outcomes of antibiotic administration versus nonadministration in nonhospitalized liver transplant recipients undergoing ERCP. Notably, this study assessed for "clinically significant infections" and did not assess for asymptomatic bacteremia.[42]

Overall, 361 liver transplant recipients undergoing 959 ERCP procedures were assessed. The pooled incidence of infections was noted to be 1.1% (95% CI, .6-2.0; I^2 = 0). Both studies noted that administration of antibiotics did not lower the risk of infections or adverse outcomes.[41,42] It is possible that the risk of infections in liver transplant recipients is very low and thus hard to detect on small, inadequately powered studies. The ability of antibiotics to further lower the risk of infectious AEs may thus be limited. Notably, bacteremia occurs often during endoscopic procedures, including ERCP, although the incidence varies based on the type of procedure and therapy. This bacteremia is transient and not definitely associated with AEs.[7,43,44]

In our systematic review of published studies, we did not find any study that compared the incidence of noninfectious AEs with administration of antibiotics versus not administering antibiotics in liver transplant recipients undergoing ERCP. We did not find any study that assessed cost-effectiveness of administering periprocedural antibiotics.

The panel noted that unrestricted use of antibiotics may increase the risk of multidrug-resistant organisms and antibiotic resistance, especially to fluoroquinolones, which is already a challenge in liver transplant patients.[45] Additionally, antibiotics can be associated with AEs such as QTc prolongation and torsade de pointes, which can be life-threatening. Fluoroquinolones, the most common antibiotics in these settings, are associated with a black box warning for tendinitis and tendon rupture. Further, fluoroquinolones are weak inhibitors of CYP3A4, which metabolizes tacrolimus, and can thus increase serum concentration of tacrolimus.[46-48] Finally, the panel noted that existing recommendations for antibiotics in all liver transplant patients are based on conflicting data and were largely extrapolated from a theoretical increase in infection risk that has not been substantiated in any study.

In the absence of high-quality data, strong evidence-based recommendations cannot be provided. The guideline acknowledges that data are limited and further research is necessary. We recommend an individualized approach for administering antibiotics based on each patient's unique biliary anatomy and clinical condition. This was a conditional recommendation with very low quality of evidence. Most importantly, patients with inadequate drainage of the biliary tree because of strictures or failed therapeutic interventions (eg, failure of stenting) may benefit from periprocedural antibiotics. These include patients with stenosed intra- or extrahepatic ducts, ischemic cholangiopathy, multiple intrahepatic strictures, or in whom contrast was injected but stricture dilation or stent placement across a stricture was unsuccessful. Otherwise, use of antibiotics should be discussed among the patient, endoscopist, and transplant team, who should consider all the above as part of a shared medical decision-making.

FUTURE DIRECTIONS

This guideline and literature review highlighted several areas in need of more data to guide decision-making for managing biliary strictures after liver transplantation. Future studies should address the following:

1. Natural history and risk factors for biliary strictures: The risk factors for the formation of biliary strictures remain to be completely characterized. Although ischemia from vascular insult has been postulated as a risk factor for ischemic cholangiopathy and nonanastomotic strictures, other factors such as medications, donor age, allograft mismatch, and pretransplant Model for End-Stage Liver Disease scores remain under investigation.[49] Further, it is unclear if there are protective factors that may mitigate the risk of stricture formation. Classifying biliary strictures[6] and tailoring therapy based on etiology and anatomy remain to be defined.
2. Optimal therapeutic approach in patients with altered foregut anatomy: This guideline focuses on patients with an unaltered foregut anatomy. However, patients with a Roux-en-Y anatomy, as seen in patients with a hepaticojejunostomy because of primary sclerosing cholangitis, may not be candidates for ERCP using a conventional side-viewing duodenoscope. A thorough evaluation of the endoscopic approaches in these patients and the role of percutaneous transhepatic interventions is needed.[50] Additionally, the role of EUS-guided biliary access in liver transplant recipients needs to be evaluated.
3. Role of antibiotics during ERCP: Prospective clinical trials are needed to define the need, pharmacologic class, optimum dosing, and duration of antibiotics in liver transplant recipients undergoing ERCP.

WHAT IS NEW

These guidelines highlight existing data to suggest ERCP as the initial therapy for biliary strictures in post–liver transplant patients, covered metal stents as the preferred implant for biliary strictures not involving intrahepatic ducts, preprocedural MRCP to confirm and delineate stricture location in patients with uncertain diagnosis, and selection of patients for periprocedural antibiotic therapy.

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GUIDELINE UPDATE

ASGE guidelines are reviewed for updates approximately every 5 years or in the event that new data may influence a recommendation. Updates follow the same ASGE guideline development process.

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Abbreviations: AE, adverse event; ASGE, American Society for Gastrointestinal Endoscopy; CI, confidence interval; cSEMS, covered self-expandable metal stent; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MPS, multiple plastic stent; OR, odds ratio; PTBD, percutaneous transhepatic biliary drainage; RCT, randomized controlled trial.

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