Choledocholithiasis: Long term follow up in patients without stone clearance at first ERCP

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GK, LG, DM, SG, PG conceived and designed the study. GK, LG, PG analysed and interpreted the data. GK, LG, PG drafted the article. DM, SG, PG critically revised the article for important intellectual content. All authors approved the final version of the article.

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Abstract

Objectives: Complete clearance during index ERCP for choledocholithiasis is not always successful and biliary stenting is commonplace. Strategies vary between temporary stent placement (TSP) with interval ERCP or permanent stent placement (PSP) and watchful waiting for recurrent biliary obstruction (RBO). This study aimed to describe outcomes between these groups, and stent patency rates in the PSP group.

Methods: All patients with incomplete clearance at first ERCP for choledocholithiasis between May 2015 and December 2018 were identified from a prospectively collected single-centre database. Clinical outcomes were obtained by retrospective interrogation of case notes. Median follow-up was 41(IQR:29-51) months.

Results: Of 1263 index ERCPs, 199(15.8%) concluded without stone clearance. All received biliary stenting, 106/199(53%) as PSP and 93/199(47%) with TSP. The TSP group had repeat ERCP after median 8(IQR:6–15) weeks; 70/93(75%) had clearance on repeat ERCP. Median age was greater in the PSP v TSP group (82 v 72 years, p<0.05). Rates of RBO (32.1 v 16.1%, p<0.05), and emergency readmissions (32.1 v 19.4%, p<0.05) were greater in the PSP group. More patients died without further biliary disease in the PSP group (39.6 v 12.9%, p<0.05). PSP stent patency rates at 6, 12, 24, 36, and 61 months were 87.7%, 82.1%, 75.5%, 69.8% and 67.9% respectively.

Conclusions: Though PSP had higher RBO and emergency readmissions, 2/3 of these patients either died or survive without recurrent biliary disease. Stent patency decreased fastest in the first 12 months. Patient criteria to guide decision making regarding biliary stenting remain unclear.

(Word count: 246/250)

Keywords

Choledocholithiasis; ERCP; Gallstones; Jaundice; Stents; Biliary disease

Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is the non-surgical treatment of choice for choledocholithiasis. Initial cannulation and successful clearance rates of >85% at first ERCP have been reported (1,2). Since its advent it has greatly reduced the frequency of surgical explorations of the common bile duct (CBD) thanks to its efficacy and relative low risk profile (1,3). Although clearance of the CBD is the aim of every ERCP, this cannot always be achieved at the index procedure.

Multiple methods have been described to manage difficult CBD gallstones. These include mechanical or laser lithotripsy (LL), cholangioscopically guided eletrohydraulic lithotripsy (EHL), gallstone dissolution with oral ursodeoxycholic acid, endoscopic biliary stenting, and open surgery (3). Endoscopic biliary stenting is commonly used to manage cases of incomplete clearance for large or multiple gallstones at first ERCP where other options have been unsuccessful or unavailable (3). Elective repeat ERCP with further attempt at clearance or stent exchange at 3 to 12 monthly intervals have been reported as safe and effective. (3–5). Evidence also shows biliary stenting having a beneficial effect on subsequent clearance by reducing the size and number of stones in follow up ERCPs (3,6).

While ERCP is generally a safe procedure, it is not without risk. It carries a measurable mortality of 0.5% to 2% and a morbidity of 5% including bleeding, perforation, pancreatitis, and cholangitis (1,2,7). In addition, the risk of serious complications is increased up to 7-fold in therapeutic ERCPs compared to diagnostic ERCPs (8,9). Reducing complications is best achieved by reducing the total number of ERCPs. This makes patient selection, particularly in the elderly and frail, of paramount importance (1,10). Strategies for long-term biliary stenting with watchful waiting and re-intervention only if clinical evidence of stent dysfunction have been described (1,3). Without available guidelines regarding long-term biliary stenting, practice varies and long-term outcomes from this strategy are uncertain.

This study describes our cohort of patients that have been managed by biliary stenting, both as temporary stent placement (TSP) with planned repeat ERCP and permanent stent placement (PSP) with watchful waiting for recurrent biliary obstruction (RBO). The primary aim was to compare rates of emergency readmissions between the two groups. Secondary aims included comparing rates of mortality without further biliary disease and describing rates of stent patency in the PSP group.

Methods

A prospective patient database of all ERCPs at Queen Elizabeth University Hospital (Glasgow, United Kingdom) was used to identify patients with incomplete clearance at first ERCP for gallstone disease between May 2015 and December 2018. ERCPs are performed by both Gastroenterologists and General Surgeons. Complete stone extraction was the primary goal in all cases, with sphincteroplasty and mechanical lithotripsy performed to achieve this, unless contraindicated. If these were unsuccessful, single or double 7 Fr double-pigtail biliary stents were used to achieve patency. Facilities for EHL or LL were unavailable.

All patients with successful biliary cannulation but incomplete stone clearance were identified. Electronic patient records were retrospectively interrogated to collect additional data on post ERCP outcomes. Demographic information included patients' age and sex. Post ERCP outcomes included total number of further ERCPs, number of emergency/non-elective ERCPs, and number of patients with clearance on subsequent ERCPs. The number of patients experiencing biliary-related complications were also recorded and categorised into early (<30 days from ERCP) and late (≧30 days from ERCP). These included RBO, ascending cholangitis, pancreatitis, and cholecystitis. Any other additional related complications were recorded and stated separately. Finally, the date of death during follow up was recorded. All patients were followed up until May 2020 or their date of death.

The post ERCP management strategy regarding TSP or PSP was retrieved from the plan reported at the conclusion of the initial ERCP report. Decisions regarding TSP vs PSP were made by the endoscopists at the time of ERCP on the basis of patient comorbidities and frailty, expected prognosis, and difficulty of index ERCP. Timing to planned stent exchange in the TSP group was 6 to 8 weeks following index ERCP. Cases where a TSP was planned but not subsequently conducted were treated as a PSP for the purpose of this study. Age was determined based on patient's age at time of their initial ERCP.

RBO was defined as an episode of jaundice or cholangitis and recorded as the date on which readmission to hospital was required. In the TSP group it was defined as an episode of jaundice or cholangitis requiring admission to hospital prior to the elective repeat ERCP. Rates of stent patency were calculated using the date of initial ERCP to the date of RBO, or date of last follow up (May 2020). Mortality related to biliary disease was defined as death during admission to hospital with complications of biliary disease. Any other cause of death and the absence of any subsequent admissions due to biliary disease was defined as mortality without

further biliary disease. Deaths that occurred outside of hospital were treated as death not due to biliary disease. Time intervals between index ERCP and death were calculated and reported in months.

Statistical analyses were performed using SPSS (SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp.) (11). Non-parametric data were described as median, and interquartile range (IQR). Categorical data were described as numbers and percentages. Non-parametric continuous variables were compared using Mann-Whitney U tests. Categorical variables were compared using Pearson χ^2 analysis. Differences were considered of statistical significance if they reached a p <0.05.

Results

A total of 2163 ERCPs were conducted between May 2015 to December 2018. Of these, 1263 had a first ERCP for choledocholithiasis. Successful cannulation with incomplete clearance was seen in 199 patients (15.8%). Reasons for incomplete clearance included large or impacted stone (n= 67, 33.7%), multiple stones (n= 78, 39.2%), no attempt at stone removal due to ongoing anticoagulation or presence of pacemaker device (n= 14, 7.0%), or reason unspecified (n= 40, 20.1%). TSP was chosen in 93 patients (47%), with the remaining 103 patients (53%) having PSP and watchful waiting. Repeat elective ERCP in the TSP group for second attempt at clearance or stent exchange was performed a median of 8 weeks later (IQR: 6 – 15 weeks). Median follow up was 41 (IQR:29-51) months. Median age was 72 (IQR: 63 – 80) in those treated with TSP and 82 (IQR: 73 – 87) for those treated with PSP, p < 0.001. Table 1 outlines complete patient characteristics and performed procedures.

Complications after initial ERCP were experienced early in 26 patients (13.1%) and late in 73 patients (36.7%). RBO was seen in 34 patients (32.1%) treated with PSP, of which 15 patients (14.2%) had cholangitis. In the TSP group, 15 patients (16.1%) had RBO of which 7 (7.6%) had cholangitis. RBO in the PSP group was significantly higher, p=0.009. Other complications were reported three and four times in the early and late period respectively. In the early phase they included 2 post ERCP upper gastrointestinal haemorrhages and 1 biloma. In the late phase they included 1 liver abscess and 3 presentations with right upper quadrant pain needing admission, but no abnormalities identified on biochemical and radiological investigations. Complete post ERCP complication and prognostic outcomes are outlined in Table 2.

Emergency readmissions by the end of the follow up interval were higher in the PSP group (32.1% v 19.4%), p=0.042. Figure 1 demonstrates the percentage of patients through time that did not require emergency readmissions for biliary disease between the TSP and PSP groups. The number of further emergency ERCPs was also less in the TSP group with 12 ERCPs (8.8%) compared to 43 ERCPs (75.4%) in the PSP group, $p < 0.001$.

There were no mortalities related to the index ERCP. Of those patients who died during the study follow-up period, the median time interval to death from index ERCP was 18 (IQR: 10 – 30) months. The median time interval to death from initial ERCP was 15 (IQR: 9 – 30) months in the PSP group, and 21 (IQR: 13 – 26) months in the TSP group, p = 0.503. As shown in Figure 2, mortality without further biliary disease was significantly higher in the PSP group, $p < 0.001$. Of the patients remaining alive at the end of the follow up period, there was no difference in the rates of survival with RBO between those treated with PSP and TSP (32.1 vs 26.9%, p = 0.438).

Stent patency rates in the PSP group at 6, 12, 24, 36, and 61 months were 87.7%, 82.1%, 75.5%, 69.8%, 67.9% respectively. Figure 3 shows the percentage of patients with patent stents over time. The frequency of stent outcomes during the follow up period classified by RBO, mortality without RBO, and alive without RBO is shown in Figure 4.

Discussion

The findings of this study support biliary stenting as a safe and effective management option in the event of incomplete clearance at time of initial ERCP. Of those that died in the follow up period, 75% did not experience any further biliary disease, and of those that remain alive 52% have not had RBO. In total, RBO occurred in a quarter of our cohort with the proportion of RBO higher in the PSP group. Though the PSP group had overall higher rates of RBO and emergency readmissions, there was a higher rate of readmissions in the TSP group with biliary disease in the first 6 months of follow up. The increased rate of readmissions in the PSP group only became significant following the one-year mark. This finding is in keeping with other published studies that support the use of timing intervals to repeat ERCP of 3-12 months (4,5).

The PSP groups showed significantly higher rates of all-cause mortality (52.8% vs 17.2%) and mortality without further biliary disease (39.6% vs 12.9%). This reflects the use of PSP as a strategy in those deemed more frail at time of initial ERCP and unlikely to benefit from multiple repeat ERCPs. Of interest, the difference in

mortality related to biliary disease between PSP and TSP group did not reach significance (3.8% vs 1.1%, *p*=0.225).

The rate of non-clearance at first ERCP of 15.8% in this study is comparable to previous literature (3). Results on stent patency are comparable to prior findings by Slattery *et al.* who reported a stent patency of 81.9% at 24 months in a cohort of 201 patients treated by PSP (1). Of note, in those managed with PSP, the sharpest drop in patency was in the first 3 months with 9/34 (26%) RBOs. Overall, 19/34 (56%) of recurrences occurred in the first 12 months. With a median time interval of 8 weeks to repeat elective ERCP, our cohort had much quicker repeat procedures than others reported thus far, ranging from 3-12 months (4,5). In view of our findings regarding stent patency, a smaller time interval between index and elective repeat ERCP in the TSP group seems appropriate for reducing the chances of emergency RBOs within the first 12 months. Our rate of RBO in the PSP group is comparable to a previous report of 29.8% by Sugiura *et al.* (12). In a randomized control study of 78 patients comparing PSP and TSP, DiGiorgio *et al*. reported cholangitis occurring in 35.9% of the PSP group and 7.7% of the TSP group (5). The rate of cholangitis in our TSP group was similar (7.6%) but comparatively lower in our PSP group (14.2%). Finally, our findings on biliary stenting as an effective method of decreasing stone burden and size with successful subsequent clearance on repeat ERCPs are also in line with previous reports in the literature (3,6). Of the patients treated with TSP, 75.3% had full clearance on repeat ERCP.

Strengths of this study include the large sample size and extended follow up interval. To our knowledge, the present study is the largest single comparison of post ERCP outcomes in those with incomplete clearance at time of first ERCP. With the exception of Chen *et al*. who had a mean follow up interval of 34 months, all other studies comparing these outcomes have reported follow up intervals of 12-14 months (3,13). Slattery *et al*. did report a longer follow up interval but their cohort included patients treated with PSP alone (1). Limitations of this study include a retrospective study design and a lack of information to help define patient criteria that would aid decision making regarding PSP or TSP treatment. Quantifiable measures of frailty or comorbidities were not included as part of our data collection. Future prospective studies should include measures such as the Clinical Frailty Scale, Charlson Comorbidity Index, or American Society of Anaesthesiologists score to improve defining patient characteristics and analysing outcomes.

Further research is needed to identify predictors of incomplete clearance on first ERCP or RBO in those treated with biliary stenting. Implementing new measures of frailty and comorbidity as predictors could prove helpful in elucidating this. Identifying predictors of short and long-term biliary stent patency is another potential source of information that could help risk stratification and patient selection. A tool to predict patients that will experience RBO could help facilitate a safe reduction in the number of further ERCPs while decreasing the number of patients experiencing early and late RBO related complications. Further research to define which patients are best suited to PSP over TSP could potentially decrease both complication rates and healthcare associated costs related to ERCP provision.

A final note is that current practice of ERCPs at our unit has evolved. Compared to ERCPs performed during the reported study period, current practice includes a more aggressive approach to sphincteroplasty and the introduction of the SpyGlass™ direct visualisation system. Repeat assessment of outcomes in a prospective cohort may reveal a lower proportion of patients needing to be treated with PSP. However, there will still be patients where stone extraction will not be possible, and this study supports PSP as a viable option to be considered on a patient-by-patient basis.

Conclusion

Biliary stenting is a safe and effective management option in the event of incomplete gallstone clearance at first ERCP where other management options have failed or are unavailable. Patients managed with TSP and elective repeat ERCP had fewer emergency readmissions and RBOs. Patients managed with PSP were older with higher rates of non-biliary disease mortality. Stent patency at 3 years was 69.8%. Two thirds of these patients either died of non-biliary disease or survive without recurrent biliary disease supporting PSP as an option to be considered for a select group of patients.

Conflict of Interests

The authors declare no conflict of interests for this article.

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Tables

Table 1. Summary of patient characteristics and procedures performed in the Permanent Stent Placement and Temporary Stent Placement groups.

	Total	**Permanent Stent Placement**	**Temporary Stent Placement**	***p****
n= (%)	199	106 (53%)	93 (47%)	
% Female	60.8%	58.5%	63.4%	0.475
Median Age (IQR)	78 (67 – 85)	82 (73 – 87)	72 (63 – 80)	<0.001**
Total Further ERCPs	194	57	137	
Median (IQR)	1 (0 – 1)	0 (0 – 1)	1 (1 – 2)	<0.001**
Total Emergency ERCPs (%)	55	43 (75.4%)	12 (8.8%)	
Median (IQR)	0 (0 – 0)	0 (0 – 1)	0 (0 – 0)	0.011**
Total Patient with clearance on repeat ERCP (%)	74 (37.2%)	4 (3.8%)	70 (75.3%)	<0.001

*χ^2 test. Except where ** Mann-Whitney *U* test

Table 2. Summary of post ERCP outcomes between the Permanent Stent Placement and Temporary Stent Placement groups.

	Total	Permanent Stent Placement	Temporary Stent Placement	*p**
n= (%)	199	106 (53%)	93 (47%)	
Biliary Complications				
Early (<30 days from ERCP)				
Recurrent Biliary Obstruction (%)	12 (6.0%)	8 (7.5%)	4 (4.3%)	0.337
Pancreatitis (%)	2 (1.0%)	1 (0.9%)	1 (1.1%)	0.926
Cholecystitis (%)	4 (2.0%)	1 (0.9%)	3 (3.2%)	0.252
Other (%)	3 (1.5%)	1 (0.9%)	2 (2.2%)	0.486
Late (≧30 days from ERCP)				
Recurrent Biliary Obstruction (%)	37 (18.6%)	26 (24.5%)	11 (11.8%)	0.022
Pancreatitis (%)	4 (2.0%)	3 (2.8%)	1 (1.1%)	0.379
Cholecystitis (%)	11 (5.5%)	4 (3.8%)	7 (7.5%)	0.248
Other (%)	4 (2.0%)	2 (1.9%)	2 (2.2%)	0.895
Prognostic Outcomes				
Recurrent Biliary Obstruction (%)	49 (24.6%)	34 (32.1%)	15 (16.1%)	0.009
Emergency Readmissions (%)	52 (26.1%)	34 (32.1%)	18 (19.4%)	0.042
All-cause mortality (%)	72 (36.2%)	56 (52.8%)	16 (17.2%)	0.001
Mortality related to biliary disease (%)	5 (2.5%)	4 (3.8%)	1 (1.1%)	0.225
Mortality without further biliary disease (%)	54 (27.1%)	42 (39.6%)	12 (12.9%)	0.001
Survival without RBO (%)	81 (40.7%)	26 (24.5%)	55 (59.1%)	0.001

*χ^2 test.

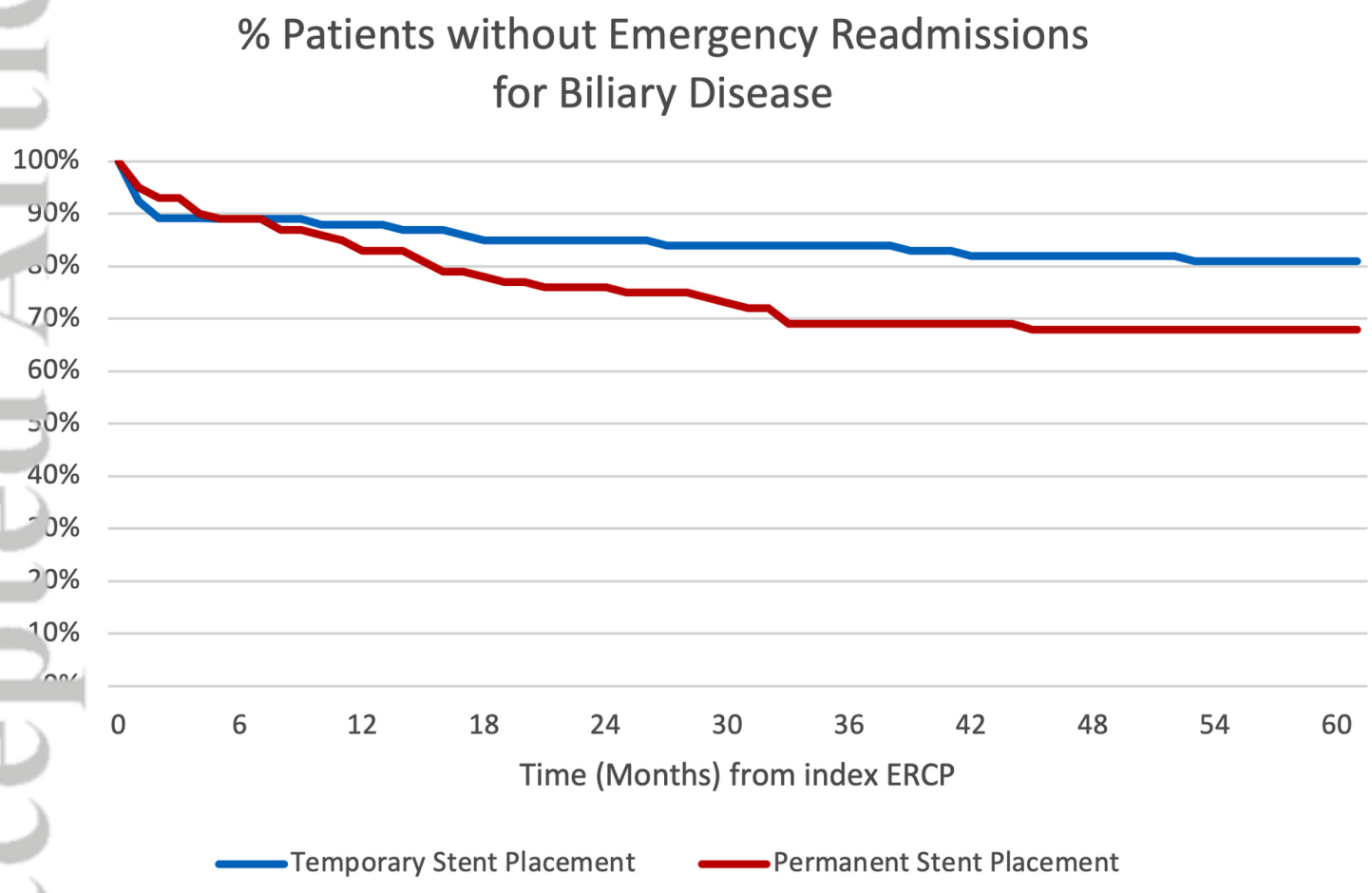
Figure Legends

Figure 1. Comparison of the percentage of patients through time that did not require emergency readmission for biliary disease between the TSP and PSP groups (32.1 v 19.4%, p=0.042).

Figure 2. Mortality rates without further biliary disease and due to biliary disease in the PSP and TSP groups. *$p < 0.001$.

Figure 3. Percentage of stents that remained patent through the follow up period in the PSP group.

Figure 4. Frequency of stent patency outcomes during the follow up period in the PSP group.



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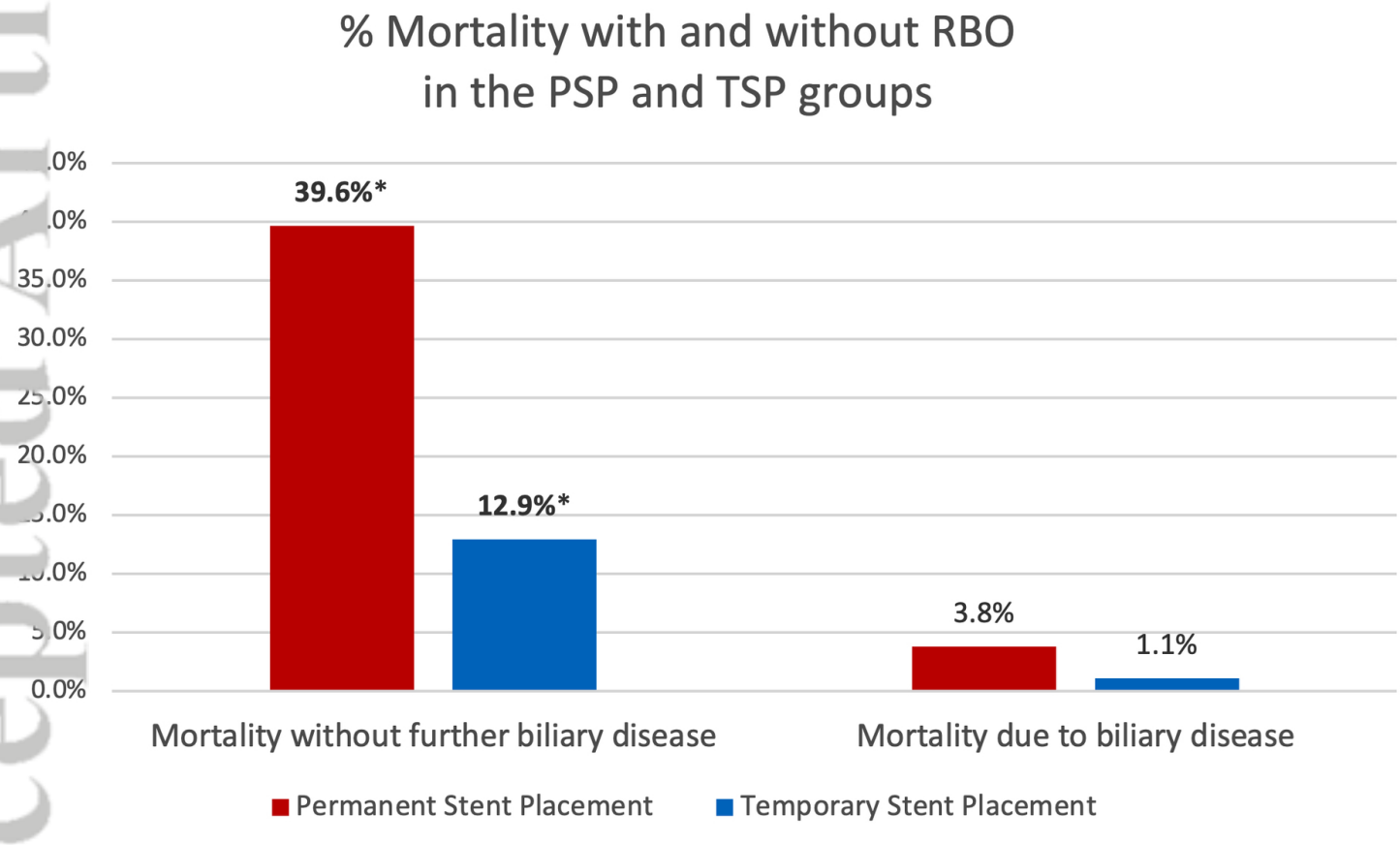

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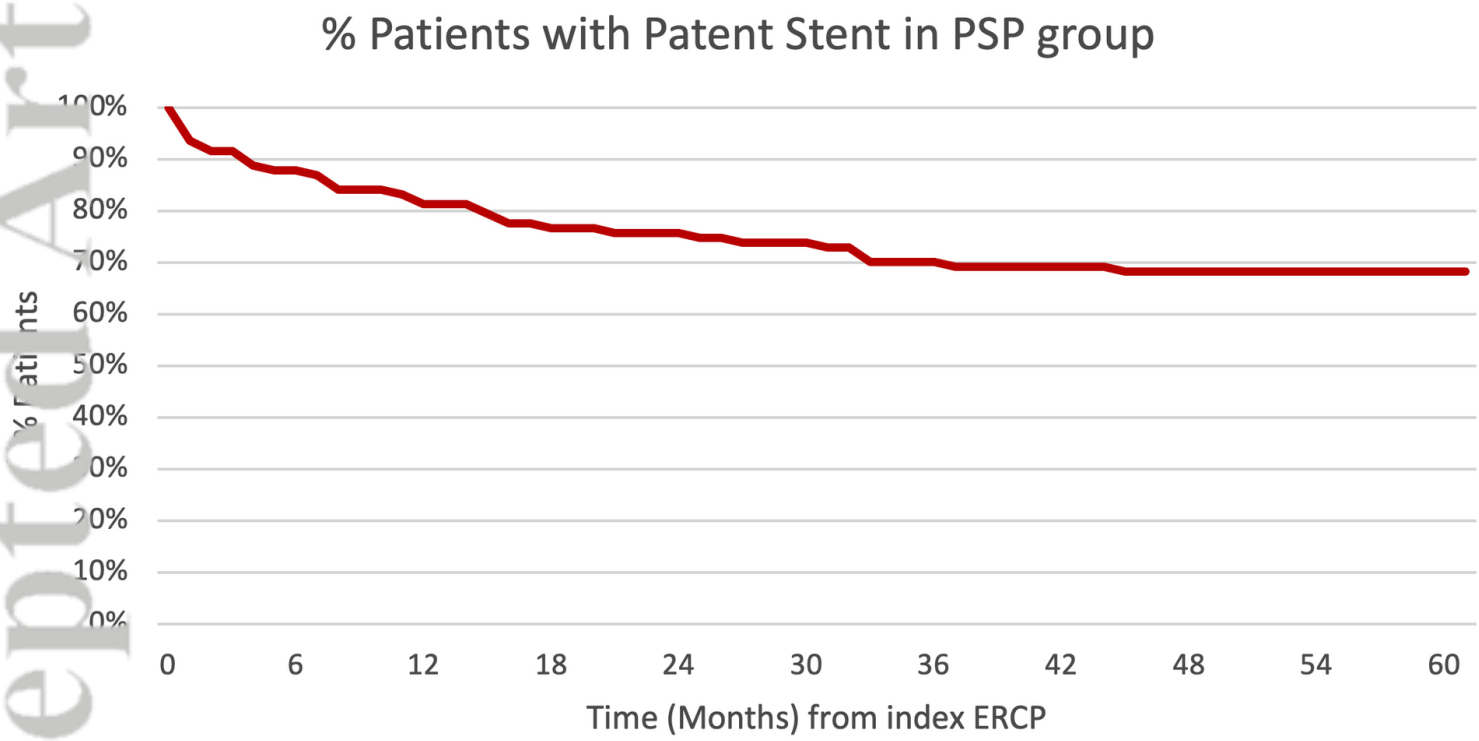

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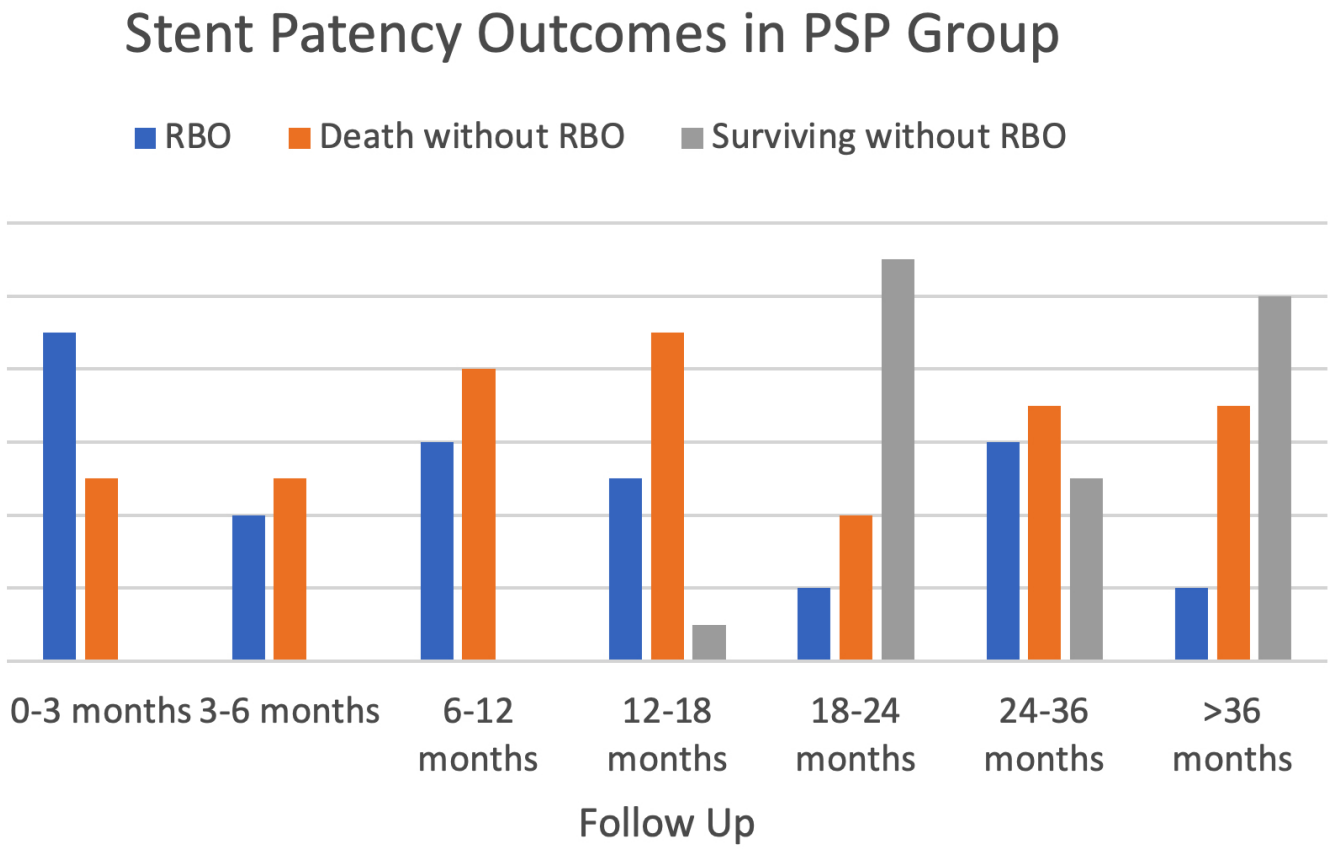

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