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# Segment-Specific Occlusion of Retrieved Plastic Biliary Stents: Direct Quantification and Microbial and Material Determinants

Akihiro Matsumi[1] | Kazuyuki Matsumoto[1] | Kentaro Oki[1] | Satoshi Kajitani[1] | Ryosuke Sato[1] | Tatsuya Kikuchi[1] | Kazuya Miyamoto[1] | Hiroyuki Terasawa[1] | Yuki Fujii[1] | Daisuke Uchida[1] | Shigeru Horiguchi[1] | Koichiro Tsutsumi[1] | Toshiharu Mitsuhashi[2] | Motoyuki Otsuka[1]

[1]Department of Gastroenterology and Hepatology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Okayama Prefecture, Japan | [2]Center for Innovative Clinical Medicine, Medical Development Field, Okayama University, Okayama, Okayama Prefecture, Japan

**Correspondence:** Kazuyuki Matsumoto (matsumoto.k@okayama-u.ac.jp)

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## ABSTRACT

**Objectives:** Plastic stents (PS) are widely used for biliary drainage, with occlusion mainly caused by biofilm formation and sludge accumulation. However, direct evaluation of luminal occlusion remains limited, and its spatial distribution is poorly understood. This study aimed to quantify luminal occlusion in retrieved PS and identify associated factors.

**Methods:** In this prospective observational study, 64 patients (196 stents) undergoing scheduled PS exchange at approximately 3-month intervals were included. Retrieved stents were divided into proximal, central, and distal segments, and occlusion was quantified using ImageJ. Clinical, microbiological, and device-related variables were analyzed. Multivariable linear regression was used to identify independent factors associated with occlusion.

**Results:** The mean occlusion rate was 28.8% ± 29.8%. Occlusion was significantly higher in the proximal segment than in the central and distal segments (35.5% vs. 25.8% and 25.0%; $p < 0.05$). Multivariable analysis showed that age > 65 years ($\beta = 11.62$, $p = 0.006$), Enterococcus-positive bile culture ($\beta = 16.00$, $p = 0.012$), and probiotic use ($\beta = 14.91$, $p = 0.007$) were independently associated with increased occlusion. Stent brand was also associated with the degree of occlusion.

**Conclusions:** Plastic stent occlusion is segment-dependent, predominantly affecting the proximal portion, and is associated with microbiological and material-related factors. Direct quantification may help optimize stent design and management.

## 1 | Introduction

Biliary stenting is widely used to manage benign and malignant biliary strictures [1]. Although self-expandable metallic stents generally provide longer patency [2, 3], plastic stents (PS) remain widely used because of their removability, lower cost, and suitability for benign strictures and preoperative drainage [4, 5].

A major limitation of PS is occlusion caused by bacterial colonization, biofilm formation, and sludge accumulation [6–8]. Patient- and stricture-related factors have been associated with early occlusion [9, 10], however, most studies have evaluated clinical stent dysfunction rather than directly quantifying luminal obstruction. Moreover, the spatial distribution of occlusion within stents remains poorly characterized.

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Stent material and surface characteristics may also affect patency [11]. Surface modifications, including polytetrafluoroethylene (PTFE) inner linings and antimicrobial coatings, have been developed to reduce bacterial adhesion and sludge accumulation [12–14], but their effects on directly measured luminal occlusion remain unclear [15].

We therefore directly quantified segment-specific luminal occlusion in PS prospectively retrieved at scheduled intervals and evaluated associated clinical, anatomical, microbiological, and device-related factors.

## 2 | Methods

### 2.1 | Study Design

This prospective observational study was conducted at Okayama University Hospital. The study adhered to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants before enrollment. The Institutional Review Board of Okayama University approved the study (approval number: 2303-027).

### 2.2 | Patient Cohort and Stent Characteristics

This analysis included 64 consecutive eligible patients (196 stents) who underwent PS placement for biliary stricture at Okayama University Hospital between January 2023 and May 2025. Stent exchanges were scheduled approximately every 3 months (80–100 days). Patients were prospectively enrolled at scheduled stent exchange. Among the enrolled 67 patients, three were excluded because the stents had spontaneously dislodged before scheduled retrieval and could not be collected for occlusion assessment. No stents from initial PS placement or conversion from endoscopic nasobiliary drainage were represented in the final analysis. Stents placed during acute cholangitis were included if retrieved at the scheduled 80–100-day exchange. All retrieved stents were systematically evaluated for occlusion. Clinical, laboratory, and procedural data were collected prospectively. The incidence of stent occlusion and associated risk factors was analyzed.

### 2.3 | Endoscopic Procedure for Biliary Stricture

Endoscopic retrograde cholangiography (ERC) was performed using a duodenoscope (TJF260V and TJF290V; Olympus Optical Co., Tokyo, Japan). Upon confirmation of biliary stricture, drainage was achieved using PSs. The type of PS (straight or pigtail), stent length, brand, and placement location were determined by the performing endoscopist. The following PSs were utilized: A: Through & Pass (Gadelius Medical, Tokyo, Japan), B: Flexima (Boston Scientific, Marlborough, MA, USA), C: Zimmon (Cook Medical, Bloomington, IN, USA), D: REGULUS (Japan Lifeline, Tokyo, Japan), E: SUZAKU (Kaneka Medix, Osaka, Japan), and F: Harmoray (Hanaco Medical, Saitama, Japan). Their polymer compositions were polyethylene (Through & Pass, Zimmon, Harmoray), polyurethane (Flexima, SUZAKU), and polyurethane with an inner PTFE layer (REGULUS).

### 2.4 | Assessment of Stent Occlusion

Stents were retrieved using forceps or a snare while avoiding mechanical disturbance to the analyzed segments. After retrieval, stents were frozen for at least 24 h before sectioning to minimize sludge loss or displacement.

Stent occlusion was evaluated at three locations: the proximal end, central portion, and distal end in straight and pigtail stents. For straight stents, sections were obtained 10 mm from each end and at the midpoint. For pigtail stents, sections were obtained at the straightened portion of the pigtail and at the midpoint (Figure 1a). Each stent was cut into cross-sectional slices approximately 1 mm in thickness and examined using a stereomicroscope. Representative cross-sectional images are provided (Figure 1b). The degree of occlusion was quantified as the ratio of the occluded area to the total luminal area. The luminal area was measured using ImageJ software, version 1.53 (National Institutes of Health, Bethesda, MD, USA) (Figure 2). All ImageJ measurements were performed by a single investigator who was blinded to the clinical information and stent brand.

The primary endpoint of this study was to identify factors associated with biliary stent occlusion. The secondary endpoint was to evaluate the degree of stent occlusion according to the location within the stent (proximal [hepatic side], central, and distal portions).

### 2.5 | Statistical Analyses

Statistical analyses were performed using JMP 18 (SAS Institute Inc., Cary, NC, USA) and Stata version 19 (StataCorp LLC, College Station, TX, USA). Continuous variables are presented as mean ± standard deviation (SD), and categorical variables as counts and percentages. For univariate analysis, Welch's *t*-test was used to compare continuous variables between two groups. One-way analysis of variance (ANOVA) was applied for comparisons involving more than two groups, such as stent brands A–F and stricture site categories. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. Multivariable linear regression models evaluated factors independently associated with stent occlusion. Candidate confounding variables were selected a priori for each exposure of interest according to the modified disjunctive cause criterion (mDCC), based on clinical knowledge and presumed causal relationships. Regression coefficients ($\beta$), 95% confidence intervals (CI), and *p*-values were reported.

To account for within-patient clustering, we fitted two-level linear mixed-effects models (stents nested within patients) with a patient-specific random intercept and the same covariates as the conventional regression models. A two-sided $p$-value $< 0.05$ was considered statistically significant. $p$-values between 0.05 and 0.10 were interpreted as indicative of a trend.

There were no missing data for variables included in the analyses. To minimize time-dependent bias, stent exchange intervals were standardized to approximately 3 months.



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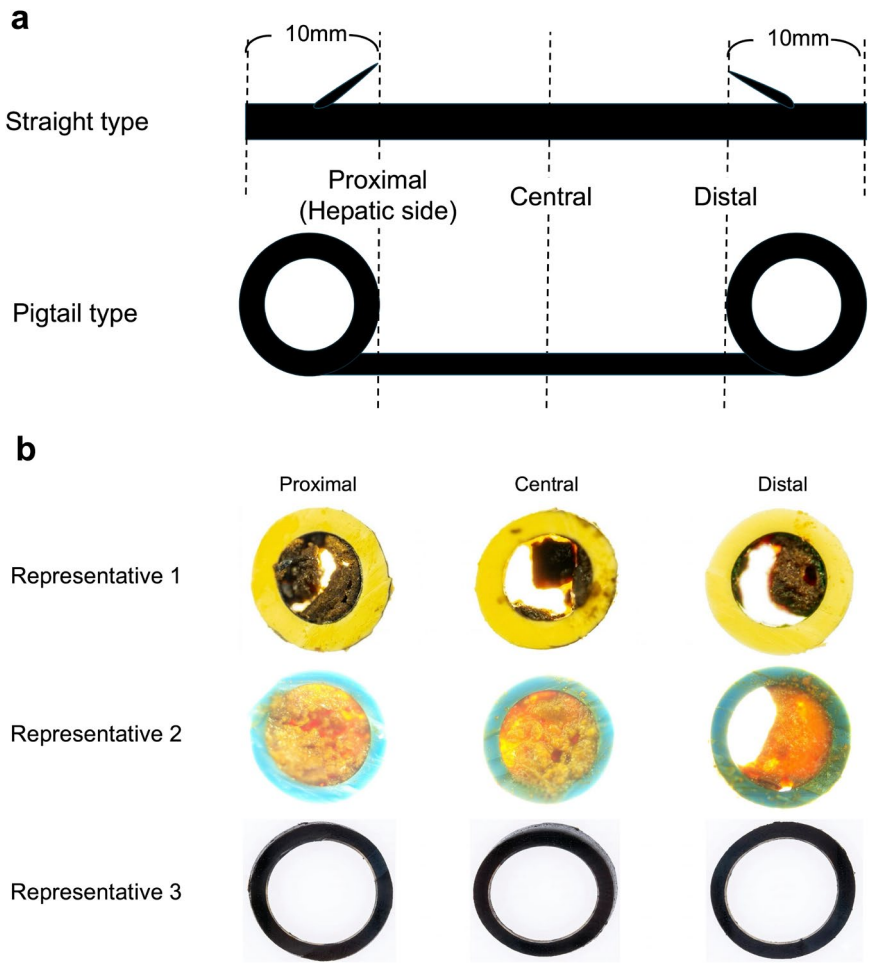



**FIGURE 1** | Assessment of stent occlusion. (a) Plastic biliary stents were divided into three segments: Proximal (hepatic side), central, and distal. For straight stents, sections were obtained 10 mm from each end and at the midpoint. For pigtail stents, sections were collected from the straightened portion and the midpoint. (b) Representative cross-sectional images of retrieved stents at each segment. Three representative cases are shown.

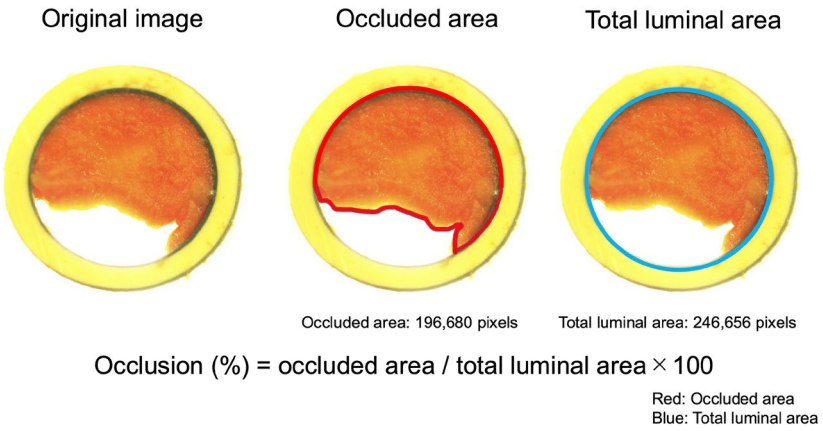



**FIGURE 2** | Image-based quantification of stent occlusion. Representative cross-sectional images of retrieved plastic biliary stents are shown. The occluded area is manually segmented and outlined in red, whereas the total luminal area is delineated in blue using ImageJ software. Stent occlusion is defined as the ratio of occluded area to total luminal area and is calculated as (occluded area/total luminal area)×100.

## 3 | Results

### 3.1 | Patient and Stent Characteristics

Of the 67 enrolled patients, 64 patients (196 stents) were included in the final analysis after exclusion of three patients with spontaneous stent dislodgement before scheduled retrieval (Supplementary Figure 1). The median age was 66 years, with 67% of patients being male. Most biliary strictures were benign (78%). The hilar site was the most common stricture site (52%), followed by choledochojejunostomy (33%) and the distal bile duct (16%). The median stent indwelling period was 91 days



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(interquartile range [IQR], 89–91; range, 82–100). Comorbidities were uncommon, with diabetes mellitus present in 15 patients (23%). Biliary tract infection at the time of stent placement occurred in 14 patients (22%), and 14 patients (22%) received antibiotics. Fourteen patients (22%) were undergoing chemotherapy. Baseline laboratory parameters indicated generally preserved liver function, with median values within reference ranges (Table 1).

A total of 196 PSs were retrieved and analyzed (Table 2). Stent placement was performed across the papilla in 81 cases (41%), above the papilla in 60 cases (31%), and at the choledochojejunal anastomosis in 55 cases (28%). Straight-type PSs comprised the majority (149 stents, 76%), while pigtail stents were used in 47 cases (24%). Stent diameters were distributed as follows: 5Fr in 4 cases (2%), 6Fr in 9 cases (5%), 7Fr in 163 cases (83%), 8.5Fr in 17 cases (9%), and 10Fr in 3 cases (1%). The most frequently used stent brands were A: Through & Pass (125 stents, 64%), followed by B: Flexima (17 stents, 9%), C: Zimmon (30 stents, 15%), D: REGULUS (17 stents, 9%), E: SUZAKU (4 stents, 2%), and F: Harmoray (3 stents, 1%). The distribution of placement sites according to stent brand is shown in Supplementary Table 1.

### 3.2 | Stent Occlusion Outcomes and Biliary Culture

The mean occlusion rate of retrieved stents was 35.5% ± 37.9% at the proximal end, 25.8% ± 34.5% at the central portion, and 25.0% ± 35.0% at the distal end. The overall mean occlusion rate, calculated across these three locations, was 28.8% ± 29.8%. The occlusion rate was significantly higher at the proximal end compared with the central and distal portions ($p = 0.008$ and $p = 0.012$, respectively). No significant difference was observed between the central and distal locations ($p = 0.957$) (Figure 3).

Bile cultures were obtained from 64 patients at the time of stent exchange, and microorganisms were detected in all cases (Table 3). The most frequently isolated organisms were *Enterococcus faecalis* (32 cases, 50.0%), *Escherichia coli* (26 cases, 40.6%), *Klebsiella pneumoniae* (25 cases, 39.1%), and *Klebsiella oxytoca* (21 cases, 32.8%). Other commonly identified organisms included *Citrobacter freundii* (16 cases, 25.0%), *Enterococcus avium* (14 cases, 21.9%), *Enterococcus casseliflavus* (12 cases, 18.8%), *Streptococcus anginosus* (11 cases, 17.2%), and *Enterococcus faecium* (11 cases, 17.2%). Multiple organisms were isolated in 60 patients.

### 3.3 | Factors Associated With Stent Occlusion

Univariate analysis (Table 4) indicated that age > 65 years ($p = 0.006$) and probiotic use ($p = 0.021$) were associated with higher mean stent occlusion of three segments. In contrast, distal bile duct stricture ($p = 0.003$) and pigtail stent type ($p = 0.007$) were associated with lower occlusion. Enterococcus-positive bile culture demonstrated a trend toward higher occlusion ($p = 0.098$). Multivariate regression analysis showed significant associations of age > 65 years

**TABLE 1** | Patient characteristics.

| | |
|---|---|
| Patients, *n* | 64 |
| Age, median (range), years | 66 (18–88) |
| Sex, Male, *n* (%) | 43 (67) |
| BMI, median (range), kg/m$^2$ | 22 (16–32) |
| Total bilirubin, median (range) (mg/dL) | 0.76 (0.26–66.15) |
| Albumin, median (range) (g/dL) | 3.7 (2.1–4.8) |
| PT, median (range) (%) | 97 (49–146) |
| Stent placement period, median (range), days | 91 (82–100) |
| Etiology of biliary stricture, *n* (%) | |
| Benign/Malignant | 50 (78)/14 (22) |
| Vater papilla, *n* (%) | |
| Present/Absent | 43 (67)/21 (33) |
| EST[a], *n* (%) | |
| Present/Absent | 38 (88)/5 (12) |
| Stricture site, *n* (%) | |
| Hilar/Distal/ Choledochojejunostomy | 33 (52)/10 (16)/21 (33) |
| Diabetes mellitus, *n* (%) | |
| Present/Absent | 15 (23)/49 (77) |
| HBV infection, *n* (%) | |
| Current/Past/Absent | 1 (2)/11 (17)/52 (81) |
| HCV infection, *n* (%) | |
| Past/Absent | 2 (3)/62 (97) |
| Ascites, *n* (%) | |
| Present/Absent | 1 (2)/63 (98) |
| Biliary tract infection at placement, *n* (%) | |
| Present/Absent | 14 (22)/50 (78) |
| Antibiotic use during stent placement, *n* (%) | |
| Present/Absent | 14 (22)/50 (78) |
| Chemotherapy, *n* (%) | |
| Ongoing/Past/Absent | 14 (22)/2 (3)/48 (75) |
| Immune modulator, *n* (%) | |
| Present/Absent | 26 (41)/38 (59) |
| UDCA, *n* (%) | |
| Present/Absent | 17 (27)/47 (73) |
| Probiotics, *n* (%) | |
| Present/Absent | 8 (13)/56 (87) |

Abbreviations: BMI, body mass index; EST, endoscopic sphincterotomy; HBV, Hepatitis B virus; HCV, Hepatitis C virus; UDCA, ursodeoxycholic acid.
[a]Patients with choledochojejunostomy were excluded from the EST classification.



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**TABLE 2** | Retrieved stent characteristics.

| | |
|---|---|
| Stents, *n* | 196 |
| Stent placement type, *n* (%) | |
| Across papilla/Above papilla/ Anastomotic | 81 (41)/60 (31)/55 (28) |
| Stent type, *n* (%) | |
| Straight/Pigtail | 149 (76)/47 (24) |
| Stent diameter, *n* (%) | |
| 5Fr/6Fr/7Fr/8.5Fr/10Fr | 4 (2)/9 (5)/163 (83)/17 (9)/3 (1) |
| Stent brand, *n* (%) | |
| A/B/C/D/E/F | 125 (64)/17 (9)/30 (15)/17 (9)/4 (2)/3 (1) |

*Note:* Stent brand: A: Through & Pass, B: Flexima, C: Zimmon, D: REGULUS, E: SUZAKU, and F: Harmoray.

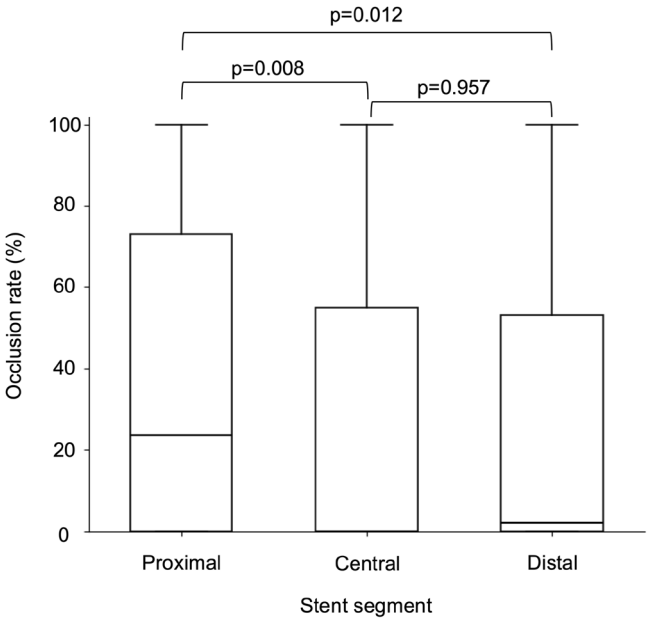



**FIGURE 3** | Segmental differences in stent occlusion. Box plots show the median and interquartile range, with whiskers indicating the range. The horizontal axis represents stent segment (proximal, central, distal), and the vertical axis represents occlusion rate (%). Pairwise comparisons between segments are indicated above the plots.

(β = 11.62, 95% CI: 3.38–19.87, $p = 0.006$), probiotic use (β = 14.91, 95% CI: 4.21–25.60, $p = 0.007$), and Enterococcus-positive bile culture (β = 16.00, 95% CI: 3.56–28.45, $p = 0.012$) with increased stent occlusion. In contrast, prothrombin time activity > 98% was independently associated with a lower mean stent occlusion rate (β = −9.69, 95% CI: −18.72 to −0.66, $p = 0.036$). When using Stent A as the reference, Stent C (β = −25.86, $p < 0.001$) and Stent D (β = −22.86, $p = 0.004$) were associated with significantly lower stent occlusion.

Segment-specific analyses were also performed (Supplementary Table 2). Distal bile duct stricture and Stent D were consistently associated with lower occlusion across multiple segments.

**TABLE 3** | Occlusion outcomes and biliary culture.

| | |
|---|---|
| Biliary culture, *n* (%) (64 patients)[a] | |
| *Enterococcus faecalis* | 32 (50.0) |
| *Escherichia coli* | 26 (40.6) |
| *Klebsiella pneumoniae* | 25 (39.1) |
| *Klebsiella oxytoca* | 21 (32.8) |
| *Citrobacter freundii* | 16 (25.0) |
| *Enterococcus avium* | 14 (21.9) |
| *Enterococcus casseliflavus* | 12 (18.8) |
| *Streptococcus anginosus* | 11 (17.2) |
| *Enterococcus faecium* | 11 (17.2) |

[a]Multiple organisms were isolated in several cases; therefore, the total number exceeds 64.

*Enterococcus*-positive bile culture was more strongly associated with proximal and central occlusion than with distal occlusion. Additionally, age > 65 years was associated with increased occlusion in the central and distal segments. Mixed-effects estimates were broadly consistent with conventional regression ($r = 0.973$; 120/132 [90.9%] concordant in direction), although confidence intervals widened and nominally significant coefficients decreased from 31 to 21. Associations remained for age > 65 years (distal and mean), Enterococcus-positive bile culture (proximal and mean), and probiotic use (distal), whereas their central-segment associations and the probiotic–mean association were attenuated. Stent-brand associations were largely preserved (Supplementary Table 3).

Stents C and D had significantly lower mean occlusion rates than Stent A ($p = 0.0062$ and $p = 0.0018$, respectively; Figure 4). Segment-specific analyses showed similar patterns, with Stent D also having significantly lower distal occlusion than Stent A (Supplementary Figures 2–4).

## 4 | Discussion

This prospective study directly quantified luminal occlusion in retrieved plastic biliary stents and demonstrated that occlusion occurs predominantly in the proximal segment. Age > 65 years, Enterococcus-positive bile cultures, and stent brand were independently associated with the degree of occlusion. These findings indicate that stent occlusion is not a uniform process but varies spatially and is influenced by host and device-related factors.

Proximal occlusion was significantly greater than central and distal occlusion. Bacterial colonization, biofilm formation, and sludge accumulation are established mechanisms of biliary stent occlusion [6–9]. Biofilm may promote sludge accumulation and further luminal narrowing [6, 8, 16]. In contrast, duodenal flow may reduce debris and biofilm accumulation in the distal segment, potentially contributing to the observed segmental difference. In an exploratory analysis of stents placed above the papilla, proximal occlusion remained greater than distal



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**TABLE 4** | Analysis of factors associated with stent occlusion.

| | Mean occlusion rate of three segments (%) | | | | |
|---|---|---|---|---|---|
| | | | Univariate | Multiple regression model | |
| | Present | Absent | *p* | Coefficient (95% CI) | *p* |
| Age (> 65 years) | 34.7 ± 30.6 | 23.1 ± 27.9 | 0.006 | 11.62 (3.38, 19.87) | 0.006 |
| Sex, Male | 27.7 ± 29.2 | 30.5 ± 30.8 | 0.534 | −2.74 (−11.43, 5.94) | 0.534 |
| BMI (> 22) | 27.4 ± 28.6 | 29.7 ± 30.6 | 0.587 | −5.68 (−14.79, 3.43) | 0.220 |
| Stent placement period (> 90 days) | 28.0 ± 29.7 | 30.5 ± 30.1 | 0.592 | −2.35 (−11.39, 6.69) | 0.608 |
| Etiology of biliary stricture (malignant) | 27.4 ± 26.4 | 29.1 ± 30.6 | 0.743 | −8.67 (−25.42, 8.07) | 0.308 |
| Stricture site (hilar) | 29.9 ± 28.7 | 27.1 ± 31.4 | 0.524 | Reference | |
| Stricture site (distal) | 11.1 ± 15.9 | 31.0 ± 30.4 | 0.003 | −18.90 (−32.32, −5.48) | 0.006 |
| Stricture site (choledochojejunostomy) | 33.4 ± 33.8 | 26.9 ± 27.9 | 0.170 | 3.30 (−6.15, 12.76) | 0.492 |
| Diabetes mellitus | 30.4 ± 31.7 | 28.2 ± 29.2 | 0.670 | 4.34 (−6.48, 15.16) | 0.430 |
| HBV infection | 25.9 ± 27.5 | 29.4 ± 30.3 | 0.535 | −6.33 (−17.90, 5.24) | 0.282 |
| HCV infection | 14.9 ± 25.0 | 29.7 ± 29.9 | 0.097 | −16.69 (−34.45, 1.07) | 0.065 |
| Ascites | 58.5 ± 0.2 | 28.4 ± 29.8 | 0.156 | 28.30 (−13.72, 70.32) | 0.186 |
| Biliary tract infection when placed | 26.8 ± 28.7 | 29.2 ± 30.0 | 0.665 | −3.01 (−14.87, 8.86) | 0.618 |
| Antibiotic use during stent placement | 30.2 ± 33.0 | 28.5 ± 29.3 | 0.784 | 4.10 (−10.30, 18.50) | 0.575 |
| Chemotherapy | 29.7 ± 30.6 | 28.5 ± 29.6 | 0.830 | 6.79 (−10.32, 23.91) | 0.435 |
| Immune modulator | 29.6 ± 28.4 | 27.9 ± 31.1 | 0.702 | 0.10 (−8.58, 8.78) | 0.982 |
| UDCA | 26.7 ± 28.4 | 29.6 ± 30.4 | 0.522 | −2.99 (−12.19, 6.20) | 0.522 |
| Probiotics | 38.1 ± 28.6 | 26.2 ± 29.6 | 0.021 | 14.91 (4.21, 25.60) | 0.007 |
| PT (> 98%) | 26.1 ± 28.9 | 33.5 ± 30.2 | 0.092 | −9.69 (−18.72, −0.66) | 0.036 |
| Albumin (> 3.5 g/dL) | 29.8 ± 31.9 | 27.2 ± 26.4 | 0.559 | 1.35 (−7.65, 10.35) | 0.768 |
| Total bilirubin (> 3.0 mg/dL) | 30.9 ± 29.9 | 28.3 ± 29.8 | 0.657 | 5.08 (−9.01, 19.16) | 0.478 |
| Stent placement type (above papilla) | 35.0 ± 30.5 | 19.7 ± 23.2 | < 0.001 | 7.42 (−3.16, 17.99) | 0.168 |
| Stent type (pigtail) | 18.6 ± 23.2 | 31.9 ± 30.9 | 0.007 | −7.35 (−21.88, 7.19) | 0.320 |
| Stent diameter (> 7Fr) | 29.0 ± 30.1 | 24.8 ± 24.8 | 0.621 | −11.38 (−32.90, 10.14) | 0.298 |
| Stent brand (A) | 35.9 ± 30.1 | | | Reference | |
| Stent brand (B) | 25.1 ± 32.6 | | | 1.75 (−15.31, 18.81) | 0.840 |
| Stent brand (C) | 15.6 ± 24.4 | | | −25.86 (−37.68, −14.05) | < 0.001 |
| Stent brand (D) | 7.6 ± 13.6 | | | −22.86 (−38.12, −7.60) | 0.004 |
| Stent brand (E) | 1.1 ± 1.8 | | | −26.10 (−55.93, 3.73) | 0.086 |
| Stent brand (F) | 37.9 ± 17.9 | | | −12.07 (−46.20, 22.05) | 0.486 |
| Biliary culture (*Klebsiella*) | 27.6 ± 29.2 | 31.6 ± 31.1 | 0.402 | −3.79 (−13.16, 5.58) | 0.426 |
| Biliary culture (*Enterococcus*) | 30.3 ± 30.3 | 20.6 ± 25.4 | 0.098 | 16.00 (3.56, 28.45) | 0.012 |
| Biliary culture (*E. coli*) | 30.5 ± 30.0 | 27.4 ± 29.6 | 0.465 | 1.92 (−7.25, 11.09) | 0.680 |
| Biliary culture (*ESBL*) | 41.9 ± 29.9 | 27.2 ± 29.4 | 0.032 | 11.92 (−2.28, 26.12) | 0.099 |
| Biliary culture (*MRSA*) | 14.0 ± 16.7 | 29.4 ± 30.0 | 0.153 | −17.05 (−38.53, 4.44) | 0.119 |

*Note:* Stent brand; A: Through & Pass, B: Flexima, C: Zimmon, D: REGULUS, E: SUZAKU, and F: Harmoray. Univariate comparisons were performed using Welch's *t*-test, except for stent brand, which was analyzed using one-way ANOVA.

Abbreviations: BMI, body mass index; CI, confidence interval; HBV, hepatitis B virus; HCV, hepatitis C virus; UDCA, ursodeoxycholic acid.



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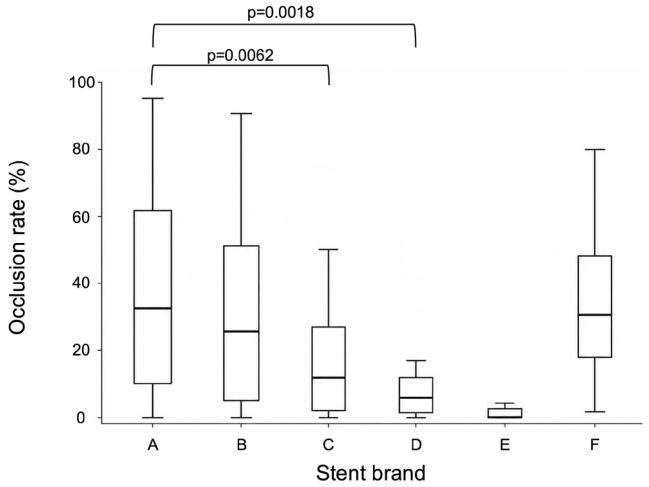



**FIGURE 4** | Comparison of stent occlusion according to stent brand. Box plots show the median and interquartile range, with whiskers indicating the range. The horizontal axis represents stent brand (A–F), and the vertical axis represents occlusion rate (%). The occlusion rate for each stent was calculated as the average of the proximal, central, and distal segment values. Stents C and D demonstrated significantly lower occlusion rates than Stent A.

occlusion (median, 40% vs. 7%; $p = 0.0023$), despite reduced duodenobiliary reflux. This suggests that other mechanisms, including regional bile flow and biofilm formation, may also contribute to segment-specific occlusion.

Enterococcus-positive bile culture was associated with increased stent occlusion. Enterococcus species have strong biofilm-forming capacity, can adhere to artificial surfaces, and are resistant to environmental stress and antimicrobial agents [17, 18]. Previous studies have demonstrated the importance of bacterial colonization in stent dysfunction, but have largely focused on bacterial presence rather than species-specific effects [6, 7, 10]. The association observed in this study suggests that Enterococcus may contribute to biological stent occlusion. The stronger association in the proximal segment may reflect an environment favorable for sustained bacterial colonization and biofilm formation. These findings suggest that microbial composition, rather than bacterial presence alone, may influence stent occlusion.

Probiotic use was also independently associated with increased stent occlusion. This finding should be interpreted cautiously because the underlying mechanism remains unclear, and no direct evidence currently supports a causal relationship between probiotic use and biliary stent occlusion. One explanation is that probiotic use may be a surrogate marker for patients with altered intestinal microbiota, prior antibiotic exposure, or greater clinical complexity rather than a direct contributing factor. Given the role of duodenobiliary reflux and microbial colonization in stent occlusion, changes in the intestinal microbial environment may influence biofilm formation within the stent lumen, as intestinal microbiota affect biliary physiology and bile acid metabolism [19]. However, this study did not assess gut or biliary microbiota composition or function, so this association should be considered exploratory. Differences in stent selection may also have contributed, as patients not receiving probiotics were significantly ($p = 0.0087$) more likely to receive Stent C, which demonstrated lower occlusion rates. This suggests the association may partly reflect residual confounding related to stent selection. Further studies should clarify whether this association is biological or reflects confounding.

Stent brand was significantly associated with stent occlusion, with Stent D demonstrating a markedly lower occlusion rate compared with the reference stent. Stent material and surface characteristics may contribute to stent occlusion. Stent D is composed of polyurethane with an inner PTFE layer, whereas conventional PSs are typically made of polyethylene or polyurethane without surface modification. PTFE has low surface energy and reduced frictional resistance, which may inhibit bacterial adhesion and biliary sludge formation [13, 15]. Experimental studies have demonstrated that smoother, more hydrophobic surfaces reduce bacterial attachment and biofilm formation, thereby delaying stent occlusion [13, 14, 20]. In contrast, polyethylene stents have relatively smooth surfaces but may have irregularities that facilitate bacterial adhesion and sludge accumulation [12]. Stent selection was nonrandom and influenced by anatomical and procedural factors; therefore, the observed brand differences may reflect residual confounding rather than material effects alone. Previous clinical studies have suggested that stent material influences patency, but most have relied on indirect clinical endpoints, such as stent dysfunction or time to occlusion [11]. Direct quantification showed an association between stent brand and luminal occlusion, supporting the potential relevance of surface modification [21]. Dual-layer PSs may also represent a future device strategy [22]. Prospective studies are needed to determine whether material characteristics directly influence occlusion.

Older age (> 65 years) was associated with increased stent occlusion. Potential mechanisms include age-related changes in bile composition that promote sludge formation [23] and immunosenescence that may facilitate bacterial persistence and biofilm formation [24, 25]. However, age has not consistently predicted stent dysfunction [10, 11] and may also reflect unmeasured clinical complexity; further studies are needed to clarify this association. Higher prothrombin time activity (> 98%) was associated with lower stent occlusion. However, because this exploratory finding has an uncertain biological mechanism, it should be interpreted cautiously and requires further validation. Mixed-effects estimates were broadly consistent with conventional regression, although some associations were attenuated after accounting for within-patient clustering; findings consistent across both approaches should therefore receive greater emphasis.

This study has several strengths. Luminal occlusion was directly quantified in retrieved plastic biliary stents, allowing segment-specific assessment of its spatial distribution. Clinical, anatomical, microbiological, and device-related factors were also evaluated simultaneously. To our knowledge, this is the first study to systematically evaluate spatial heterogeneity of luminal occlusion within plastic biliary stents.

This study has several limitations, which also highlight important directions for future research. First, the study was conducted at a single center with a relatively small sample size; however, the standardized stent exchange protocol and detailed clinical data enabled a focused analysis of factors associated with stent occlusion. Larger multicenter studies are needed to validate these findings.



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Second, although multivariable analyses were performed using prespecified confounders, residual confounding cannot be fully excluded. Enrollment at scheduled exchange did not capture early stent dysfunction or pre-enrollment dislodgement, potentially biasing stent-brand comparisons. Third, the microbiological evaluation relied on conventional culture methods, which may underestimate the complexity of the biliary microbiome. Incorporating molecular techniques, including 16S rRNA sequencing or metagenomic analysis, may offer deeper insight into microbial mechanisms underlying stent dysfunction. Because bile cultures were obtained only at scheduled exchange, the temporal relationship between Enterococcus colonization and stent occlusion remains unclear, precluding determination of whether colonization preceded or followed occlusion. Fourth, despite standardization of the stent exchange interval, variations in patient characteristics and clinical management may have affected the results. Despite standardized retrieval and specimen handling, some sludge loss or displacement cannot be excluded, although the same protocol was applied to all stents. Although ImageJ measurements were performed by a single blinded assessor, intraobserver reproducibility was not formally evaluated and should be assessed in future studies. Finally, while the observational design precludes definitive causal inference, this study provides a basis for future prospective and mechanistic studies aimed at refining strategies to prevent stent occlusion.

In conclusion, plastic biliary stent occlusion is a segment-dependent process that predominantly affects the proximal segment and is associated with microbiological and material-related factors. These findings may inform strategies to reduce plastic stent occlusion.

### Author Contributions

**Akihiro Matsumi, Kentaro Oki, Satoshi Kajitani, Ryosuke Sato, Tatsuya Kikuchi, Kazuya Miyamoto, Hiroyuki Terasawa, Yuki Fujii, Daisuke Uchida, Shigeru Horiguchi, and Koichiro Tsutsumi:** collecting and interpreting data. **Akihiro Matsumi, Kazuyuki Matsumoto, and Toshiharu Mitsuhashi:** substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work. **Akihiro Matsumi, Kazuyuki Matsumoto, and Motoyuki Otsuka:** drafting the work or revising it critically for important intellectual content. **Kazuyuki Matsumoto and Motoyuki Otsuka:** final approval of the version to be published.


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### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Supplementary Figure 1.** Study flow diagram. **Supplementary Figure 2**. Comparison of stent occlusion according to stent brand (Proximal segment). **Supplementary Figure 3**. Comparison of stent occlusion according to stent brand (Central segment). **Supplementary Figure 4**. Comparison of stent occlusion according to stent brand (Distal segment). **Supplementary Table 1**. Distribution of stent placement sites according to stent brand. **Supplementary Table 2**. Analysis of factors associated with stent occlusion. **Supplementary Table 3**. Patient-level random-intercept linear mixed-effects analyses of factors associated with stent occlusion.



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