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Primary Duct Closure versus T-Tube Drainage after Laparoscopic Common Bile Duct Exploration in Older Patients: A Propensity Score-Matched Study

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Abstract

Objective: This paper aims to compare the safety and clinical effectiveness of primary duct closure and T-tube drainage after laparoscopic cholecystectomy combined with laparoscopic common bile duct exploration (LC + LCBDE) in older patients with common bile duct stones. **Methods:** We reviewed records from one center. The cohort included 202 patients aged 65 years or older who underwent LC + LCBDE. Eighty-one received primary closure, and 121 received T-tube drainage. We matched patients 1:1 without replacement. The model used 13 preoperative variables and a propensity-score caliper of 0.1. We checked balance with standardized mean differences (SMDs). We analyzed 73 matched pairs with paired Wilcoxon signed-rank or exact McNemar tests. We report paired effects with 95% confidence intervals (CIs). **Results:** PSM produced 73 matched pairs. The largest absolute SMD fell from 0.364 before matching to 0.134 after matching. The primary-closure group had a shorter hospital stay [8.00 (6.00, 11.00) vs 12.00 (9.00, 15.00) days; paired median difference, −3.0 days; 95% CI, −5.0 to −2.0; $P < 0.001$]. This group also had shorter operations ($P = 0.026$), lower blood loss ($P = 0.037$), and earlier flatus ($P = 0.011$). Intraoperative stone clearance was similar in both groups (97.3% vs 95.9%; paired risk difference, 1.4 percentage points; 95% CI, −4.1 to 6.8; $P = 1.000$). Overall 30-day complications were 15.1% and 28.8%. The paired comparison was not significant ($P = 0.087$). Major complications, stones found within 6 months, and recurrent stones were also similar. **Conclusion:** In this matched cohort of older patients, primary closure was linked to faster recovery. The clearest difference was a shorter hospital stay. Stone outcomes and major complications were similar. Residual confounding remains possible, and the database lacked details on individual complication types. These findings cannot prove cause and effect. Primary closure remains an option when the surgeon can close the duct securely.

Keywords

Older Patients, Choledocholithiasis, Laparoscopic Common Bile Duct Exploration, Primary Duct Closure, T-Tube Drainage, Propensity Score Matching

1. Introduction

Choledocholithiasis is a common biliary disorder in older adults and may cause obstructive jaundice, acute cholangitis, and biliary pancreatitis. Severe cases can progress to septic shock and may be life-threatening [1]. Older patients frequently have impaired cardiopulmonary function, poor nutritional status, and multiple comorbidities, resulting in greater perioperative risk and a heavier postoperative recovery burden [2]. With advances in laparoscopic and choledochoscopic techniques, laparoscopic cholecystectomy combined with laparoscopic common bile duct exploration (LC + LCBDE) has become an important minimally invasive treatment for common bile duct stones. It permits biliary exploration and stone clearance during a single operation while preserving the function of the sphincter of Oddi [3]-[5].

After choledochotomy and stone extraction, the duct is generally managed by primary closure or T-tube drainage. A T-tube can decompress the biliary tract, drain bile, and provide a route for managing residual stones. However, prolonged tube placement may lead to bile loss, fluid and electrolyte disturbances, tube dislodgement, ascending infection, and bile leakage after tube removal, while also extending the duration of external drainage and hospitalization. Improvements in choledochoscopic stone extraction, absorbable sutures, and perioperative management have supported the increasing use of primary closure in patients in whom secure closure is feasible. Previous studies have shown that primary closure can shorten operative time and postoperative hospital stay without increasing the risks of bile leakage, residual stones, or bile duct stricture [6]-[8].

Nevertheless, older patients have distinct organ reserve, inflammatory responses, and postoperative tube-care requirements. Moreover, the choice of duct management is often influenced by common bile duct diameter, stone burden, degree of inflammation, distal duct patency, and the surgeon's judgment; conventional retrospective comparisons are therefore vulnerable to selection bias. Clinical evidence specifically comparing primary closure with T-tube drainage in older patients remains limited, and their effects on perioperative recovery, postoperative complications, and long-term stone recurrence have not been established consistently [9]-[12]. We therefore used propensity score matching to balance measured baseline differences and compared the safety and clinical outcomes of primary closure versus T-tube drainage after LC + LCBDE in older patients with choledocholithiasis.

2. Materials and Methods

2.1. Study Design and Patients

We conducted a single-center retrospective cohort study. We used records from patients who underwent LC + LCBDE at the Affiliated Hospital of Youjiang Medical University for Nationalities. The operations took place between January 2018 and December 2025. The analytic database contained 202 eligible operations. It did not retain the number of patients screened or each reason for exclusion. The institutional ethics committee approved the study. All procedures followed the applicable ethical standards. All patients received study information and gave written informed consent.

We included patients aged 65 years or older. Imaging and liver tests had to support a diagnosis of common bile duct stones. Patients had to undergo LC + LCBDE with attempted stone extraction. The surgeon then used primary closure or T-tube drainage. The record had to document an intraoperative assessment of duct clearance by choledochoscopy, cholangiography, or the operative note. Core baseline and perioperative data also had to be available. We excluded biliary malignancy, a confirmed benign bile duct stricture, and obstruction from an ampullary lesion. We also excluded complex stones that required hepatectomy or biliary-enteric anastomosis. Conversion to open surgery or another major concurrent procedure also led to exclusion. For repeat admissions, we kept only the first eligible operation. We excluded records without key exposure or primary-outcome data. All 202 records contained the 13 PSM covariates and the reported perioperative outcomes. We did not impute missing values. The final cohort included 81 primary-closure patients and 121 T-tube patients.

2.2. Grouping and Surgical Procedures

We grouped patients by the final treatment of the choledochotomy. Direct closure was classified as primary closure. Closure around an external T-tube was classified as T-tube drainage. The surgeon removed stones and assessed clearance before choosing the closure method. Treatment was not randomized. The surgeon considered the bile duct wall, confidence in clearance, distal duct patency, biliary pressure, inflammatory edema, and the patient's overall condition. We treated choledochoscopy as an intraoperative process measure. We did not use it as a baseline matching variable. Operative complexity and procedural progress may affect its use.

2.2.1. Primary Closure Group

After induction of general anesthesia, pneumoperitoneum was established and laparoscopic cholecystectomy and exposure of the common bile duct were performed routinely. A longitudinal incision was made on the anterior wall of the common bile duct. Stones were extracted using forceps, a retrieval basket, or choledochoscopy; lithotripsy and saline irrigation were used when necessary. After confirming the absence of obvious residual stones, distal duct patency, and acceptable blood supply and suturability of the bile duct wall, the choledochotomy was closed with appropriately sized absorbable sutures using a continuous or interrupted full-thickness technique. After confirming the absence of active bile leakage, a subhepatic drain was placed at the surgeon's discretion.

2.2.2. T-Tube Drainage Group

Surgeons exposed the common bile duct and removed stones as described for the primary-closure group. They chose a silicone T-tube according to the duct diameter. The short limbs entered the proximal and distal ducts. The surgeon closed the choledochotomy around the tube with absorbable sutures. The team checked patency and looked for leakage. The long limb exited through the abdominal wall and was secured. A subhepatic drain was placed. After surgery, T-tube output, liver tests, symptoms, and imaging guided care. T-tube removal was not a discharge requirement. Patients who met the usual discharge criteria could leave with the tube in place. During follow-up, the team generally completed clamping and T-tube cholangiography before removal. When needed, surgeons treated residual stones through the mature tract.

Both groups received individualized antimicrobial treatment, analgesia, nutritional support, and fluid management. Early ambulation and oral intake were encouraged when clinically appropriate. Discharge criteria included stable vital signs, no uncontrolled infection or bile leakage, adequate oral intake, controllable pain, and no need for inpatient-level intervention.

2.3. Outcomes and Definitions

Postoperative hospital stay was the primary outcome. We counted calendar days from the day after surgery until discharge. Secondary outcomes included operative time, blood loss, intraoperative stone clearance, choledochoscopy use, ICU admission, and time to first flatus. We also recorded surgical reintervention, ERCP, and unplanned readmission within 30 days. Intraoperative stone clearance meant that no definite stone required immediate further treatment at the end of exploration. The surgeon based this assessment on choledochoscopy, cholangiography, or the operative record. This measure differs from stones found later during follow-up.

Safety and follow-up outcomes included complications within 30 days, major complications, bile duct stricture, stones found within 6 months, and recurrent stones. We defined any postoperative complication as a departure from expected recovery at Clavien-Dindo grade I or higher. Major complications were grade III or higher [13]. The database recorded overall and major-complication indicators. It did not consistently record biliary, infectious, or T-tube-related subtypes. We could not report those details without reviewing the source records again. Bile duct stricture required compatible symptoms or biochemical abnormalities plus imaging or endoscopic confirmation. Stones found within 6 months may have been missed at surgery or identified later. Their number can therefore exceed the number of intraoperative clearance failures. Recurrent stones were identified 6 months or more after documented initial clearance.

2.4. Follow-Up

Follow-up data were obtained from outpatient records, subsequent hospitalization records, and telephone interviews. In principle, symptoms, liver function, and abdominal ultrasonography were assessed 1 month after surgery, followed by evaluations at 3 and 6 months and annually thereafter. Computed tomography, magnetic resonance cholangiopancreatography, endoscopic ultrasonography, or ERCP was performed when fever, jaundice, or abdominal pain occurred. Follow-up was censored in June 2026.

2.5. Statistical Analysis

We used SPSS version 27.0 and R version 4.4.3. We present continuous variables as median (25th percentile, 75th percentile). We present categorical variables as n (%). Before matching, we used the Mann-Whitney U test, chi-square test, or Fisher exact test, as appropriate. A binary logistic model estimated each patient's propensity for primary closure. It included age, sex, common bile duct diameter, maximum stone diameter, stone number, BMI, WBC, CRP, TBIL, ALT, AST, gamma-glutamyl transferase, and serum amylase. These covariates had no missing values, so we used no imputation. We performed 1:1 nearest-neighbor matching without replacement. The absolute caliper was 0.1. We assessed balance mainly with absolute SMDs. Values below 0.10 indicated good balance [14]. We also inspected propensity-score overlap and within-pair distances. For the matched sample, we used paired Wilcoxon signed-rank tests for continuous outcomes. We used exact McNemar tests for binary outcomes [15]. We report median within-pair differences for continuous outcomes. We report paired risk differences for binary outcomes, calculated as primary closure minus T-tube drainage. We estimated 95% CIs using 20,000 paired bootstrap resamples. All tests were two-sided. We used $P < 0.05$ as the significance threshold. Analyses of secondary outcomes were exploratory and had no multiplicity adjustment.

3. Results

3.1. Baseline Characteristics before and after PSM

The analytic database included 202 eligible older patients. It contained 81 primary-closure patients and 121 T-tube patients. None of the 13 matching variables was missing. Matching produced 73 pairs. Eight primary-closure patients and 48 T-tube patients remained unmatched (**Figure 1**). The largest absolute SMD fell from 0.364 to 0.134. Twelve of the 13 post-matching SMDs were below 0.10. TBIL still showed mild imbalance (SMD = 0.134). In the matched sample, propensity scores ranged from 0.095 to 0.690 for primary closure. They ranged from 0.100 to 0.709 for T-tube drainage. The mean within-pair absolute difference was 0.015, and the largest was 0.089 (**Table 1** and **Figure 2**).

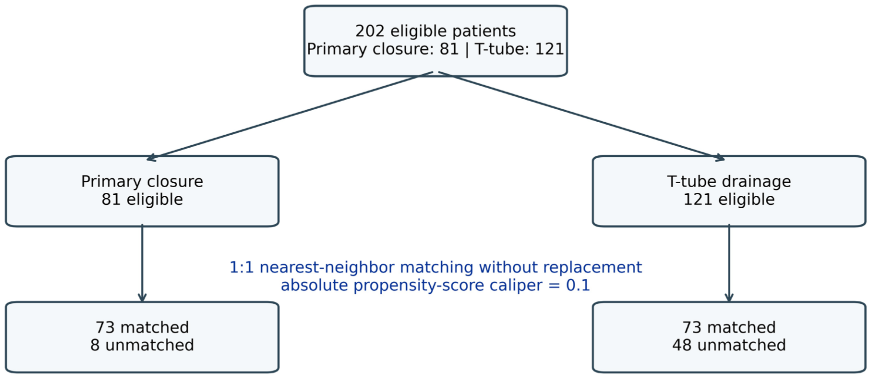

Figure 1. Patient flow and propensity score matching.

Table 1. Baseline characteristics before and after propensity score matching.

Variable	Before PSM				After PSM			
	Primary closure (n = 81)	T-tube drainage (n = 121)	P value	SMD	Primary closure (n = 73)	T-tube drainage (n = 73)	P value	SMD
Age (years)	71.00 (66.00, 77.00)	69.00 (66.00, 75.00)	0.491	0.152	69.00 (66.00, 75.00)	70.00 (66.00, 75.00)	0.619	0.062
Male sex, n (%)	31 (38.3)	59 (48.8)	0.142	0.212	30 (41.1)	31 (42.5)	0.867	0.028
BMI (kg/m^2)	20.78 (19.22, 22.95)	20.83 (18.55, 23.78)	0.928	0.013	20.78 (19.44, 22.83)	20.81 (18.55, 23.78)	0.739	0.033
Common bile duct diameter (mm)	16.00 (12.00, 20.00)	20.00 (15.00, 22.00)	0.029	0.275	18.00 (12.00, 20.00)	16.00 (12.00, 20.00)	0.978	0.063
Maximum stone diameter (mm)	11.00 (8.00, 16.00)	13.00 (9.00, 18.00)	0.193	0.178	12.00 (8.00, 16.00)	12.00 (8.00, 16.00)	0.808	0.029
Number of stones	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)	0.225	0.164	2.00 (1.00, 3.00)	2.00 (1.00, 3.00)	0.942	0.050
WBC ($\times 10^9$/L)	6.97 (5.57, 10.05)	8.38 (6.20, 12.46)	0.053	0.141	7.01 (5.57, 11.03)	7.94 (6.20, 10.70)	0.265	0.009
CRP (mg/L)	53.36 (32.00, 83.44)	61.30 (24.00, 78.44)	0.693	0.005	52.00 (32.00, 83.30)	62.00 (24.00, 82.36)	0.920	0.061
TBIL (μmol/L)	18.50 (12.70, 30.30)	30.90 (12.70, 82.30)	0.007	0.364	19.00 (12.90, 34.00)	22.00 (10.40, 66.30)	0.634	0.134
ALT (U/L)	46.10 (26.40, 88.00)	63.00 (30.00, 137.00)	0.053	0.268	46.00 (26.40, 88.00)	47.00 (29.00, 96.00)	0.540	0.040
AST (U/L)	38.00 (26.50, 72.00)	45.10 (25.90, 114.80)	0.162	0.334	38.00 (27.00, 68.00)	32.10 (23.00, 74.30)	0.543	0.015
γ-GT (U/L)	206.00 (78.00, 369.00)	172.00 (111.00, 285.00)	0.856	0.007	206.00 (85.00, 408.00)	147.00 (111.00, 266.00)	0.728	0.003
Serum amylase (U/L)	64.00 (45.00, 102.00)	77.00 (48.00, 112.00)	0.365	0.144	64.00 (45.00, 98.00)	65.00 (47.00, 105.00)	0.774	0.005

Note: Continuous variables are reported as median (25th percentile, 75th percentile). Sex is reported as n (%). SMD, standardized mean difference. An absolute SMD below 0.10 indicates good balance. TBIL showed mild residual imbalance after matching (SMD = 0.134).

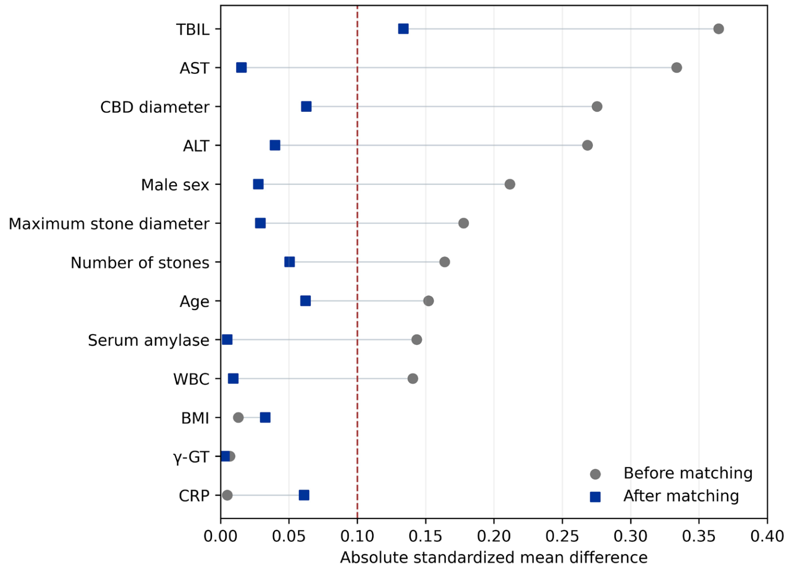

Figure 2. Covariate balance before and after propensity score matching. The dashed line marks an absolute SMD of 0.10.

3.2. Intraoperative and 30-Day Postoperative Outcomes

In the matched analysis, primary closure was linked to shorter operating time (P = 0.026) and lower blood loss (P = 0.037). It was also linked to earlier flatus (P = 0.011) and a shorter hospital stay (P < 0.001). The median within-pair difference in hospital stay was −3.0 days (95% CI, −5.0 to −2.0). Intraoperative stone clearance was 97.3% with primary closure and 95.9% with T-tube drainage. The paired risk difference was 1.4 percentage points (95% CI, −4.1 to 6.8; P = 1.000). Choledochoscopy use, ICU admission, 30-day reintervention, ERCP, and readmission did not differ between groups (Table 2).

Table 2. Intraoperative and 30-day postoperative outcomes after propensity score matching.

Outcome	Primary closure (n = 73)	T-tube drainage (n = 73)	Paired effect (95% CI)	Paired P value
Operative time (min)	140.00 (120.00, 170.00)	160.00 (120.00, 185.00)	−10.0 min (−30.0 to 5.0)	0.026
Intraoperative blood loss (mL)	20.00 (10.00, 30.00)	30.00 (20.00, 50.00)	−5.0 mL (−10.0 to 0.0)	0.037
Intraoperative stone clearance, n (%)	71 (97.3)	70 (95.9)	1.4 pp (−4.1 to 6.8)	1.000
Intraoperative choledochoscopy, n (%)	17 (23.3)	27 (37.0)	−13.7 pp (−28.8 to 1.4)	0.121
ICU admission, n (%)	1 (1.4)	6 (8.2)	−6.8 pp (−13.7 to 0.0)	0.125
Time to first flatus (days)	2.00 (1.00, 2.00)	2.00 (1.00, 2.00)	0.0 days (−1.0 to 0.0)	0.011
Postoperative hospital stay (days)	8.00 (6.00, 11.00)	12.00 (9.00, 15.00)	−3.0 days (−5.0 to −2.0)	<0.001
Surgical reintervention within 30 days, n (%)	1 (1.4)	1 (1.4)	0.0 pp (−4.1 to 4.1)	1.000
ERCP within 30 days, n (%)	0 (0.0)	2 (2.7)	−2.7 pp (−6.8 to 0.0)	0.500
Readmission within 30 days, n (%)	0 (0.0)	0 (0.0)	0.0 pp (0.0 to 0.0)	1.000

Note: For continuous outcomes, effects are median within-pair differences. For binary outcomes, effects are paired risk differences in percentage points. Each risk difference is primary closure minus T-tube drainage. We used 20,000 paired bootstrap resamples to calculate CIs. P values come from paired Wilcoxon signed-rank or exact McNemar tests.

3.3. Postoperative Complications and Follow-Up Outcomes

Overall 30-day complications occurred in 11 primary-closure patients (15.1%). They occurred in 21 T-tube patients (28.8%). The paired comparison was not significant (P = 0.087). The paired risk difference was −13.7 percentage points (95% CI, −27.4 to 0.0). Major complications occurred in 1 patient (1.4%) after primary closure and 3 patients (4.1%) after T-tube drainage (P = 0.625). Stones found within 6 months occurred in 5 patients (6.8%) and 12 patients (16.4%), respectively (P = 0.092). Recurrent stones at 6 months or later occurred in 4 patients (5.5%) in each group (P = 1.000) (**Table 3**). The source dataset did not consistently record biliary, infectious, or tube-related event types. We did not reconstruct these events after the analysis.

Table 3. Postoperative complications and follow-up outcomes after propensity score matching.

Outcome	Primary closure (n = 73)	T-tube drainage (n = 73)	Paired effect (95% CI)	Paired P value
Any postoperative complication, n (%)	11 (15.1)	21 (28.8)	−13.7 pp (−27.4 to 0.0)	0.087
Major complication (Clavien-Dindo grade ≥ III), n (%)	1 (1.4)	3 (4.1)	−2.7 pp (−8.2 to 2.7)	0.625
Postoperative bile duct stricture, n (%)	0 (0.0)	1 (1.4)	−1.4 pp (−4.1 to 0.0)	1.000
Stones detected within 6 months, n (%)	5 (6.8)	12 (16.4)	−9.6 pp (−19.2 to 0.0)	0.092
Recurrent stones (≥6 months), n (%)	4 (5.5)	4 (5.5)	0.0 pp (−8.2 to 6.8)	1.000

Note: Any complication was Clavien-Dindo grade I or higher. Major complications were grade III or higher. We analyzed stones found within 6 months separately from intraoperative clearance. They may include stones missed during surgery or found later. Effects are paired risk differences in percentage points. CIs come from paired bootstrap resampling. P values come from exact McNemar tests.

4. Discussion

This PSM analysis produced 73 matched pairs. Primary closure was linked to a hospital stay that was 3 days shorter by the median within-pair estimate. Operating time, blood loss, and bowel recovery also favored primary closure. In contrast, the paired analyses found no clear group differences in intraoperative clearance, 30-day reintervention, overall complications, major complications, stones found within 6 months, or recurrence.

The recovery pattern in this cohort agrees with earlier reports. Zhu *et al.* [6] found that primary closure shortened operating time and hospital stay. They found similar rates of residual stones and bile leakage in the two groups. A later review also advised against routine T-tube use in suitable patients [7]. Cui [16] reported shorter operations, shorter stays, and fewer complications after primary closure in an unmatched cohort of 160 patients. Our study focused on patients aged 65 years or older. We also matched for duct diameter, stone burden, inflammatory markers, and liver-function measures. Recovery differences remained after matching. Measured baseline factors may not fully explain those differences.

Studies of older patients show a similar pattern. La *et al.* [9] reported shorter operations and hospital stays after primary closure. Their groups had similar long-term recurrence. Fan *et al.* [10] and Luo *et al.* [11] also reported that selected older patients could undergo primary closure safely. In our cohort, recurrence was 5.5% in both groups. The unpaired comparison suggested fewer overall complications after primary closure. That difference became weaker when we used the matched pairs ($P = 0.087$). Differences among studies may reflect patient mix, outcome definitions, local T-tube care, and small event counts.

The recovery advantages of primary closure are physiologically and practically plausible. Secure closure of the choledochotomy avoids prolonged irritation from an indwelling foreign body and bile loss through external drainage, while reducing traction-related pain, tube dislodgement, ascending infection, and bile leakage from the tract after tube removal. Continued delivery of bile to the intestine may facilitate lipid digestion, enterohepatic circulation, and early oral intake. Avoiding the need to await T-tube cholangiography, clamping trials, and tube removal can also directly shorten the care pathway. Together, these mechanisms may help explain the shorter operative time, lower blood loss, and faster recovery observed in our study. Nevertheless, operative time and blood loss also reflect surgical complexity. Patients with severe inflammation, impacted stones, uncertain distal patency, or concern about residual stones are more likely to receive a T-tube; consequently, part of the observed difference may still be attributable to confounding by indication.

T-tube drainage still has a clinical role. A T-tube can decompress the bile duct and allow postoperative cholangiography. It also keeps access for stone removal through the mature tract. It may be useful when infection remains poorly controlled. It may also help when papillary edema or distal resistance is marked. Other reasons include a friable bile duct wall, uncertain clearance, or a high risk of residual stones after treating many or large stones. Intraoperative lithotripsy can also increase this concern [8] [17]. Our study found no significant difference in stone clearance or major complications. These results do not support replacing every T-tube with primary closure. They support avoiding routine external drainage in patients who are suitable for direct closure. For older patients, the decision should also consider frailty, cognition, self-care ability, family support, and follow-up access. We did not measure these factors in this database.

Clinically, these findings support considering primary closure preferentially in older patients when intraoperative assessment confirms stone clearance, distal duct patency, adequate perfusion of the bile duct wall, and secure suture closure, and when neither continued decompression nor preserved access for subsequent stone extraction is required. Its practical value lies chiefly in shortening hospitalization and reducing the burden of external tube care. T-tube drainage should remain available on an individualized basis for patients with severe infection, friable edematous tissue, a high risk of residual stones, or uncertain biliary pressure. The choice should integrate choledochoscopic findings, local anatomy, frailty, and the patient's capacity to complete postoperative follow-up.

This study has important limits. It was a retrospective study from one center, so unmeasured confounding remains possible. We could not include ASA class, Charlson Comorbidity Index, frailty, cholangitis severity, bile duct wall edema, stone impaction, distal stricture, surgeon, or calendar year in the propensity model. TBIL also retained mild imbalance after matching. The analytic database did not preserve an upstream screening log. Although all 202 eligible records had complete matching covariates, we could not reconstruct exclusions by reason or missing outcomes before database creation. The database also lacked consistent complication subtypes. We could not reliably separate biliary, infectious, and T-tube-related events. Follow-up duration and censoring were not available for each patient. Stone outcomes are therefore crude event proportions. PSM left 56 patients outside the matched sample. The findings apply mainly to patients with overlapping treatment indications. Complex cases may have been more likely to receive T-tube drainage. If so, primary closure may appear more favorable than it truly is. These limits also reduce generalizability.

Future multicenter prospective studies should stratify patients by frailty and cholangitis severity; standardize the choledochotomy, suture material, T-tube management, and enhanced recovery pathway; and prespecify bile leakage, Clavien-Dindo grade III or higher complications, patient-reported outcomes, total costs, and time to stone recurrence as study outcomes. Testable hypotheses include whether the reduction in hospital stay with primary closure is greater in patients with a smaller common bile duct, less severe inflammation, or lower frailty, and whether internal stenting or transcystic drainage can provide decompression while reducing the burden of external drainage in patients at high risk of residual stones.

5. Conclusion

After matching, primary closure was linked to a shorter hospital stay and faster early recovery in selected older patients. The paired analyses found no significant differences in intraoperative clearance, overall or major complications, stones found within 6 months, or recurrence. This observational study cannot prove that primary closure caused these results. Duct management should remain individualized. The surgeon should consider anatomy, operative findings, the need for drainage or future duct access, and the patient's overall risk.

Author Contributions

Conceptualization, H. H. and J. W.; methodology, H. H. and L. X.; software, H. H.; validation, L. X., Z. F., and X. H.; formal analysis, H. H. and L. X.; investigation, H. H., Z. F., and X. H.; resources, J. W.; data curation, H. H. and L. X.; writing—original draft preparation, H. H.; writing—review and editing, H. H., L. X., Z. F., X. H., and J. W.; visualization, H. H.; supervision, J. W.; project administration, J. W. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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