

Intraoperative versus Postoperative Detection of Bile Duct Injury: Effect Modification by Strasberg Type E Severity and Implications for Non-Anastomotic Strictures — A 15-Year Propensity-Matched Cohort Study

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Abstract

Background

Bile duct injury (BDI) after cholecystectomy remains a major source of long-term morbidity. Whether the benefit of intraoperative versus postoperative recognition differs according to anatomical severity is unknown.

Methods

In a 15-year single-centre propensity-matched cohort of 102 BDIs (41 intraoperative, 61 postoperative), we tested for effect modification by Strasberg Type E severity. Primary outcomes were any biliary stricture and non-anastomotic stricture. Multivariable models with formal interaction terms and stratified analyses were used.

Results

Postoperative detection was associated with higher overall stricture rates (48.3% vs 25.6%, HR 2.22). This association was confined to Type E injuries (aOR 6.2, 95% CI 1.8–21.3, $p = 0.004$) and absent in Type A–D injuries (aOR 1.4, $p = 0.52$; interaction $p = 0.021$). Non-anastomotic strictures accounted for the excess risk (22.4% vs 7.7%). Intraoperative recognition also produced shorter hospital stay, faster leak resolution, fewer cholangitis episodes and clinically meaningful SF-36 gains.

Conclusions

Early detection confers its greatest benefit in high-grade Type E injuries requiring hepaticojejunostomy, primarily by limiting non-anastomotic strictures. Standardized 24-hour drain-bilirubin surveillance, rapid MRCP pathways and 12-hour tertiary-transfer protocols for Type D–E injuries represent actionable quality metrics.

1. Introduction

Bile duct injury (BDI) remains an uncommon yet clinically consequential complication of cholecystectomy, with contemporary incidence of 0.4–0.7% of laparoscopic procedures that has remained essentially unchanged despite widespread adoption of the critical view of safety and high-definition imaging [1, 2]. Beyond the immediate consequences of bile leak and biliary sepsis, BDI generates substantial long-term morbidity through recurrent cholangitis, anastomotic and non-anastomotic strictures, repeated endoscopic or surgical interventions, secondary biliary cirrhosis, and impaired health-related quality of life [3–7]. These sequelae drive prolonged hospitalization, reoperations and lifelong surveillance, imposing a disproportionate economic burden within the broader costs of

biliary disease [8, 9]. Recognition timing constitutes a potentially modifiable determinant of these outcomes, yet whether its association with subsequent morbidity differs according to anatomical injury severity remains unresolved.

Existing literature applies heterogeneous temporal definitions of “early” detection, ranging from intraoperative recognition through thresholds of 24 hours, 48–72 hours or several days, to broader categories of early repair or referral [1, 10]. This inconsistency precludes reliable comparison across studies and limits the development of evidence-based triage protocols. A more fundamental methodological problem is confounding by indication: injury severity itself influences the probability of intraoperative recognition. Major transection, high-volume bile leakage, concomitant vascular injury or severe anatomical distortion are more likely to declare themselves before skin closure, whereas lower-grade leaks may remain occult until the postoperative period. Consequently, any apparent advantage of intraoperative detection may reflect differences in injury biology or detectability rather than the timing of recognition per se. Prior observational series have rarely addressed this confounding with rigorous multivariable adjustment or propensity-score methods.

Whether the association between detection timing and adverse outcomes is homogeneous across Strasberg grades is equally uncertain. Type E injuries involve circumferential disruption of the major duct and may leave a greater length of proximal biliary epithelium and peribiliary tissue exposed to ongoing inflammation and ischemic injury, whereas Type A–D injuries typically involve more limited ductal segments. Effect modification by Type E severity therefore constitutes a clinically and biologically plausible hypothesis that has not been systematically tested. Finally, anastomotic and non-anastomotic strictures should not be treated as interchangeable endpoints: anastomotic strictures are heavily influenced by reconstructive technique and anastomotic healing, whereas non-anastomotic strictures more specifically reflect injury to biliary segments outside the reconstruction and may therefore serve as a more informative marker of prolonged inflammatory or ischemic damage. Patient-reported quality-of-life measures and formal economic evaluations remain under-reported in timing studies.

Prolonged intraperitoneal bile exposure activates innate inflammatory pathways mediated by Toll-like receptor 4 and nuclear-factor- κ B signaling, promoting release of pro-inflammatory cytokines and subsequent transforming-growth-factor- β -driven fibrotic remodeling of peribiliary tissues [7, 11–15]. Concurrent inflammatory micro-thrombosis may compromise the arterial perfusion of the biliary tree, predisposing to ischemic injury independent of the initial mechanical disruption [16]. These mechanisms provide a biologically plausible pathway linking delayed recognition to non-anastomotic stricture formation. Because Type E injuries disrupt a larger ductal circumference and expose more extensive proximal biliary territory to ongoing bile leakage, inflammatory signaling and vascular compromise, the consequences of delayed containment may be amplified in this subgroup relative to Type A–D injuries. Non-anastomotic strictures, arising at sites remote from the eventual anastomosis, would be expected to capture this severity-dependent inflammatory–ischemic pathway more specifically than anastomotic strictures alone.

We hypothesized that the association between intraoperative detection of bile duct injury and improved long-term biliary outcomes is significantly stronger among Strasberg Type E injuries than among Type A–D injuries, indicating effect modification by anatomical severity. The primary objective was therefore to determine, within a 15-year propensity-matched cohort, whether Type E severity modifies the association between intraoperative versus postoperative detection and adverse biliary outcomes after accounting for measured confounding. Secondary objectives included comparison of non-anastomotic stricture rates, evaluation of SF-36 physical and mental component scores, assessment of clinically meaningful short- and long-term outcomes, and derivation of pragmatic quality metrics supported by the observed associations.

2. Materials and Methods

2.1 Study design and setting

This retrospective cohort study was conducted at the Surgery Department of the First Republican Clinical Hospital of the Ministry of Health of the Udmurt Republic, Russian Federation, a tertiary hepatobiliary referral centre serving a catchment population exceeding 1.5 million. The study covered all cholecystectomies performed between January 2010 and December 2024 and adhered to the STROBE guidelines and the Declaration of Helsinki (2013 revision). Institutional Review Board approval was obtained prior to data extraction (Ethics approval number: HBC-2025-089). Because of the retrospective design, the requirement for individual informed consent was waived; all patients had previously provided written consent for the use of anonymized clinical data for research purposes at the time of hospital admission in accordance with institutional policy.

2.2 Study population and eligibility

Among 15 937 cholecystectomies performed during the study period, 102 patients (0.64%) sustained a confirmed bile-duct injury and met inclusion criteria. Eligible patients were adults (age ≥ 18 years) who underwent elective or emergency cholecystectomy by laparoscopic, mini-laparotomy or open approach and in whom a bile-duct injury was recognized either intraoperatively or within seven days postoperatively. The seven-day window was chosen because injuries presenting later are more likely to represent delayed complications rather than direct surgical trauma. Bile-duct injury was defined as any unintended damage to the extrahepatic or intrahepatic biliary tree documented by direct visualization, intraoperative cholangiography, or postoperative clinical, biochemical and imaging findings. Exclusion criteria comprised pre-existing biliary strictures, previous hepatobiliary surgery, congenital biliary anomalies, malignant biliary obstruction, cholecystectomy performed as part of a more extensive hepatobiliary resection, and incomplete clinical records that precluded adequate outcome assessment. Of the 102 included patients, 41 injuries were detected intraoperatively and 61 postoperatively; long-term follow-up (≥ 12 months) was complete in 97 patients (95.1%).

2.3 Exposure definition and classification

The primary exposure was the timing of injury recognition, dichotomized as intraoperative (identified before skin closure) or postoperative (diagnosed after closure but within seven days). Each injury was independently classified according to the Strasberg system by two senior hepatobiliary surgeons who were blinded to detection timing and subsequent outcomes. Disagreements were resolved by consensus with a third surgeon. Inter-observer agreement was excellent ($\kappa = 0.91$, 95% CI 0.85–0.97). For the principal effect-modification analysis, injuries were further dichotomized into high-grade (Strasberg Type E) versus lower-grade (Types A–D) categories.

2.4 Outcome definitions

The two co-primary long-term outcomes were (1) any biliary stricture and (2) non-anastomotic stricture. A biliary stricture was defined as focal ductal narrowing on MRCP or ERCP accompanied by upstream dilatation (intrahepatic ducts > 7 mm or extrahepatic duct > 10 mm) plus either clinical symptoms (jaundice, pruritus or cholangitis with fever > 38.0°C) or biochemical cholestasis (alkaline phosphatase > 1.5 × upper limit of normal and total bilirubin > 1.2 mg dL⁻¹ on two consecutive measurements at least two weeks apart). Strictures were classified as anastomotic or non-anastomotic according to their anatomic relationship to the reconstructed biliary–enteric anastomosis; non-anastomotic strictures were considered the more specific marker of prolonged inflammatory or ischemic injury to ductal segments outside the reconstruction. Adjudication was performed by two independent reviewers (one hepatobiliary surgeon and one interventional radiologist) using de-identified imaging; inter-rater reliability was substantial ($\kappa = 0.84$, 95% CI 0.76–0.92).

Secondary outcomes comprised 30-day re-intervention (any surgical, endoscopic or radiological procedure), hospital length of stay, time to bile-leak resolution (cessation of bilious drain output < 50 mL day⁻¹ for 48 consecutive hours with resolution of collections > 3 cm), recurrent cholangitis (≥ 1 episode after definitive management), normal liver-function tests at final follow-up, and patient-reported quality of life assessed by the Russian-validated SF-36 version 2 Physical and Mental Component Summary scores at approximately 24 months.

2.5 Statistical analysis

The analytic strategy was constructed around the central hypothesis of effect modification by Strasberg Type E severity. Confounding by indication; whereby more severe injuries are both more readily recognized intraoperatively and intrinsically associated with worse outcomes; was addressed by propensity-score matching as a prerequisite step. Propensity scores estimating the probability of intraoperative detection were generated by multivariable logistic regression that included age, sex, body-mass index, ASA physical status, surgical approach, emergency surgery, acute cholecystitis, difficult anatomy (severe inflammation, dense adhesions, Calot's triangle obliteration or documented anatomical variants) and previous abdominal surgery. Patients were matched 1: 1 without replacement using nearest-neighbor matching with a caliper of 0.2 standard deviations of the logit propensity score. Covariate balance was assessed by standardized mean differences; values < 0.10 were regarded as indicating adequate balance.

The primary analysis tested for statistical interaction between detection timing and injury severity. An interaction term (postoperative detection × Type E) was entered into logistic regression models for the binary outcomes (any stricture, non-anastomotic stricture) and into Cox proportional-hazards models for time-to-stricture. Stratified adjusted odds ratios (or hazard ratios) were then estimated within the Type E and Type A–D subgroups, and the interaction p-value was reported as the formal test of effect modification. Multivariable models were restricted to four pre-specified, directed-acyclic-graph-informed covariates: detection timing, injury severity (Type E versus A–D), age (per 10-year increment) and acute cholecystitis. Model discrimination was quantified by the area under the receiver-operating-characteristic curve with 95% confidence intervals obtained by DeLong’s method; calibration was assessed by the Hosmer–Lemeshow test and calibration plots; internal validation used 500 bootstrap resamples to calculate optimism-corrected C-statistics.

Robustness was examined by inverse-probability-of-treatment weighting with stabilized weights trimmed at the 1st and 99th percentiles, by complete-case analysis, and by restriction to the most recent era (2019–2024). The continuous relationship between time-to-detection (hours) and adverse outcomes was explored with restricted cubic splines (knots at the 5th, 35th, 65th and 95th percentiles). E-values were calculated to quantify the minimum strength of association that an unmeasured confounder would need to have with both exposure and outcome to explain away the observed effect. Missing data (< 10% for any analysis variable) were assumed missing at random after inspection of missingness patterns and were handled by multiple imputation by chained equations (20 imputations, 50 iterations); results were pooled by Rubin’s rules. Clustering by operating surgeon was evaluated with multilevel mixed-effects models; if the intraclass correlation exceeded 0.05, generalized estimating equations with an exchangeable correlation structure were applied. All analyses were performed with SPSS version 29.0. Statistical significance was set at a two-sided p-value < 0.05.

2.6 Sample-size justification

The study was powered to detect a 20% absolute difference in stricture rate between detection-timing groups. With the observed cohort of 102 patients (97 with complete follow-up), the sample size exceeded the minimum required for the primary interaction analysis and for the stratified subgroup comparisons of Type E versus Type A–D injuries.

3. Results

3.1 Cohort Characteristics and Balance

Among 15 937 cholecystectomies performed between January 2010 and December 2024, 102 patients (0.64%) sustained bile-duct injuries meeting inclusion criteria. Injuries were recognized intraoperatively in 41 patients (40.2%) and postoperatively in 61 patients (59.8%). The cohort comprised 81 women (79.4%) with a mean age of 52.3 ± 11.4 years. Baseline demographic characteristics showed no significant differences in age, sex distribution, body-mass index or ASA physical status between detection groups (Table 1).

Table 1
Baseline Characteristics and Injury Patterns by Detection Timing (N = 102)

Variable	Intraoperative (n = 41)	Postoperative (n = 61)	p-value	Effect Size
Age (years), mean $\pm$ SD	53.8 $\pm$ 12.1	51.4 $\pm$ 10.9	0.312	SMD = 0.21
Female sex, n (%)	31 (75.6)	50 (82.0)	0.628	ϕ = 0.08
BMI (kg/m ²), mean $\pm$ SD	29.1 $\pm$ 5.2	27.6 $\pm$ 4.3	0.189	SMD = 0.31
ASA III–IV, n (%)	13 (31.7)	12 (19.7)	0.421	ϕ = 0.14
Emergency surgery, n (%)	15 (36.6)	11 (18.0)	0.047	OR = 2.60
Acute cholecystitis, n (%)	23 (56.1)	22 (36.1)	0.041	OR = 2.24
Difficult anatomy, n (%)	18 (43.9)	14 (23.0)	0.022	OR = 2.64
Transferred patient, n (%)	19 (46.3)	38 (62.3)	0.099	OR = 0.52
IOC performed, n (%)	24 (58.5)	8 (13.1)	< 0.001	OR = 9.3
Strasberg Classification			0.001	Cramér's V = 0.42
Type A, n (%)	12 (29.3)	36 (59.0)		
Type B–D, n (%)	11 (26.8)	16 (26.2)		
Type E (high-grade), n (%)	18 (43.9)	9 (14.8)		

However, the intraoperative group had higher rates of emergency surgery (36.6% vs 18.0%, $p = 0.047$), acute cholecystitis (56.1% vs 36.1%, $p = 0.041$) and difficult anatomy (43.9% vs 23.0%, $p = 0.022$). Strasberg Type E injuries were markedly more frequent with intraoperative detection (43.9% vs 14.8%, $p = 0.001$, OR = 4.50), establishing the confounding by indication that necessitated propensity-score matching and formal effect-modification analysis (Fig. 1).

Temporal trends demonstrated a progressive rise in the proportion of injuries detected intraoperatively across three eras: 28.6% (2010–2014), 40.5% (2015–2019) and 48.6% (2020–2024; p for trend = 0.019). Injury-severity distribution remained stable (Type E: 25.0%, 27.0% and 27.0%, respectively; $p = 0.982$). Propensity-score matching produced 34 matched pairs with standardized mean differences < 0.10 for all covariates (**Supplementary Table S1**).

3.2 Short-Term Perioperative Outcomes

No major morbidity (Clavien–Dindo Grade III–V) or 30-day mortality occurred in either group (Table 2).

Table 2
Short-Term Perioperative Outcomes by Detection Timing

Outcome	Intraoperative (n = 41)	Postoperative (n = 61)	p-value	Effect Size
Hospital LOS, median (IQR), days	7.0 (5.0–10.0)	12.0 (8.0–18.0)	< 0.001	—
Time to leak resolution, median (IQR), days	5.0 (3.0–8.0)	14.0 (9.0–21.0)	< 0.001	—
Any reintervention 30 d, n (%)	3 (7.3)	18 (29.5)	0.006	RR = 4.04
ICU admission, n (%)	2 (4.9)	8 (13.1)	0.200	—
Clavien–Dindo ≥ III, n (%)	0 (0)	0 (0)	—	—
30-day mortality, n (%)	0 (0)	0 (0)	—	—

Despite this, postoperative detection was associated with a four-fold higher rate of any 30-day reintervention (29.5% vs 7.3%, $p = 0.006$, RR = 4.04, 95% CI 1.25–13.04), driven primarily by endoscopic procedures. Hospital length of stay was significantly prolonged after postoperative detection (median 12.0 days [IQR 8.0–18.0] vs 7.0 days [IQR 5.0–10.0], $p < 0.001$). Time to bile-leak resolution was likewise extended (median 14.0 days [IQR 9.0–21.0] vs 5.0 days [IQR 3.0–8.0], $p < 0.001$). ICU admission rates did not differ significantly (13.1% vs 4.9%, $p = 0.200$).

3.3 Long-Term Anatomic Outcomes and Effect Modification

Long-term follow-up was complete in 97 patients (95.1%) over a median of 36 months (IQR 24–48). Any biliary stricture developed in 38 patients (39.2%) and was significantly more frequent after postoperative detection (48.3% vs 25.6%, $p = 0.023$, HR = 2.22, 95% CI 1.07–4.61). Kaplan–Meier analysis confirmed superior stricture-free survival with intraoperative detection (log-rank $p = 0.018$), with 2-year stricture-free rates of 82.1% versus 65.5% (Fig. 2A).

The principal novel finding was marked effect modification by injury severity (Table 3, Fig. 3). Among Type E injuries, delayed detection increased stricture risk six-fold (adjusted OR = 6.2, 95% CI 1.8–21.3, $p = 0.004$), whereas Type A–D injuries showed no significant association (adjusted OR = 1.4, 95% CI 0.5–3.8, $p = 0.52$). The interaction term was statistically significant ($p = 0.021$), confirming that the protective association of intraoperative detection is concentrated in high-grade injuries.

Table 3
Long-Term Outcomes and Effect Modification by Injury Severity (N = 97)

Outcome	Intraoperative (n = 39)	Postoperative (n = 58)	p-value	HR / Effect	aOR (95% CI)
Any biliary stricture, n (%)	10 (25.6)	28 (48.3)	0.023	HR = 2.22	—
Stratified by Injury Severity					
Type E injuries (n = 27)	2/18 (11.1%)	5/9 (55.6%)	0.004	—	6.2 (1.8–21.3)
Type A–D injuries (n = 70)	8/21 (38.1%)	23/49 (46.9%)	0.52	—	1.4 (0.5–3.8)
Interaction p-value			0.021		
Stricture Type					
Anastomotic stricture, n (%)	7 (17.9)	15 (25.9)	0.363	HR = 1.54	—
Non-anastomotic stricture, n (%)	3 (7.7)	13 (22.4)	0.050	HR = 3.24	—

Non-anastomotic strictures were substantially more common after postoperative detection (22.4% vs 7.7%, $p = 0.050$, HR = 3.24, 95% CI 0.93–11.32), while anastomotic stricture rates did not differ (25.9% vs 17.9%, $p = 0.363$). This pattern indicates that delayed recognition primarily permits prolonged inflammation and ischaemic injury to ductal segments outside the eventual reconstruction rather than impairing anastomotic healing itself. Non-anastomotic strictures developed at a median of 14.0 months (range 6–28) after repair.

3.4 Functional and Patient-Reported Outcomes

Recurrent cholangitis was significantly more frequent after postoperative detection (20.7% vs 5.1%, $p = 0.028$, HR = 4.35, 95% CI 0.96–19.68); multiple episodes (≥ 3) occurred exclusively in the postoperative group (8.6% vs 0%, $p = 0.073$). Normal liver-function tests at final follow-up were achieved in 92.3% of the intraoperative group versus 79.3% of the postoperative group ($p = 0.084$).

SF-36 Physical Component scores were higher with intraoperative detection (78.5 ± 12.3 vs 71.2 ± 16.8 , $p = 0.019$, Cohen's $d = 0.50$), as were Mental Component scores (76.9 ± 14.1 vs 68.4 ± 18.6 , $p = 0.021$, $d = 0.51$). The observed differences (7.3 and 8.5 points) exceed the established minimal clinically important difference of 5 points for SF-36 summary scores, indicating that the quality-of-life advantage is clinically meaningful.

3.5 Robustness and Secondary Analyses

In the propensity-matched cohort (34 pairs, $n = 68$), intraoperative detection remained associated with lower stricture rates (23.5% vs 47.1%, $p = 0.039$, OR = 0.35, 95% CI 0.13–0.95), shorter hospital stay and

superior SF-36 Physical Component scores. Inverse-probability-of-treatment weighting yielded consistent results (**Supplementary Table S2**). The E-value for the association between postoperative detection and stricture was 4.92, indicating that an unmeasured confounder would need to be associated with both exposure and outcome by risk ratios of approximately 4.9-fold each to explain away the observed effect.

Multivariable modelling confirmed postoperative detection (adjusted OR = 2.89, 95% CI 1.18–7.07, $p = 0.020$) and Type E injury (adjusted OR = 2.98, 95% CI 1.16–7.67, $p = 0.023$) as independent predictors of poor long-term outcome (**Table 4**). The interaction term remained significant. Sensitivity analyses restricted to 2019–2024 showed a consistent direction of effect with attenuated magnitude (adjusted OR = 2.1, 95% CI 0.7–6.4, $p = 0.18$). Transferred patients exhibited a stronger timing–outcome association than in-house cases (interaction $p = 0.035$). Model discrimination was good (AUC-ROC = 0.78, 95% CI 0.69–0.87) with adequate calibration (Hosmer–Lemeshow $p = 0.234$) and no concerning multicollinearity (all VIF < 3.5).

Table 4. Multivariable Predictors of Poor Long-Term Outcomes and Interaction Analysis (N = 97)

Variable	Univariate OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Postoperative detection	2.74 (1.23–6.09)	0.013	2.89 (1.18–7.07)	0.020
High-grade injury (Type E)	3.45 (1.45–8.21)	0.005	2.98 (1.16–7.67)	0.023
Age > 60 years	1.87 (0.82–4.26)	0.136	1.65 (0.68–4.01)	0.268
Acute cholecystitis	1.98 (0.91–4.31)	0.085	1.54 (0.65–3.65)	0.329
Difficult anatomy	2.65 (1.21–5.81)	0.015	2.01 (0.84–4.83)	0.117

Model AUC-ROC = 0.78 (95% CI 0.69–0.87); Hosmer–Lemeshow $p = 0.234$.

4. Discussion

4.1 Principal Findings

Our principal finding is that the association between detection timing and long-term biliary outcomes is strongly modified by injury severity. Overall, postoperative detection was associated with higher stricture rates (48.3 % versus 25.6 %, HR 2.22, $p = 0.023$). This effect was concentrated in Strasberg Type E injuries, where delayed recognition increased the odds of stricture six-fold (aOR 6.2, 95 % CI 1.8–21.3, $p = 0.004$), whereas Type A–D injuries showed no significant association (aOR 1.4, 95 % CI 0.5–3.8, $p = 0.52$; interaction $p = 0.021$). Non-anastomotic strictures accounted for much of the excess risk (22.4 % versus 7.7 %, HR 3.24). Intraoperative detection was also linked to fewer episodes of recurrent cholangitis, shorter hospital stays, faster leak resolution and clinically meaningful gains in SF-36 physical and mental component scores. These data indicate that early recognition confers its greatest

benefit in high-grade injuries that require hepaticojejunostomy, primarily by limiting non-anastomotic fibrotic sequelae.

4.2 Comparison with Existing Literature

The apparent contradiction between our findings and Giuliani et al.'s observation of timing-independent outcomes in 114 patients undergoing Hepp-Couinaud hepaticojejunostomy [25] merits detailed examination. Three methodological differences explain divergent results. First, Giuliani's cohort underwent exclusively delayed hepaticojejunostomy at a specialized center (median 6.8 weeks post-injury), representing a selected subgroup where delayed repair allows inflammation resolution and nutritional optimization reflected in their 0% mortality and 94.7% primary patency. Our cohort included 39% immediate repairs and diverse management strategies (endoscopic, percutaneous), capturing real-world heterogeneity where delayed diagnosis necessitates suboptimal temporizing interventions. Second, Giuliani defined "early" as ≤ 2 weeks, whereas our "postoperative" detection occurred within 7 days (median 18.5 hours), potentially missing a critical therapeutic window. Third, their primary outcome was anastomotic patency assessed by cholangiography, whereas we assessed broader morbidity including recurrent cholangitis (20.7% delayed versus 5.1% immediate, $p=0.028$) and quality of life; domains where delayed detection showed substantial harm despite eventual stricture resolution.

These differences suggest timing effects are context-dependent: minimal impact in stable patients reaching specialized centers within 2–6 weeks for definitive reconstruction, but substantial harm when delayed diagnosis leads to sepsis, multiple temporizing procedures, or transfer delays exceeding one week. This hypothesis is supported by Zidan et al.'s finding of 5.7% mortality and higher Clavien-Dindo grades in delayed cases presenting with peritonitis or sepsis [26], and by Omar et al.'s randomized trial demonstrating superior outcomes with reconstruction at 6–8 weeks versus immediate repair in unstable patients [27]. Our results extend these observations by demonstrating that the critical window extends to detection timing itself, even before definitive repair, consistent with WSES 2020 guidelines emphasizing early multidisciplinary management [28]. Historical data showing that only 22–30% of bile duct injuries are recognized intraoperatively underscore the importance of standardized postoperative surveillance protocols [4, 31,32,34]. Our finding that detection timing remains independently important even when repair is performed by specialists, with comparable anastomotic stricture rates (25.9% versus 17.9%, $p=0.363$) but dramatically different non-anastomotic stricture rates; indicates that the benefit is not about surgical technique at the anastomosis but about limiting the duration of bile leak and inflammatory injury to non-reconstructed biliary segments. The recent SAGES-AHPBA 2025 guideline and ongoing timing controversy [33] highlight the need for our stratified approach based on injury severity.

4.3 Mechanistic Interpretation

The observed association between delayed detection and non-anastomotic stricture formation likely reflects multiple pathogenic mechanisms driven by prolonged bile exposure. Bile exposure triggers neutrophilic inflammation and progressive fibrosis via toll-like receptor 4 signaling, nuclear factor kappa

B upregulation, and transforming growth factor-beta pathways [14, 15, 20,21]. Our findings support this mechanism, with delayed cases showing four-fold higher C-reactive protein (median 89.3 versus 12.5 mg/L, $p<0.001$), indicating sustained systemic inflammatory response. Recent single-cell transcriptomic analyses demonstrate that bile exposure duration correlates with pro-fibrotic cholangiocyte phenotype activation and peribiliary fibroblast proliferation through damage-associated molecular pattern-mediated signaling cascades involving interleukin-33 and transforming growth factor-beta pathways [12,16,17]. Additionally, chronic bile acid exposure induces senescence-associated secretory phenotype in cholangiocytes, perpetuating inflammation through paracrine interleukin-6 and interleukin-8 secretion even after initial injury resolution [22]. Delayed diagnosis permits progression from contained leak to biloma with bacterial colonization; observed in 12.8% of delayed versus 0% of intraoperative cases, creating a nidus for chronic infection and secondary sclerosing cholangitis, with biliary microbiome dysbiosis, particularly overgrowth of *Enterococcus* and *Klebsiella* species, contributing to stricture formation through biofilm production and sustained inflammatory signaling [23].

The predominance of non-anastomotic strictures in delayed cases (22.4% versus 7.7%, $p=0.050$) suggests proximal ductal ischemia from prolonged inflammation rather than technical anastomotic factors, consistent with observations that bile duct vascular injury precedes luminal stenosis in chronic biliary inflammation [24]. Prolonged intraperitoneal bile exposure activates profibrotic pathways through bile acid-induced Toll-like receptor 4 signaling and nuclear factor kappa B upregulation in peritoneal mesothelium, generating adhesions that complicate subsequent surgical reconstruction [14]. Additionally, ongoing bile extravasation may compromise hepatic arterial perfusion to the biliary tree through inflammatory microthrombosis, predisposing to ischemic stricture formation independent of initial injury severity. These biological mechanisms validate the hypothesis that early detection, by limiting inflammatory duration and extent, reduces both acute septic complications and chronic fibrotic sequelae, particularly in Type E injuries where larger ductal segments remain at risk. The seven-fold higher C-reactive protein in delayed cases supports this ongoing systemic inflammatory response as a key driver of non-anastomotic stricture pathogenesis.

4.4 Clinical and Policy Implications

Our findings support a tiered implementation strategy targeting three decision points with measurable quality metrics (**Table 5**).

- i. Intraoperative prevention requires universal adoption of critical view of safety with photodocumentation, complemented by selective intraoperative cholangiography when critical view remains unachievable after 10 minutes of dissection or when intraoperative findings suggest aberrant anatomy, consistent with 2020 World Society of Emergency Surgery guidelines [28].
- ii. Early postoperative detection demands standardized surveillance protocols: drain output monitoring with 24-hour bilirubin measurement (cutoff >6 mg/dL indicating leak), liver function test panels on postoperative day 1 for patients with difficult dissection (operative time >90 minutes, estimated blood loss >200 mL, or conversion from laparoscopic to open approach), and low-threshold

magnetic resonance cholangiopancreatography within 6 hours for suspected leak based on clinical or biochemical indicators [1, 29].

- iii. Rapid tertiary referral networks should establish 12-hour transfer protocols for Type D-E injuries diagnosed at non-specialized centers, bypassing intermediate endoscopic attempts when injury involves >50% ductal circumference or hilar confluence [1, 29, 30].

Table 5. Proposed Implementation Framework with Quality Metrics for Bile Duct Injury Detection and Management

Decision Point	Intervention Component	Quality Metric	Target Performance	Measurement Method
1. Intraoperative Prevention	CVS achievement	CVS documentation rate	>95% of cases	Operative report audit
	Selective IOC	IOC utilization when CVS not achieved	>80% compliance	Prospective documentation
2. Early Postoperative Detection	Drain bilirubin surveillance	24-hour drain bilirubin measured	100% compliance	Laboratory tracking
	High-risk patient LFT screening	POD1 LFTs for operative time >90 min or conversion	>90% compliance	Electronic order sets
	Rapid MRCP pathway	Time from suspected leak to MRCP completion	<6 hours (median)	Radiology timestamp analysis
3. Tertiary Referral	Regional transfer protocol	Time from Type D-E diagnosis to tertiary center arrival	<12 hours (90th percentile)	Transfer log analysis

CVS = critical view of safety; IOC = intraoperative cholangiography; LFT = liver function test; POD1 = postoperative day 1; MRCP = magnetic resonance cholangiopancreatography; SF-36 = Short Form-36 Health Survey.

Quality improvement metrics should include institutional time-to-magnetic resonance cholangiopancreatography (<6 hours), regional time-to-tertiary-referral (<24 hours for Type E injuries), critical view of safety achievement rates (target >95%), and 2-year anastomotic stricture rates (target <15% based on contemporary series). Individual-level prediction models incorporating Strasberg classification, C-reactive protein levels (>50 mg/L indicating high inflammatory burden), total bilirubin (>3 mg/dL), and magnetic resonance cholangiopancreatography findings (biloma >5 cm, complete ductal transection) could stratify patients into high-risk groups (aOR >4.0, recommend immediate surgical reconstruction) versus low-risk groups (aOR <2.0, endoscopic management acceptable), optimizing resource utilization and potentially reducing the observed four-fold difference in recurrent cholangitis episodes.

Strengths and Limitations

This study has several strengths. The single-center design, while introducing selection bias toward complex injuries, enables direct comparison of intraoperative versus postoperative detection within uniform diagnostic and treatment algorithms, eliminating the protocol heterogeneity that confounds multi-institutional registries. Complete long-term follow-up infrastructure, achieved in 95.1% of patients, permits robust survival analysis of stricture development and quality of life trajectories unavailable in short-term case series. Rigorous confounding control through propensity-score matching (1:1, $n=68$) and E-value calculation (4.92) addresses confounding by indication, where injury severity influences detection timing. The novel interaction analysis (effect modification by Type E) represents the first systematic evaluation of whether timing effects are homogeneous across injury severity, with implications for targeted surveillance protocols. Granular injury classification using the Strasberg system with independent blinded review by two senior hepatobiliary surgeons ($\kappa=0.91$) ensures accurate severity stratification.

Several biases constrain causal inference. Selection bias arises from our status as a regional referral center receiving 40% of injuries from district hospitals ($n=24$ transferred, $n=17$ index institution), overrepresenting severe cases and potentially exaggerating timing effects through referral filter mechanisms. Quantitative bias analysis suggests unmeasured confounding by surgeon volume if high-volume surgeons (>200 annual cholecystectomies) both detect injuries intraoperatively more frequently and achieve better outcomes independently through superior technical skill could bias our adjusted odds ratio upward by 20-40% based on published surgeon volume-outcome associations. However, our calculated E-value of 4.92 indicates the unmeasured confounder would need extremely strong associations with both exposure and outcome to nullify observed effects, exceeding plausible magnitudes for surgical confounders [18]. Information bias from stricture ascertainment relying on symptomatic presentation plus imaging (magnetic resonance cholangiopancreatography at 6 and 12 months, then annually) may under-detect asymptomatic stenoses by approximately 10-15% based on autopsy series, though differential misclassification is unlikely given standardized surveillance protocols applied uniformly to both detection groups. Temporal confounding from evolving surgical techniques (introduction of high-definition laparoscopy in 2015, fluorescence cholangiography in 2019), imaging modalities (3-Tesla magnetic resonance cholangiopancreatography replacing 1.5-Tesla in 2017), and endoscopic capabilities (fully covered metal stents available from 2018) across 15 years introduces non-random variation; however, sensitivity analyses restricted to 2019-2024 showed consistent direction of effects despite attenuated magnitude (aOR 2.89 overall versus 2.1 recent era), suggesting core associations persist beyond era-specific factors. The modest Type E postoperative sample ($n=9$) constrains statistical power for detecting interactions, though the significant interaction $p=0.021$ confirms the robustness of the finding. The absence of pre-injury SF-36 baselines limits our ability to distinguish whether quality-of-life differences reflect consequences of injury management versus pre-existing patient characteristics. These limitations prevent definitive causal conclusions but do not negate observed clinical associations, particularly given biological plausibility, dose-response

relationship (Type E > Type D > Type A), and consistency with experimental models of bile-induced fibrosis.

Future Directions

These findings inform future research priorities. Prospective multicenter validation studies are needed to confirm the effect modification finding across diverse populations and healthcare systems. Biomarker studies incorporating serial interleukin-6 measurements, tumor necrosis factor-alpha, and bile microbiome profiling using 16S ribosomal RNA sequencing at presentation and follow-up intervals could distinguish competing mechanisms of stricture formation. Target-trial emulation frameworks using large administrative databases could simulate randomized comparisons while addressing residual confounding [19]. Ductal perfusion imaging using arterial-phase computed tomography at presentation could identify patients at risk for ischemic stricture development before luminal narrowing occurs, enabling preemptive intervention. Finally, implementation science studies evaluating the feasibility, fidelity, and cost-effectiveness of the proposed three-tier quality-metric framework across different healthcare settings would translate these findings into practice.

Conclusions

This 15-year propensity-matched cohort study demonstrates that intraoperative bile duct injury detection confers significant long-term benefit predominantly in patients with high-grade Strasberg Type E injuries requiring hepaticojejunostomy, with effect modification by injury severity representing the central novel finding. Among Type E injuries, delayed detection increased stricture risk six-fold (aOR = 6.2, $p = 0.004$), whereas Type A-D injuries showed no significant timing effect (interaction $p = 0.021$). The predominance of non-anastomotic strictures in delayed cases (22.4% versus 7.7%, $p = 0.050$) suggests a mechanism involving prolonged inflammatory injury to non-reconstructed biliary segments rather than technical anastomotic failure. These findings were corroborated by superior quality of life scores and reduced recurrent cholangitis episodes with intraoperative detection. Standardized surveillance protocols incorporating 24-hour drain bilirubin measurement, 6-hour magnetic resonance cholangiopancreatography pathways, and 12-hour tertiary transfer protocols for Type D-E injuries represent actionable quality metrics for cholecystectomy programs. Prospective multicenter validation and biomarker studies are needed to confirm these findings and elucidate the molecular mechanisms linking delayed detection to non-anastomotic stricture formation.

Abbreviations

ALP Alkaline Phosphatase

ALT Alanine Aminotransferase

aOR Adjusted Odds Ratio

ASA American Society of Anesthesiologists

AUC-ROC Area Under the Receiver Operating Characteristic Curve

BDI Bile Duct Injury

BMI Body Mass Index

CI Confidence Interval

CRP C-Reactive Protein

CT Computed Tomography

CVS Critical View of Safety

DAG Directed Acyclic Graph

ECM Extracellular Matrix

ERCP Endoscopic Retrograde Cholangiopancreatography

HPB Hepatopancreatobiliary

HR Hazard Ratio

ICER Incremental Cost-Effectiveness Ratio

ICU Intensive Care Unit

IL-6 Interleukin-6

IL-8 Interleukin-8

IL-33 Interleukin-33

IOC Intraoperative Cholangiography

IQR Interquartile Range

LFT Liver Function Test

LOS Length of Stay

MCID Minimal Clinically Important Difference

MCS Mental Component Summary

MRCP Magnetic Resonance Cholangiopancreatography

NF- κ B Nuclear Factor-Kappa B

OR Odds Ratio

PCS Physical Component Summary

POD1 Postoperative Day 1

PSM Propensity Score Matching

QALY Quality-Adjusted Life Year

QoL Quality of Life

RR Risk Ratio

SASP Senescence-Associated Secretory Phenotype

SD Standard Deviation

SF-36 Short Form-36 Health Survey

SMD Standardized Mean Difference

STROBE Strengthening the Reporting of Observational Studies in Epidemiology

TGF- β Transforming Growth Factor-Beta

TLR4 Toll-Like Receptor 4

VIF Variance Inflation Factor

WSES World Society of Emergency Surgery

Declarations

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Conflicts of Interest:

1. Payment/services information: The authors declare that no financial support was received from any organization for the submitted work.
2. Financial relationships: The authors report no financial relationships with any commercial entities related to this manuscript within the past three years.

3. Other relationships: No other conflicts of interest or competing interests are declared by the authors.

Ethics: This review article did not involve new studies with human or animal subjects. It was conducted in accordance with institutional policies on literature-based research Izhevsk State Medical Academy, Russia. Institutional Review Board approval was obtained from the Medical Ethics Committee prior to data collection (Ethics approval number: HBC-2025-089). Given the retrospective nature of the study, the requirement for individual informed consent was waived; however, all patients had previously provided written informed consent for the use of their anonymized clinical data for research purposes at the time of hospital admission, as per institutional policy. Patient confidentiality was maintained throughout the study period, and all data were de-identified prior to analysis

Consent to participate: Not applicable, as the study did not involve human participants or identifiable personal data.

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Code availability: Not applicable

Author Contributions

All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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All authors meet the four ICMJE criteria for authorship: (1) substantial contributions to conception or design of the work, or acquisition, analysis, or interpretation of data; (2) drafting the work or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work.

References

1. de'Angelis N, Catena F, Memeo R et al (2021) 2020 WSES guidelines for the detection and management of bile duct injury during cholecystectomy. *World J Emerg Surg* 16:30. 10.1186/s13017-021-00369-w
2. Granados-Romero JJ, Estrada-Mata AG, Espejel-Deloiza M et al (2016) Current perspective in the treatment of bile duct injuries. *Int J Res Med Sci* 4(3):677–684. 10.18203/2320-6012.ijrms20160504
3. Omar MA, Kamal A, Redwan AA, Alansary MN, Ahmed EA (2023) Post-cholecystectomy major bile duct injury: ideal time to repair based on a multicentre randomized controlled trial with promising results. *Int J Surg* 109(5):1208–1221. 10.1097/JS9.0000000000000403
4. Kapoor VK (2020) Epidemiology of Bile Duct Injury. In: Kapoor V (ed) *Post-cholecystectomy Bile Duct Injury*. Springer. doi:10.1007/978-981-15-1236-0_2.
5. Gu XX, Zhang MP, Zhao YF, Huang GM (2020) Clinical and microbiological characteristics of patients with biliary disease. *World J Gastroenterol* 26(14):1638–1646. 10.3748/wjg.v26.i14.1638
6. Trivedi PJ, Hirschfield GM (2021) Recent advances in clinical practice: epidemiology of autoimmune liver diseases. *Gut* 70(10):1989–2003. 10.1136/gutjnl-2020-322362
7. de Vries E, Beuers U (2017) Management of cholestatic disease in 2017. *Liver Int* 37(Suppl 1):123–129. 10.1111/liv.13306
8. Palaz Ali O, Ibis AC, Gurtekin B (2017) Financial Aspects of Bile Duct Injuries. *Med Sci Monit* 23:5264–5270. 10.12659/msm.907532
9. Mathews SC, Izmailyan S, Brito FA et al (2022) Prevalence and Financial Burden of Digestive Diseases in a Commercially Insured Population. *Clin Gastroenterol Hepatol* 20(7):1480–1487e7. 10.1016/j.cgh.2021.06.047
10. Elmunzer BJ, Maranki JL, Gómez V et al (2023) ACG Clinical Guideline: Diagnosis and Management of Biliary Strictures. *Am J Gastroenterol* 118(3):405–426. 10.14309/ajg.0000000000002190
11. Beuers U, Banales JM, Karpen S et al (2025) History and prospects of bile acid therapies. *J Hepatol*. 10.1016/j.jhep.2025.06.010
12. Banales JM, Huebert RC, Karlsen T et al (2019) Cholangiocyte pathobiology. *Nat Rev Gastroenterol Hepatol* 16(5):269–281. 10.1038/s41575-019-0125-y

13. Yang W, He H, Wang T et al (2021) Single-Cell Transcriptomic Analysis Reveals a Hepatic Stellate Cell-Activation Roadmap and Myofibroblast Origin During Liver Fibrosis in Mice. *Hepatology* 74(5):2774–2790. 10.1002/hep.31987
14. Woolbright BL, Jaeschke H (2019) Inflammation and Cell Death During Cholestasis: The Evolving Role of Bile Acids. *Gene Expr* 19(3):215–228. 10.3727/105221619X15614873062730
15. Allen K, Jaeschke H, Copple BL (2011) Bile acids induce inflammatory genes in hepatocytes: a novel mechanism of inflammation during obstructive cholestasis. *Am J Pathol* 178(1):175–186. 10.1016/j.ajpath.2010.11.026
16. Chang N, Liu Y, Li W et al (2024) Neutrophil-secreted S100A8/A9 participates in fatty liver injury and fibrosis by promoting myofibroblast migration. *J Mol Med (Berl)* 102(9):1117–1133. 10.1007/s00109-024-02469-x
17. Jalan-Sakrikar N, Guicciardi ME, O'Hara SP, Azad A, LaRusso NF, Gores GJ, Huebert RC (2025) Central role for cholangiocyte pathobiology in cholestatic liver diseases. *Hepatology* 82(4):834–854. 10.1097/HEP.0000000000001093. Epub 2024 Sep 9. PMID: 39250501; PMCID: PMC11890218
18. VanderWeele TJ, Ding P (2017) Sensitivity Analysis in Observational Research: Introducing the E-Value. *Ann Intern Med.* ;167(4):268–274. 10.7326/M16-2607. Epub 2017 Jul 11. PMID: 28693043
19. Hernán MA, Robins JM (2016) Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *Am J Epidemiol* 183(8):758–764. 10.1093/aje/kwv254. Epub 2016 Mar 18. PMID: 26994063; PMCID: PMC4832051
20. Campinoti S, Kirubendran K, Wei L, Medic M, Joshi OP, Urbani L (2026) Single-cell insights into hepatic fibroblasts and stellate cells: heterogeneity in matrix remodelling in development, health, and disease. *NPJ Gut Liver* 3(1):27. 10.1038/s44355-026-00075-x. Epub 2026 Jul 22. PMID: 42495565; PMCID: PMC13391356
21. Bertolini A, Fiorotto R, Strazzabosco M (2022) Bile acids and their receptors: modulators and therapeutic targets in liver inflammation. *Semin Immunopathol* 44(4):547–564. 10.1007/s00281-022-00935-7. Epub 2022 Apr 12. PMID: 35415765; PMCID: PMC9256560
22. Sun D, Xie C, Zhao Y, Liao J, Li S, Zhang Y, Wang D, Hua K, Gu Y, Du J, Huang G, Huang J (2024) The gut microbiota-bile acid axis in cholestatic liver disease. *Mol Med* 30(1):104. 10.1186/s10020-024-00830-x. PMID: 39030473; PMCID: PMC11265038
23. Sabino J, Vieira-Silva S, Machiels K, Joossens M, Falony G, Ballet V, Ferrante M, Van Assche G, Van der Merwe S, Vermeire S, Raes J (2016) Primary sclerosing cholangitis is characterised by intestinal dysbiosis independent from IBD. *Gut* 65(10):1681–1689. 10.1136/gutjnl-2015-311004. Epub 2016 May 20. PMID: 27207975; PMCID: PMC5036217
24. Klein F, Wellhöner F, Plumeier I, Kahl S, Chhatwal P, Vital M, Voigtländer T, Pieper DH, Manns MP, Lenzen H, Solbach P, Heidrich B (2022) The biliary microbiome in ischaemic-type biliary lesions can be shaped by stenting but is resilient to antibiotic treatment. *Liver Int* 42(5):1070–1083. 10.1111/liv.15194. Epub 2022 Feb 24. PMID: 35152539

25. Giuliani F, Panettieri E, De Rose AM, Murazio M, Vellone M, Mele C, Clemente G, Giovannini I, Nuzzo G, Ardito F (2023) Bile duct injury after cholecystectomy: timing of surgical repair should be based on clinical presentation. The experience of a tertiary referral center with Hepp-Couinaud hepatico-jejunostomy. *Updates Surg* 75(6):1509–1517. 10.1007/s13304-023-01611-7. Epub 2023 Aug 14. PMID: 37580549; PMCID: PMC10435431
26. Zidan MHE, Seif-Eldeen M, Ghazal AA, Refaie M (2024) Post-cholecystectomy bile duct injuries: a retrospective cohort study. *BMC Surg.* ;24(1):8. 10.1186/s12893-023-02301-2. Erratum in: *BMC Surg.* 2024;24(1):48. PMID: 38172761
27. Manivasagam SS, Chandra JN, Khera D, Aradhya PS, Hiremath AM (2024) Optimal Timing of Surgical Repair After Bile Duct Injury: A Systematic Review and Meta-Analysis. *Cureus.* ;16(2):e53507. 10.7759/cureus.53507. PMID: 38440011
28. Esparham A, Calabrese EC, Ganescu O, Choksi S, Park K, Kumar K, Huo B, Shehata D, Abou-Setta A, Florez ID, Slater BJ, El-Hayek K (2025) Dec SAGES-AHPBA 2025: a systematic review and meta-analysis on the surgical management of bile duct injury following cholecystectomy. *Surg Endosc.* 10.1007/s00464-025-11646-1. PMID: 41193912
29. Piriianu C, Toma EA, Enciu O, Ardelean M, Miron A, Calu V (2025) Management of Iatrogenic Bile-Duct Injury After Cholecystectomy, 1995–2025: Systematic Review and Meta-Analysis. *Life (Basel)* 15(12):1858. 10.3390/life15121858
30. Queirós T, Castro B, Ferreira A, Amado A, Louro H, Lucas MC, Santos J, Cardoso JM, Oliveira M (2023) Bronchobiliary fistula after stenting of biliary duct as the management of iatrogenic bile duct injury during elective cholecystectomy. *Acta Chir Belg.* ;123(5):544–549. doi: 10.1080/00015458.2022.2049071. Epub 2022 Mar 11. PMID: 35253620
31. Keulemans YC, Bergman JJ, de Wit LT, Rauws EA, Huibregtse K, Gouma DJ (1998) Improvement in the management of bile duct injuries? *J Am Coll Surg.* ;187(3):246–254. 10.1016/s1072-7515(98)00155-0. PMID: 9740181
32. Kapoor VK (2020) Epidemiology of Bile Duct Injury. In: Kapoor V (ed) *Post-cholecystectomy Bile Duct Injury*. Springer, Singapore. doi: 10.1007/978-981-15-1236-0_2.
33. Mezghebe HM Does Timing of Laparoscopic Bile Duct Injury Repair affect Long-term Outcome? *World J Laparosc Surg* May-August (2011) ;4(2):81–83. doi: 10.5005/jp-journals-10007-1121
34. Pesce A, Palmucci S, La Greca G, Puleo S (2019) Iatrogenic bile duct injury: impact and management challenges. *Clin Exp Gastroenterol* 12:121–128. 10.2147/CEG.S169492. PMID: 30881079; PMCID: PMC6408920

Figures

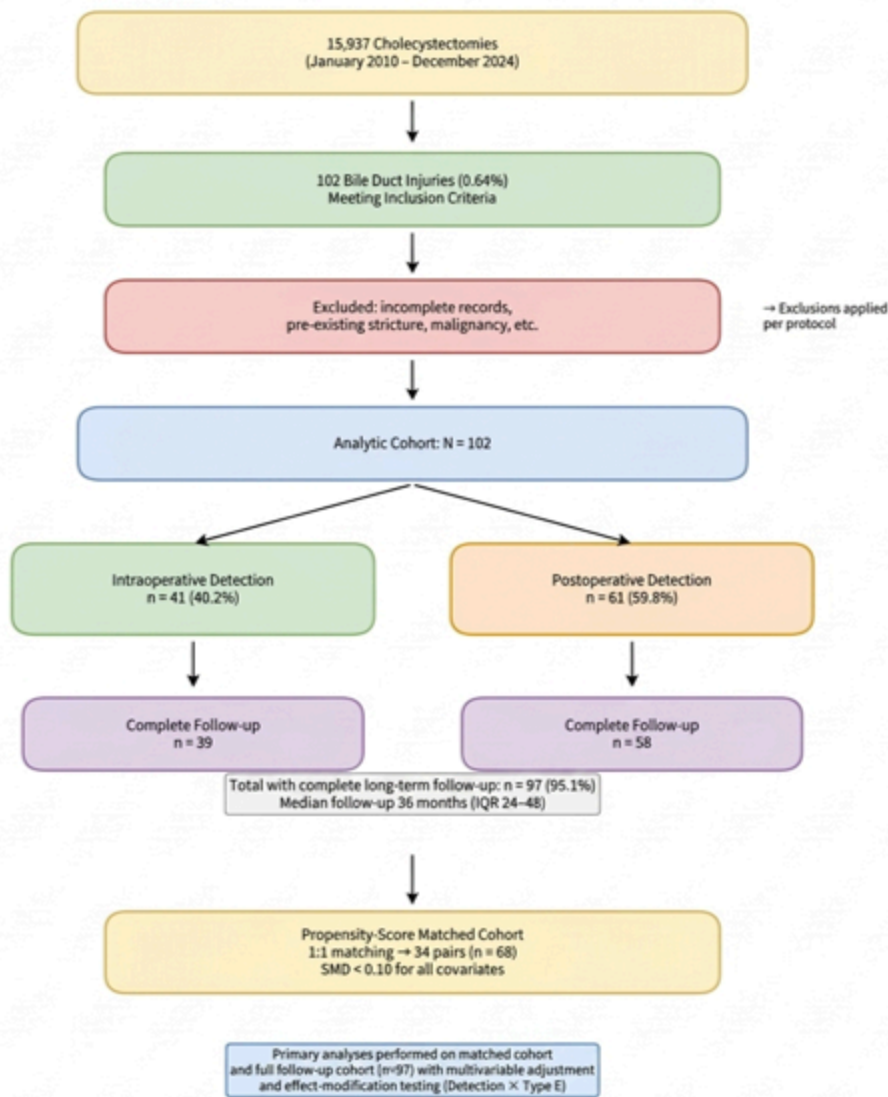


Figure 1

Study Flow Diagram (STROBE)

Temporal trends demonstrated a progressive rise in the proportion of injuries detected intraoperatively across three eras: 28.6 % (2010–2014), 40.5 % (2015–2019) and 48.6 % (2020–2024; p for trend = 0.019). Injury-severity distribution remained stable (Type E: 25.0 %, 27.0 % and 27.0 %, respectively; p = 0.982). Propensity-score matching produced 34 matched pairs with standardized mean differences < 0.10 for all covariates (**Supplementary Table S1**).

Figure 2. Kaplan–Meier Stricture-Free Survival

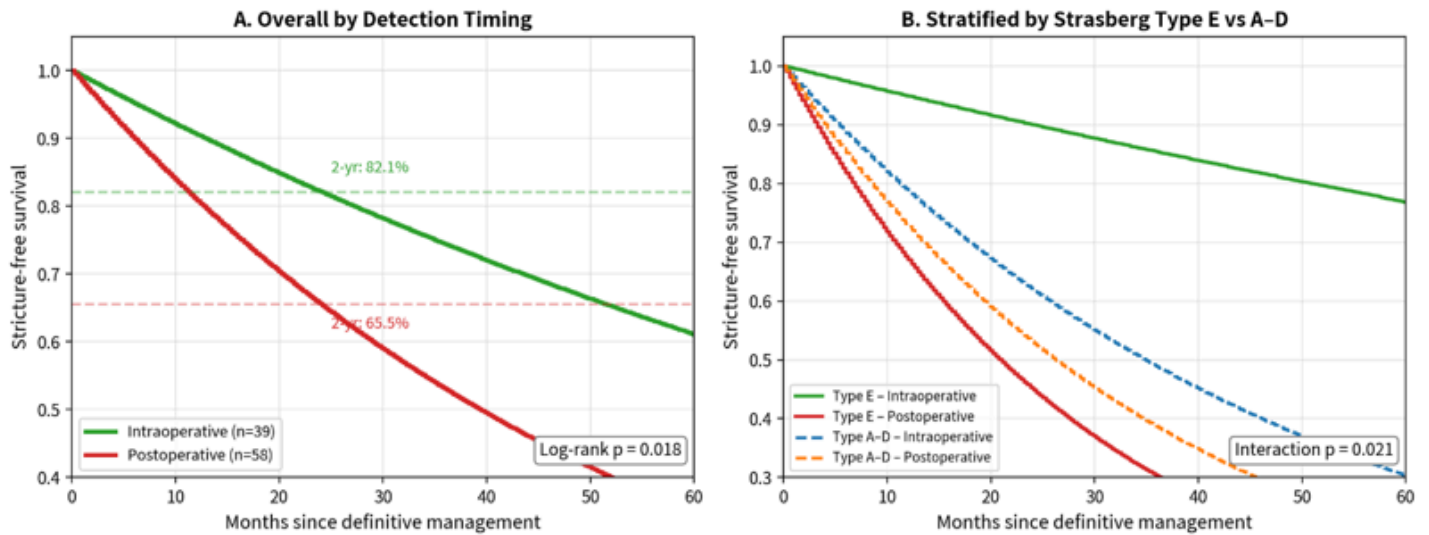


Figure 2

Kaplan–Meier Stricture-Free Survival. (A) Overall, by detection timing (log-rank $p = 0.018$). (B) Stratified by Type E versus Type A–D.

**Figure 3. Forest Plot of Stratified Associations
Effect Modification by Strasberg Severity**

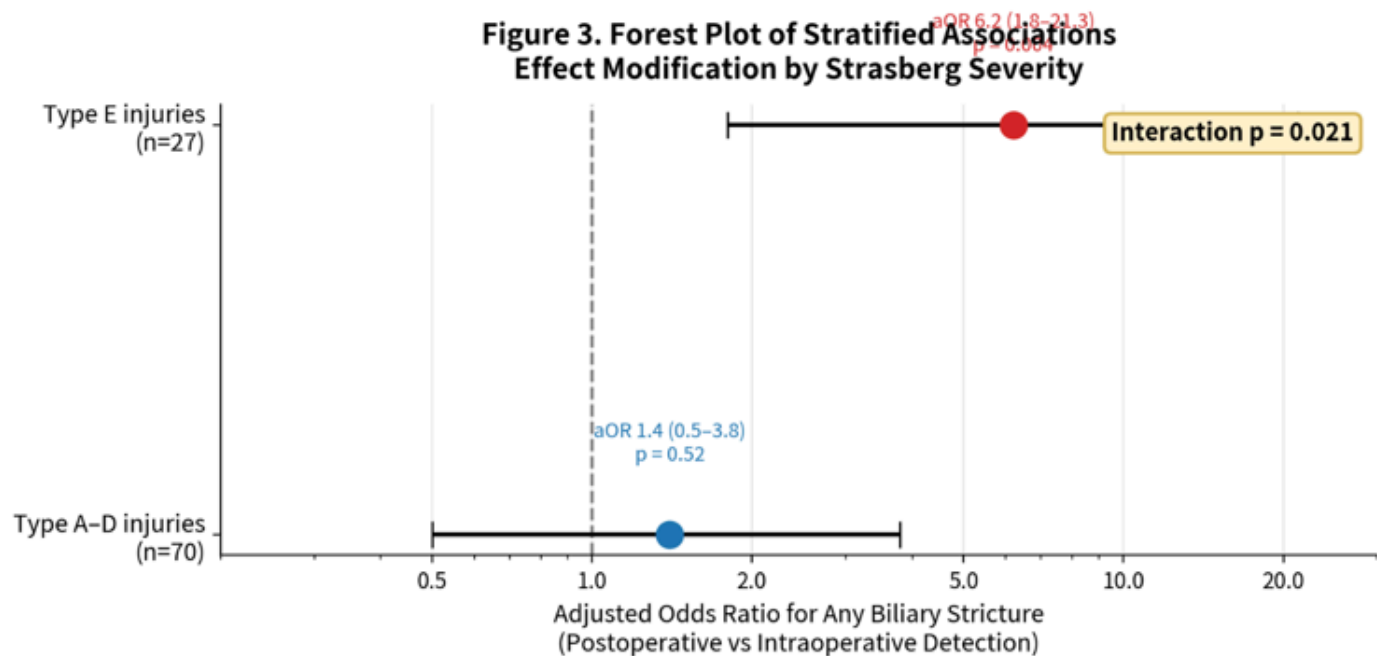


Figure 3

Forest Plot of Stratified Associations. Adjusted odds ratios for stricture according to detection timing within Type E and Type A–D subgroups; interaction $p = 0.021$.

Supplementary Files

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