

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Surgical management of post-cholecystectomy bile duct injuries: referral patterns and factors influencing early and long-term outcome

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1565575> since 2016-06-12T23:31:00Z

Published version:

DOI:10.1007/s13304-015-0311-6

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)



UNIVERSITÀ DEGLI STUDI DI TORINO

This is an author version of the contribution published on:

Questa è la versione dell'autore dell'opera:

Updates Surg, 67(3):283-291, 2015

DOI: 10.1007/s13304-015-0311-6

The definitive version is available at:

La versione definitiva è disponibile alla URL:

<http://link.springer.com/article/10.1007%2Fs13304-015-0311-6>

Surgical management of post-cholecystectomy bile duct injuries: referral patterns and factors influencing early and long-term outcome

Damiano Patrono, MD, PhD, Rosa Benvenga, MD, Fabio Colli, MD, Paolo Baroffio, MD,

Renato Romagnoli, MD, and Mauro Salizzoni, MD

From the General Surgery 2U and Liver Transplantation Center, A.O.U. Città della Salute e della Scienza di Torino, University of Torino, Torino, Italy.

Correspondence and reprints: Renato Romagnoli, MD, Professor of Surgery. General Surgery 2U and Liver Transplantation Center, A.O.U. Città della Salute e della Scienza di Torino, University of Torino, Corso Bramante 88 – 90, 10126, Torino, Italy. Tel +390116334374. Email: renato.romagnoli@unito.it.

Running title: Post-cholecystectomy bile duct injuries

Disclosure: The authors declare they have nothing to disclose

1
2
3 **Surgical management of post-cholecystectomy bile duct injuries:**
4 **referral patterns and factors influencing early and long-term outcome**
5

6
7 Running title: Post-cholecystectomy bile duct injuries
8

9
10 Disclosure: The authors declare they have nothing to disclose
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Abstract

Background: Cholecystectomy-related bile duct injuries (BDI) remain a cause of significant morbidity and debate concerning optimal management is ongoing. **Methods:** We reviewed our experience with surgical management of BDI to assess patterns of referral along with postoperative and long-term outcomes. **Results:** In the period September 1996 – August 2013, 35 patients were operated in our tertiary care center for a Bismuth-Strasberg grade > A BDI after a cholecystectomy performed elsewhere. Injury grade distribution was as follows: D, n=3; E1, n=4; E2, n=15; E3, n=5; E4, n=5; E5, n=3. Four patients (11.4%) had an associated vascular injury (arterial, n=2; portal, n=1; both, n=1). Treatment was direct repair + Kehr drain placement (n=1), hepatico-jejunostomy (n=28), hepatico-jejunostomy + hepatic resection (n=5) and liver transplantation (n=1). There was one postoperative death (2.8%) due to hepatic failure after liver resection; severe (Dindo-Clavien grade $\geq 3b$) complications were observed in 12 (34.3%) patients. Sepsis at referral (OR 17.33, p=0.007) and laparotomy prior to definitive repair (OR 14, p=0.04) were the factors associated with severe complications. Median follow-up was 81 (range 12–182) months; two patients were lost to follow-up. Treatment failure (defined as need for reoperation or interventional radiology procedure during follow-up) was observed in 7/32 (21.9%) patients. No association between baseline variables and treatment failure was observed. **Conclusions:** Post-cholecystectomy BDI represent a heterogeneous entity. The whole armamentarium of the hepato-biliary surgeon is required to achieve proper management. Patients referred with sepsis and requiring laparotomy prior to definitive repair are more prone to develop severe complications.

Keywords: cholecystectomy, bile duct injury, laparoscopy, injury progression, outcome.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Introduction

1
2
3 Post-cholecystectomy bile duct injuries (BDI) represent a well-known cause of early and long-term
4
5 morbidity and mortality and are associated with reduced health-associated quality of life and frequent legal
6
7 litigation [1 - 3]. Furthermore, most patients suffering from BDI are in their working age and underwent
8
9 cholecystectomy for a benign pathology. The introduction of laparoscopic cholecystectomy has been
10
11 associated with an increase in BDI incidence rate from 0.3% to 0.5-0.8% [4, 5]. A large body of literature
12
13 has been dedicated to study BDIs types and the technical principles to prevent them [6]. Nevertheless, BDI
14
15 do and will occur, as even experienced hepato-biliary surgeons are exposed to cause them [7]. Early
16
17 experience with other minimally invasive techniques, like natural orifices transluminal endoscopic surgery
18
19 and single-port laparoscopic surgery, has shown that this figure could further increase [8, 9].
20
21

22
23
24 As BDI management is frequently challenging and inappropriate therapy can possibly complicate or
25
26 jeopardize results of further treatment, many Authors have plead for an early referral of BDI patients to
27
28 tertiary care centers, where all necessary therapeutic means and expertise are available [10 - 12].
29
30

31
32 Unfortunately, even nowadays BDI patients are sometimes referred to specialized hepatobiliary units late
33
34 and their management could still be improved. Thus, we reviewed our experience with surgically treated
35
36 BDI referred to our institution to describe injury evolution and patterns of referral, and to identify factors
37
38 associated with postoperative morbidity and long-term outcome.
39
40

Patients and methods

Patient selection and data collection

41
42
43
44
45
46
47
48
49 Patients referred to our tertiary care center for surgical management of a Bismuth-Strasberg [13] grade > A
50
51 BDI during the period September 1996 – August 2013 were identified through ICD-9-CM codes 5762 (bile
52
53 duct stricture), 5763 and 5764 (bile duct fistula). Medical charts were obtained to confirm the relationship of
54
55 BDI with previous cholecystectomy, excluding patients in whom injury was not deemed unequivocally
56
57 related to the index operation. Collected data included details concerning index cholecystectomy, injury
58
59 grade, pre-referral presentation and management, patient comorbidities, repair technique, postoperative
60
61
62
63
64
65

1 course and long-term results. Reports of previous operations, radiological exams, endoscopic and
2 interventional radiology procedures were thoroughly reviewed. Whenever possible, original cholangiograms
3 were directly evaluated.
4
5

6 **Patient management**

7
8
9
10 After referral, the anatomy of BDI was defined by thorough analysis of previous cholangiograms; in doubtful
11 cases patients were studied by endoscopic retrograde cholangiopancreatography (ERCP), percutaneous
12 transhepatic cholangiography (PTC) or magnetic resonance cholangiopancreatography. Patients presenting
13 with biliary peritonitis or abdominal bile collections were managed by percutaneous drainage, percutaneous
14 transhepatic drainage (PTD) or laparotomy, as indicated, deferring definitive BDI repair after the resolution
15 of sepsis. Pre-operative positioning of a PTD was considered in difficult cases to facilitate intra-operative
16 localization of injured bile ducts. Intra-operatively, the choice of stenting the biliary anastomosis was based
17 on the caliber, number and viability of the bile ducts proximal to the anastomosis. When already present, the
18 PTD was replaced with a soft pig-tail drain, positioned across the anastomosis. If a PTD was not already in
19 place and was deemed necessary, it was positioned intra-operatively as previously described [14]. In some
20 cases a transjejunal drain was preferred, positioning the tip of the drain into the bile duct and pulling it out of
21 the jejunum 20 cm downstream through a serosal tunnel on the antimesenteric border, similarly to a Witzel
22 procedure [15]. In the absence of complications, stents were removed three weeks after the operation, after
23 having verified the patency of biliary anastomosis and the absence of leaks by cholangiography. Patients
24 were followed-up by ultrasonography and liver function tests at six months and one year after the operation,
25 and yearly thereafter.
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45

46 **Classifications**

47
48
49
50 Bile duct injuries were classified according to the Bismuth-Strasberg classification [13]. Injury progression
51 was defined as an increase in the severity grade or as the development of cirrhosis. Dindo-Clavien
52 classification was used for postoperative complications, defining grade $\geq 3b$ complications as severe [16].
53 Standard definition was used for sepsis [17]. Long-term treatment failure was defined as the need for further
54 surgical or interventional radiology procedure. Outcome was defined fair when an asymptomatic stricture
55
56
57
58
59
60
61
62
63
64
65

1 was diagnosed at imaging exams or in case of a mild, clinically silent alteration of liver function tests. In the
2 remaining patients the outcome was defined as good.
3

4 **Study endpoints**

5
6
7
8 Study endpoints were the rate of severe postoperative complications and of long-term treatment failure.
9

10 **Statistical analysis**

11
12
13 Data are presented as median (interquartile range) or number (percentage). Fisher's exact and Mann-Whitney
14
15 tests were used to compare categorical and continuous variables, respectively. Factors associated with severe
16
17 postoperative complications and treatment failure were identified by logistic regression. All analyses were
18
19 carried out using R statistical software package version 3.1.2.
20
21

22 **Results**

23
24
25
26
27 During the study period, a total of 35 patients with grade > A BDI were managed. In 19 (54.3%) patients the
28
29 indication for surgical repair was a bile duct stricture, whereas 16 (45.7%) patients presented with a fistula
30
31 (Table 1). There were no differences among study groups, except for a non-significant trend towards acute
32
33 cholecystitis as the indication for initial cholecystectomy in the stricture group ($p = 0.06$) and for the fact that
34
35 sepsis at referral was observed only in patients in the fistula group ($p = 0.001$). Most patients ($n = 26, 74.3\%$)
36
37 were managed with ERCP +/- stenting before referral. In 7 (20%) patients an attempt at repair was made
38
39 during the initial cholecystectomy, whereas in further 7 (20%) an operative repair was attempted afterwards.
40
41 At referral, biliary bifurcation (grade \geq E3) was involved in 13 (37.1%) patients, with complete separation of
42
43 right and left systems in 8 (22.8%). A vasculo-biliary injury was observed in 4 (11.4%) patients.
44
45

46
47
48 The comparison between the injuries as initially described and at the time of repair showed that 15 (42.8%)
49
50 patients experienced an injury progression towards a higher grade (Figure 1 and Table 2). This was more
51
52 frequently observed in patients presenting with a stricture (63.1% versus 18.7%, $p = 0.006$). Patients in the
53
54 stricture group presented an injury progression mainly in the form of a more proximal involvement of the
55
56 bile duct ($n = 10, 52.6\%$) or of a hepatic fibrosis ($n = 2, 10.5\%$) or cirrhosis ($n = 3, 15.8\%$) due to chronic
57
58 cholangitis, associated with prolonged (> 3 months) stenting in 7 (36.8%) cases. Patients in the fistula group
59
60
61
62
63
64
65

1 presented an injury progression most frequently due to bile duct necrosis (n = 2, 12.5%). In one patient
2 (6.2%) presenting with biliary peritonitis, necrosis of the right bile duct was consequent to the injury of the
3 right branch of hepatic artery during PTD positioning.
4

5 Patients with biliary leak were referred earlier after injury (44 versus 577 days, p < 0.001) and required more
6 frequently drainage of bile collections immediately after referral (37.5% versus 0%, p = 0.004) (Table 3).
7

8 Three patients underwent laparotomy prior to definitive repair. In two cases the indication was the control of
9 abdominal bile collections and sepsis. In the third patient, presenting with a late stricture, laparotomy was
10 indicated to directly assess injury anatomy and repair feasibility. This patient had a history of subclinical
11 hepatitis C-related cirrhosis and presented with a grade E4 stricture that would have ideally required a right
12 hepatectomy and a hepaticojejunostomy on the left bile duct. Due to subjacent cirrhosis, the risk of
13 posthepatectomy liver failure was deemed unacceptable and the patient was scheduled for liver
14 transplantation.
15

16 Treatment consisted in most cases in a single (n = 30, 85.7%) or double-barrel (n = 3, 8.6%) hepatico-
17 jejunostomy on a Roux-n-Y jejunal loop; patients referred for biliary fistula were more prone to require a
18 double biliary anastomosis (p = 0.01). Stenting of the biliary anastomosis using a transhepatic, transjejunal or
19 Kehr drain was performed in 20 (57.1%), 4 (11.4%) and 1 (2.8%) patients, respectively. A major hepatic
20 resection was carried out in 6 (17.1%) patients, including the patient who required liver transplantation. At
21 logistic regression, factors associated with hepatic resection were grade \geq E3 (OR: 13.12, p = 0.027) and
22 grade \geq E4 injury (OR: 43.3, p = 0.002).
23

24 One patient (2.8%) suffering from a vasculo-biliary injury involving the right hepatic duct and the
25 homolateral branch of hepatic artery died in the postoperative period due to posthepatectomy liver failure
26 after right hepatectomy and hepatico-jejunostomy on the left bile duct (Table 4). A biliary leak was observed
27 in 4 (11.4%) patients, one case being due to a leakage from the entry point of the PTD into the liver
28 parenchyma. Although frequent (n = 9, 25.7%), PTD-related complications were generally low-grade and
29 easily managed by drain replacement or repositioning. Severe complications rate was 34.3%. At logistic
30 regression, the variables associated with severe morbidity were sepsis at referral (OR = 17.3, p = 0.007) and
31 laparotomy after referral prior to definitive repair (OR = 14, p = 0.04) (Table 5).
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 Median follow-up was 81 (12 – 182) months. Excluding the patient who died in the postoperative period and
2 two patients who were lost to follow-up, a good long-term outcome was achieved after the first treatment in
3 22 (68.7%) patients. Three (17.6%) patients experienced a fair outcome due to chronic alteration of liver
4 function tests (n = 1) or evidence of a clinically indolent anastomosis sub-stenosis (n = 2). Treatment failure
5 was observed in 7 (21.9%) patients, with no significant differences among the study groups. Median time to
6 failure was 48 (range 18 – 86) months (Figure 2). However, all seven patients experiencing failure were
7 successfully managed with antibiotic therapy and percutaneous balloon dilatation, finally achieving a fair
8 result. Logistic regression did not identify a significant association of treatment failure with any baseline and
9 operative variables.
10
11
12
13
14
15
16
17
18
19
20

21 **Discussion**

22 The main finding of the present study is that the progression of BDI severity from the moment of injury to
23 that of referral still occurs in nearly half of the patients, and is more frequent in patients presenting with a
24 stricture. On the other side, patients having a biliary leak are more frequently septic at referral and pose a
25 greater technical challenge, as suggested by the higher number of required anastomoses. Sepsis at referral
26 and need for laparotomy before surgical repair are the factors significantly associated with the development
27 of severe complications.
28
29
30
31
32

33 The analysis of referral patterns and subsequent surgical treatment confirms that BDI management requires
34 the most comprehensive array of surgical techniques in the armamentarium of the hepatobiliary surgeon,
35 including complex biliary reconstructions, major hepatic resections and, in selected cases, liver
36 transplantation [18]. Furthermore, surgery needs to be properly integrated with operative endoscopy and
37 interventional radiology. The availability of skilled interventional radiologists capable of performing difficult
38 percutaneous drainages and dealing with non-dilated biliary systems is fundamental [19 - 22]. In our series
39 only two patients required laparotomy to control abdominal sepsis prior to definitive repair, whereas all the
40 others were successfully managed by percutaneous drainage and transhepatic biliary drainage. Pre-operative
41 positioning of a PTD also facilitates defining the biliary anatomy during the repair operation, especially in
42 complex injuries [19, [23]. It would be very unlikely and uneconomical to dispose of such expertise in every
43 hospital where a BDI can occur. Consequently, treatment availability influenced management strategy: most
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 patients were managed first by reoperation or ERCP, whereas PTC, which is less diffusely available in
2 community hospitals, was most frequently performed after referral.
3

4
5 In our study nearly a half of the patients presented an injury progression. To a certain extent, injury
6 progression can be considered an expected event, as in the case of strictures resulting from the healing of a
7 lateral injury. Injury progression can also result from failed attempts at surgical repair, which frequently
8 entail a more proximal involvement of the bile duct. This is observed in particular when a hepatico-
9 jejunostomy is performed as the first treatment. For this reason, De Reuver et al. suggested that end-to-end
10 anastomosis could be a reasonable option as a first-line repair [24]. In our series, however, the most frequent
11 cause of injury progression was chronic cholangitis, issue of unrelieved bile duct stenosis and prolonged
12 stenting, resulting in progressive ductal fibrosis. Consequently, some injuries initially limited to the bile duct
13 eventually involved the confluence. We described the same mechanism of injury progression in a case of
14 Mirizzi syndrome with persistent bile duct obstruction after laparoscopic cholecystectomy, which was finally
15 managed with liver transplantation due to massive hilar plate fibrosis complicated by portal vein thrombosis
16 [25]. Injury progression has been observed previously by many other Authors and in some cases it was
17 associated with worse early and long-term outcome [22, 26, 27]. In our series grade \geq E3 injuries were more
18 likely to require a hepatic resection. Therefore, injury progression should be prevented as much as possible.
19 Undoubtedly, as the denominator of our series (BDIs successfully managed in the hospital of origin and not
20 referred) remains unknown, it is difficult to assess the magnitude of the problem. However, complex injuries
21 and those not responding to initial treatment should be promptly referred to tertiary care centers and
22 prolonged stenting should be avoided.
23
24
25
26
27
28
29

30
31 From a surgical standpoint, the most frequently applied technique was a hepaticojejunostomy on a Roux-n-Y
32 loop, as previously reported [10, [13, [28, [29]. It should be noted that in most cases surgical repair requires a
33 high degree of experience in hepatobiliary surgery: hilar plate dissection and identification of injured bile
34 ducts is often difficult due to local inflammation and anatomical distortion. In our series, 17.1% of the
35 patients required a hepatic resection and 11.4% a double barrel hepatico-jejunostomy. Patients presenting
36 with a fistula required more frequently a double barrel hepaticojejunostomy. Furthermore, in 68.5% of the
37 patients a transanastomotic drain was positioned due to doubts concerning bile duct quality. The use of a
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

1 transanastomotic drain is debatable. In the course of our experience, use of transjejunal drains was
2 progressively abandoned due to their tendency to dislocate postoperatively. On the other hand, almost a half
3 of the patients (9/20) having a PTD experienced some low-grade catheter-related complication. Our data do
4 not allow formulating any recommendation; we can only argue that the incidence of bile leaks in our series
5
6
7
8
9 can be considered low in the light of the severity of treated injuries.

10
11
12 Presentation with sepsis and need for laparotomy immediately after referral emerged as the only factors
13 associated with severe complications, whereas no factor (including technical ones) resulted associated with
14 long-term outcome. This stresses once more the importance of the right treatment from the very beginning.
15
16
17 In contrast with previous reports [26], timing of intervention did not influence postoperative morbidity or
18
19
20
21 treatment failure. This was true also at subgroup analysis of patients presenting with fistula (data not shown).
22
23 This is in line with a previous study by Stewart et al. [30] showing that results of surgical repair may be
24 acceptable regardless of timing, provided that sepsis and local inflammation have been previously controlled
25
26
27 and that surgical repair is technically correct.

28
29
30
31 In conclusion, even nowadays some patients suffering from post-cholecystectomy BDI still experience an
32
33 injury progression due to initial mismanagement and late referral. Treatment of BDI requires the integration
34
35 of proper surgical technique with operative endoscopy and interventional radiology. Thus, these patients
36
37 should be timely referred to tertiary care centers, especially those having a BDI presenting with sepsis or
38
39 involving the biliary confluence.

Figure captions:

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65

Fig. 1. Barplot representing injury grade distribution at the onset and at referral

Fig. 2. Kaplan-Meier curve representing failure-free survival. Median time to failure was 48 months.

References

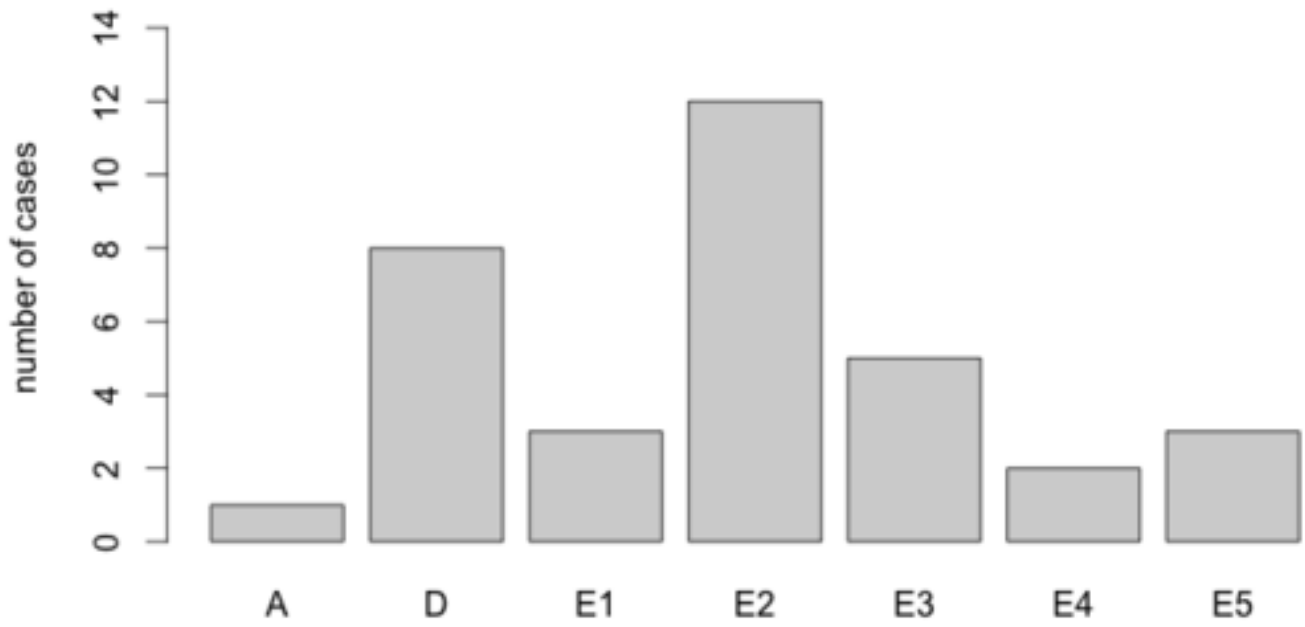
1. Landman MP, Feurer ID, Moore DE, Zaydfudim V, Pinson CW (2013) The long-term effect of bile duct injuries on health-related quality of life: a meta-analysis. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 15 (4):252-9; doi: 10.1111/j.1477-2574.2012.00586.x.
2. Strasberg SM (2005) Biliary injury in laparoscopic surgery: part 2. Changing the culture of cholecystectomy. *Journal of the American College of Surgeons* 201 (4):604-11; doi: 10.1016/j.jamcollsurg.2005.04.032.
3. Strasberg SM (2005) Biliary injury in laparoscopic surgery: part 1. Processes used in determination of standard of care in misidentification injuries. *Journal of the American College of Surgeons* 201 (4):598-603; doi: 10.1016/j.jamcollsurg.2005.05.009.
4. Deziel DJ, Millikan KW, Economou SG, Doolas A, Ko ST, Airan MC (1993) Complications of laparoscopic cholecystectomy: a national survey of 4,292 hospitals and an analysis of 77,604 cases. *American journal of surgery* 165 (1):9-14.
5. Gouma DJ, Go PM (1994) Bile duct injury during laparoscopic and conventional cholecystectomy. *Journal of the American College of Surgeons* 178 (3):229-33.
6. Strasberg SM, Brunt LM (2010) Rationale and use of the critical view of safety in laparoscopic cholecystectomy. *Journal of the American College of Surgeons* 211 (1):132-8; doi: 10.1016/j.jamcollsurg.2010.02.053.
7. Gigot J, Etienne J, Aerts R, Wibin E, Dallemagne B, Deweer F, et al (1997) The dramatic reality of biliary tract injury during laparoscopic cholecystectomy. An anonymous multicenter Belgian survey of 65 patients. *Surgical endoscopy* 11 (12):1171-8.
8. Allemann P, Demartines N, Schafer M (2014) Remains of the day: biliary complications related to single-port laparoscopic cholecystectomy. *World journal of gastroenterology : WJG* 20 (3):843-51; doi: 10.3748/wjg.v20.i3.843.
9. Cheah SW, Yuan S, Mackay S, Grigg M (2015) Single incision laparoscopic cholecystectomy is associated with a higher bile duct injury rate: a review and word of caution. *Annals of surgery* 261 (2):e54; doi: 10.1097/SLA.0000000000000555.

10. de Santibanes E, Palavecino M, Ardiles V, Pekolj J (2006) Bile duct injuries: management of late complications. *Surgical endoscopy* 20 (11):1648-53; doi: 10.1007/s00464-006-0491-8.
11. de Reuver PR, Rauws EA, Vermeulen M, Dijkgraaf MG, Gouma DJ, Bruno MJ (2007) Endoscopic treatment of post-surgical bile duct injuries: long term outcome and predictors of success. *Gut* 56 (11):1599-605; doi: 10.1136/gut.2007.123596.
12. Sikora SS (2012) Management of post-cholecystectomy benign bile duct strictures: review. *The Indian journal of surgery* 74 (1):22-8; doi: 10.1007/s12262-011-0375-6.
13. Bismuth H, Majno PE (2001) Biliary strictures: classification based on the principles of surgical treatment. *World journal of surgery* 25 (10):1241-4.
14. Salizzoni M, Romagnoli R, Mirabella S, Paraluppi G, Franchello A, Lupo F (2008) Intraoperative placement of transparietohepatic biliary drainage in remedial hepaticojejunostomy: technique and clinical experience. *American journal of surgery* 195 (4):528-32; doi: 10.1016/j.amjsurg.2007.02.029.
15. Tapia J, Murguia R, Garcia G, de los Monteros PE, Onate E (1999) Jejunostomy: techniques, indications, and complications. *World journal of surgery* 23 (6):596-602.
16. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of surgery* 240 (2):205-13.
17. Klein Klouwenberg PM, Ong DS, Bonten MJ, Cremer OL (2012) Classification of sepsis, severe sepsis and septic shock: the impact of minor variations in data capture and definition of SIRS criteria. *Intensive care medicine* 38 (5):811-9; doi: 10.1007/s00134-012-2549-5.
18. Parrilla P, Robles R, Varo E, Jimenez C, Sanchez-Cabus S, Pareja E, et al (2014) Liver transplantation for bile duct injury after open and laparoscopic cholecystectomy. *The British journal of surgery* 101 (2):63-8; doi: 10.1002/bjs.9349.
19. Lillemoe KD, Martin SA, Cameron JL, Yeo CJ, Talamini MA, Kaushal S, et al (1997) Major bile duct injuries during laparoscopic cholecystectomy. Follow-up after combined surgical and radiologic management. *Annals of surgery* 225 (5):459-68; discussion 68-71.
20. Pitt HA, Sherman S, Johnson MS, Hollenbeck AN, Lee J, Daum MR, et al (2013) Improved outcomes of bile duct injuries in the 21st century. *Annals of surgery* 258 (3):490-9; doi: 10.1097/SLA.0b013e3182a1b25b.

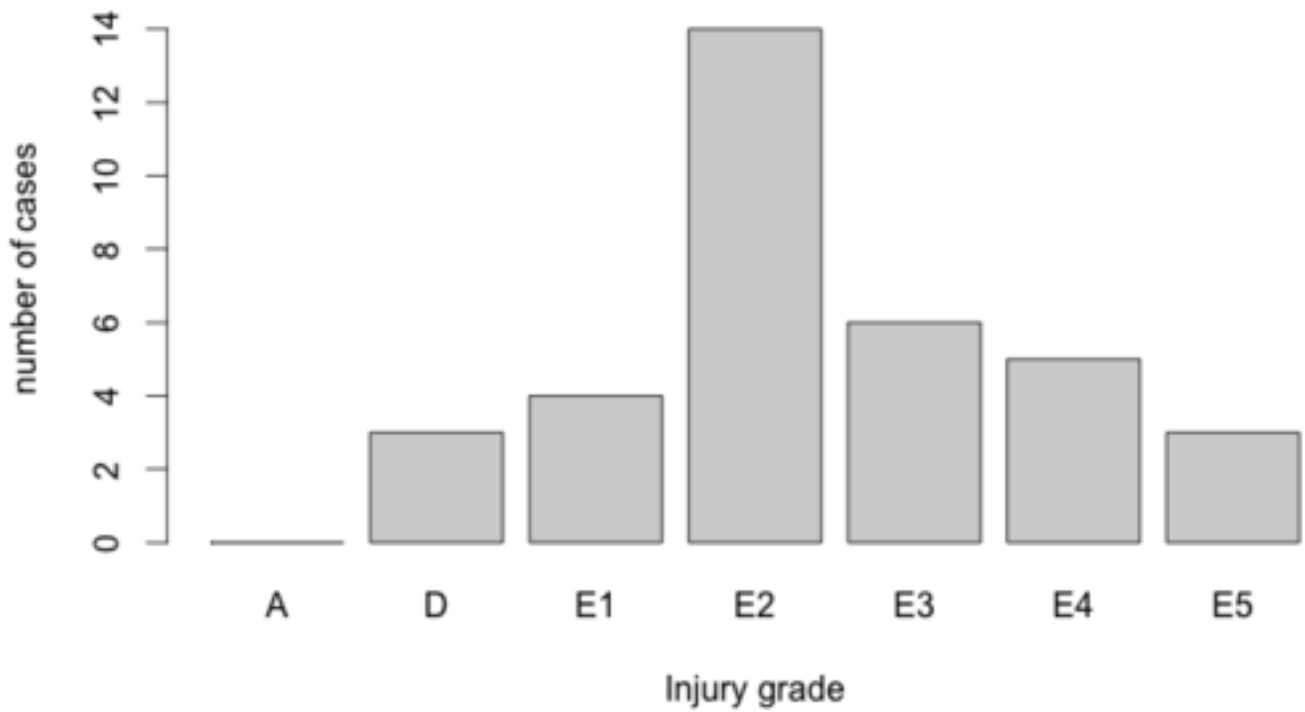
- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
21. Righi D, Franchello A, Ricchiuti A, Breatta AD, Versace K, Calvo A, et al (2008) Safety and efficacy of the percutaneous treatment of bile leaks in hepaticojejunostomy or split-liver transplantation without dilatation of the biliary tree. *Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society* 14 (5):611-5; doi: 10.1002/lt.21416.
 22. Sicklick JK, Camp MS, Lillemoe KD, Melton GB, Yeo CJ, Campbell KA, et al (2005) Surgical management of bile duct injuries sustained during laparoscopic cholecystectomy: perioperative results in 200 patients. *Annals of surgery* 241 (5):786-92; discussion 93-5.
 23. Lillemoe KD, Melton GB, Cameron JL, Pitt HA, Campbell KA, Talamini MA, et al (2000) Postoperative bile duct strictures: management and outcome in the 1990s. *Annals of surgery* 232 (3):430-41.
 24. de Reuver PR, Busch OR, Rauws EA, Lameris JS, van Gulik TM, Gouma DJ (2007) Long-term results of a primary end-to-end anastomosis in peroperative detected bile duct injury. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract* 11 (3):296-302; doi: 10.1007/s11605-007-0087-1.
 25. Patrono D, Mazza E, Paraluppi G, Strignano P, David E, Romagnoli R, et al (2013) Liver transplantation for "mass-forming" sclerosing cholangitis after laparoscopic cholecystectomy. *International journal of surgery case reports* 4 (10):907-10; doi: 10.1016/j.ijscr.2013.07.021.
 26. de Reuver PR, Grossmann I, Busch OR, Obertop H, van Gulik TM, Gouma DJ (2007) Referral pattern and timing of repair are risk factors for complications after reconstructive surgery for bile duct injury. *Annals of surgery* 245 (5):763-70; doi: 10.1097/01.sla.0000252442.91839.44.
 27. Sahajpal AK, Chow SC, Dixon E, Greig PD, Gallinger S, Wei AC (2010) Bile duct injuries associated with laparoscopic cholecystectomy: timing of repair and long-term outcomes. *Archives of surgery* 145 (8):757-63; doi: 10.1001/archsurg.2010.153.
 28. Bektas H, Schrem H, Winny M, Klempnauer J (2007) Surgical treatment and outcome of iatrogenic bile duct lesions after cholecystectomy and the impact of different clinical classification systems. *The British journal of surgery* 94 (9):1119-27; doi: 10.1002/bjs.5752.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
29. Johnson SR, Koehler A, Pennington LK, Hanto DW (2000) Long-term results of surgical repair of bile duct injuries following laparoscopic cholecystectomy. *Surgery* 128 (4):668-77; doi: 10.1067/msy.2000.108422.
30. Stewart L, Way LW (2009) Laparoscopic bile duct injuries: timing of surgical repair does not influence success rate. A multivariate analysis of factors influencing surgical outcomes. *HPB : the official journal of the International Hepato Pancreato Biliary Association* 11 (6):516-22; doi: 10.1111/j.1477-2574.2009.00096.x.

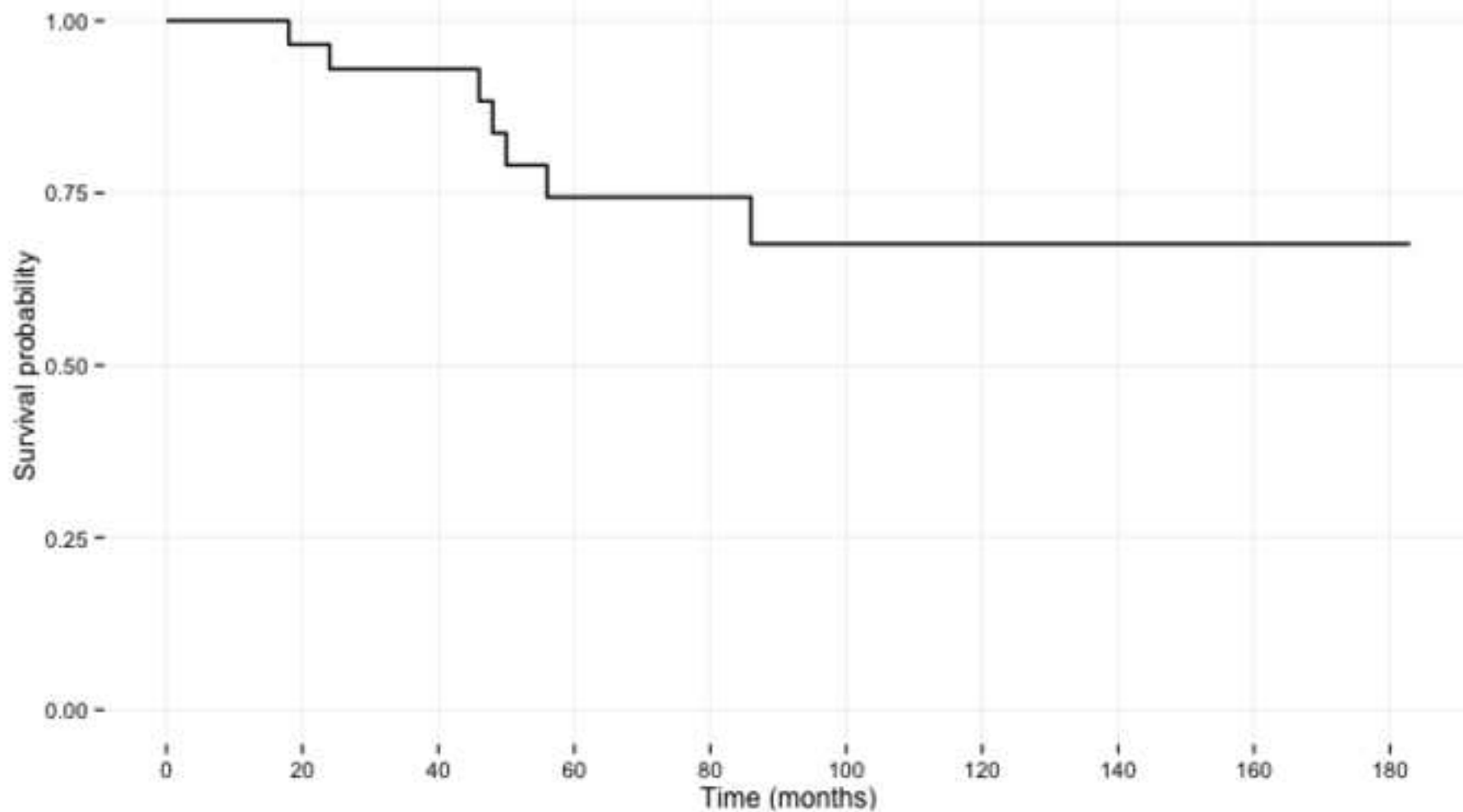
Initial injury



Injury at referral



Failure-free survival



All 32 28 22 16 12 8 6 4 2 1

Numbers at risk

Table 1. Baseline, previous treatment and injury features according to the type of injury (stricture or fistula)

	Whole series	Stricture (n = 19)	Fistula (n = 16)	p
Age	57 (42 - 65)	53 (42 - 64)	60 (42 - 66)	0.55*
Sex (female/male)	21/14 (60%)	11/8 (57%)	10/6 (62.5%)	1
Indication				
- Gallstones	19 (54.3%)	5 (26.3%)	10 (62.5%)	0.06
- Acute cholecystitis	15 (42.8%)	13 (68.4%)	6 (37.5%)	
- Mirizzi syndrome	1 (2.8%)	1 (5.3%)	0	
ERCP prior to operation	2 (5.7%)	1 (5.3%)	1 (6.2%)	1
Technique				
- Open	11 (31.4%)	9 (47.4%)	2 (12.5%)	0.09
- Laparoscopic	14 (40%)	6 (31.6%)	8 (50%)	
- Laparoscopic converted to open	10 (28.6%)	4 (21%)	6 (37.5%)	
Intra-operative cholangiography	7 (20%)	5 (26.3%)	2 (12.5%)	0.41
Intra-operative detection	10 (28.6%)	5 (26.3%)	5 (31.2%)	0.7
Intra-operative repair attempt	7 (20%)	4 (21%)	3 (18.7%)	1
Technique of intra-operative repair				
- Suture + T-tube	3 (8.6%)	2 (10.5%)	1 (6.2%)	0.52
- Hepaticojejunostomy	2 (5.7%)	0	2 (12.5%)	
- Suture	1 (2.8%)	1 (5.3%)	0	
- Transcystic drain + drainage	1 (2.8%)	1 (5.3%)	0	
ERCP before referral	26 (74.3%)	16 (84.2%)	10 (62.5%)	0.24
PTC before referral	8 (22.8%)	5 (26.3%)	3 (18.7%)	0.7
Repair attempt before referral	7 (20%)	6 (31.6%)	1 (6.2%)	0.09
Technique of repair attempt before referral				
- Suture + T-tube	2 (5.7%)	2 (10.5%)	0	0.39
- Laparotomy without repair	2 (5.7%)	2 (10.5%)	0	
- Hepaticojejunostomy	1 (2.8%)	1 (5.3%)	0	
- End-to-end anastomosis + T-tube	1 (2.8%)	0	1 (6.2%)	
- Suture	1 (2.8%)	1 (5.3%)	0	
Injury grade at referral				
- D	3 (8.6%)	1 (5.3%)	2 (12.5%)	0.48
- E1	4 (11.4%)	3 (15.8%)	1 (6.2%)	
- E2	14 (40%)	8 (42.1%)	6 (37.5%)	
- E3	6 (17.1%)	4 (21%)	2 (12.5%)	
- E4	5 (14.3%)	3 (15.8%)	2 (12.5%)	
- E5	3 (8.6%)	0	3 (18.7%)	
Bifurcation involved (\geq E3)	13 (37.1%)	6 (31.6%)	7 (43.7%)	0.5
Grade \geq E4	8 (22.8%)	3 (15.8%)	5 (31.2%)	0.42
Vasculo-biliary injury	4 (11.4%)	1 (5.3%)	3 (18.7%)	0.31
- Arterial injury	2 (5.7%)	0	2 (12.5%)	
- Portal injury	1 (2.8%)	1 (5.3%)	0	
- Combined arterial + portal	1 (2.8%)	0	1 (6.2%)	
Sepsis at referral	7 (20%)	0	7 (43.7%)	0.001

Data are expressed as median (interquartile range) or number (percentage). Fisher's exact test and Mann-Whitney test (*) were used to compare variables among different groups. Abbreviations: ERCP, endoscopic retrograde cholangio-pancreatography; PTC, percutaneous transhepatic cholangiography

Table 2. Injury progression according to the type of injury at referral				
	Whole series (n = 35)	Stricture (n = 19)	Fistula (n = 16)	p*
Injury progression	15 (42.8%)	12 (63.1%)	3 (18.7%)	0.001
Progression type				
- More proximal involvement of the bile duct	8 (22.8%)	6 (31.6%)	2 (12.5%)	
- Fistula evolving to more proximal stricture	4 (11.4%)	4 (21%)	0	
- Development of secondary biliary cirrhosis	2 (5.7%)	2 (10.5%)	0	
- Development of hepatic fibrosis	2 (5.7%)	2 (10.5%)	0	
- Secondary biliary cirrhosis + portal vein cavernoma	1 (2.8%)	1 (5.3%)	0	
- Right bile duct necrosis after PTC	1 (2.8%)	0	1 (6.2%)	
Data are expressed as number (percentage). * Fisher exact test. In some patients types of injury progression overlapped.				

Table 3. Treatment according to the type of injury at referral				
	Whole series (n = 35)	Stricture (n = 19)	Fistula (n = 16)	p
Days from injury to referral	44 (11-651)	577 (126-3037)	14 (7-25)	<0.001*
Treatment after referral				
- Laparotomy [§]	3 (8.6%)	1 (5.3%)	2 (12.5%)	0.58
- PTC	13 (37.1%)	7 (36.8%)	6 (37.5%)	1
- ERCP	0	0	0	1
- Percutaneous drainage of bile collection	6 (17.1%)	0	6 (37.5%)	0.004
Type of repair				
- Hepaticojejunostomy	26 (74.3%)	17 (89.5%)	9 (56.2%)	0.07
- Hepaticojejunostomy + hepatic resection	4 (11.4%)	1 (5.3%)	3 (18.7%)	
- Double barrel hepaticojejunostomy	2 (5.7%)	0	2 (12.5%)	
- Double barrel hepaticojejunostomy + hepatic resection	1 (2.8%)	0	1 (6.25%)	
- Direct repair + T-tube	1 (2.8%)	0	1 (6.25%)	
- Liver transplantation	1 (2.8%)	1 (5.3%)	0	
Hepatic resection	6 (17.1%)	2 (10.5%)	4 (25%)	0.37
- Right hepatectomy	2 (33.3%)	0	2 (50%)	
- Left hepatectomy	2 (33.3%)	1 (50%)	1 (25%)	
- Right lobectomy	1 (16.7%)	0	1 (25%)	
- Liver transplantation	1 (16.7%)	1 (50%)	0	
Number of biliary anastomoses				
- 0	1 (2.8%)	0	1 (6.25%)	0.01
- 1	30 (85.7%)	19 (100%)	11 (68.7%)	
- 2	4 (11.4%)	0	4 (25%)	
Transanastomotic drain				
- None	10 (28.6%)	7 (36.8%)	3 (18.75%)	0.34
- Transhepatic	20 (57.1%)	10 (52.6%)	10 (62.5%)	
- Transjejunal	4 (11.4%)	2 (10.5%)	2 (12.5%)	
- T-tube	1 (2.8%)	0	1 (6.25%)	

Data are expressed as median (interquartile range) or number (percentage). Fisher's exact test and Mann-Whitney (*) test were used for variables comparison. [§] Patients requiring laparotomy after referral prior to definitive surgical repair. Abbreviations: PTC, percutaneous transhepatic cholangiography; ERCP, endoscopic retrograde cholangiopancreatography.

Table 4. Postoperative and long-term outcome

<i>Postoperative outcome</i>				
	Whole series (n = 35)	Stricture (n = 19)	Fistula (n = 16)	p
Length of stay (days)	14 (10-22)	12 (8-22)	14 (11-23)	0.29*
Grade 1 – 2 complication	15 (42.8%)	10 (52.6%)	5 (31.25%)	0.30
Grade 3 – 4 complication	12 (34.3%)	5 (26.3%)	7 (43.75%)	0.31
Postoperative death	1 (2.8%)	0	1 (6.25%)	0.45
Transhepatic drain complication	9 (25.7%)	5 (26.3%)	4 (25%)	1
- Drain dislocation	3 (33.3%)	3 (15.8%)	0	
- Cholangitis	2 (22.2%)	1 (5.3%)	1 (6.25%)	
- Cholangitis + drain dislocation	1 (11.1%)	0	1 (6.25%)	
- Bile duct obstruction	1 (11.1%)	1 (5.3%)	0	
- Biliary leak	1 (11.1%)	0	1 (6.25%)	
- Subcapsular hematoma	1 (11.1%)	0	1 (6.25%)	
Biliary leak	4 (11.4%)	1 (5.3%)	3 (18.75%)	0.31
Cholangitis	4 (11.4%)	1 (5.3%)	3 (18.75%)	0.31
Bleeding	1 (2.8%)	1 (5.3%)	0	1
Posthepatectomy liver failure	1 (2.8%)	0	1 (6.25%)	0.46
<i>Long-term outcome^s</i>				
	Whole series (n = 32)	Stricture (n = 17)	Fistula (n = 15)	
Anastomotic stricture	7 (21.9%)	4 (23.5%)	3 (20%)	1
Outcome				
- Good	22 (68.7%)	10 (58.8%)	12 (80%)	0.28
- Fair	3 (9.4%)	3 (17.6%)	0	
- Failure	7 (21.9%)	4 (23.5%)	3 (20%)	

Data are expressed as median (interquartile range) or number (percentage). Fisher exact test and Mann-Whitney test (*) were used to compare variables among different groups. Dindo-Clavien classification was applied to postoperative complications. ^s One patient died in the postoperative period and two patients lost to follow-up were excluded from analysis.

Table 5. Results of univariate logistic regression of variables associated with severe (≥ 3) postoperative complications

	OR	2.5%	97.5%	p
Age	1.04	0.001	1.13	0.18
Sex (male)	0.7	0.08	4.26	0.71
Index operation technique:				
- laparoscopic versus converted	0.38	0.04	2.89	0.35
- open versus converted	0.23	0.01	2.26	0.24
Intraoperative injury diagnosis	1.31	0.15	8.22	0.77
Intraoperative repair attempt	2.4	0.27	16.49	0.37
Grade \geq E3 injury	4.44	0.73	36.58	0.11
Grade \geq E4 injury	4.8	0.71	33.81	0.09
Vasculo-biliary injury	1.73	0.07	17.17	0.66
Surgical repair attempt before referral	1.91	0.22	12.62	0.5
ERCP before referral	0.63	0.09	5.29	0.64
PTC before referral	0.62	0.03	4.85	0.69
PTC after referral	0.81	0.1	4.95	0.83
Laparotomy after referral*	14	1.1	347.15	0.04
Percutaneous bile collection drainage	3.12	0.35	22.96	0.26
Delay \geq 6 weeks after injury	0.46	0.05	2.78	0.41
Stricture versus fistula	0.35	0.04	2.11	0.27
Previous cholangitis	1.63	0.26	10.27	0.58
Sepsis at referral	17.33	2.41	176.24	0.007
Hepatic resection	3.12	0.35	22.96	0.26
Anastomosis stenting by transhepatic drain	4.67	0.64	95.37	0.18

Results are expressed as odds ratio and 95% confidence interval. *Laparotomy performed after referral prior to definitive surgical repair. Abbreviations: ERCP, endoscopic retrograde cholangio-pancreatography; PTC, percutaneous transhepatic cholangiography.