INTRODUCTION

Currently, hepatectomy can be carried out safely because of the improvement in surgical techniques and perioperative management.\(^1,2\) Mortality rates after hepatectomy have decreased from 2.6% to 1.6%.\(^1,3\) However, the incidence of bile leakage has been reported to be 3.3%–8.7% and has not changed over the past few decades.\(^1–5\) According to the International Study Group of Liver Surgery (ISGLS), bile leakage after hepatectomy is defined as drainage of fluid with bilirubin level three times greater than the serum level at postoperative day 3 or the need for interventions owing to bilious collection or biliary peritonitis.\(^6\) Postoperative bile leakage is associated with an increased risk of post-hepatectomy liver failure and mortality.\(^7,8\)

Most bile leakage cases are treated with simple drainage. However, some types of bile leakage require interventions, such as endoscopic bile drainage or percutaneous abdominal drainage. Intractable bile leakage is defined as bile leakage that does not improve after a drainage procedure. Bile leakage was classified by Nagano et al into the following four groups: type A, minor leakage from a cut surface; type B, leakage caused by insufficient closure of the bile duct stump; type C, leakage caused by insufficient closure of the bile duct wall at the intestinal anastomosis; and type D, leakage due to intestinal ischemia.

KEYWORDS
anatomical variation, bile leakage, divided bile ducts, hepatectomy, isolated bile duct
the exposed bile duct or hilar bile duct; and type D, leakage from the
distal orifice of the isolated bile duct.4,9 Type D bile leakage is intractable and cannot be treated by simple drainage alone. Patients with Type D bile leakage undergo surgical procedures, such as liver resection or choledochojejunostomy, or non-surgical procedures, such as bile duct ablation with absolute ethanol, transcatheter arterial embolization (TAE), or percutaneous transhepatic portal embolization (PTPE) of the liver segment that produced the bile leak. We summarized the reports of leakage from the isolated bile duct (isolated bile leakage [IBL]), regardless of the size of the independent bile duct, after hepatectomy to establish treatment strategies for IBL.

2 | LITERATURE SEARCH

PubMed (URL: https://www.ncbi.nlm.nih.gov/pubmed) was searched for previous reports on IBL after hepatectomy that were published from 1998 to June 2018. The search was carried out using the terms "bile leakage" and "hepatectomy." Through the literature search, no systematic reviews on IBL were found, and there were 29 studies reporting IBL, including 33 cases of IBL. We focused on the management of IBL. These findings are summarized in Figure 1.

3 | RISK FACTORS FOR IBL

Risk factors for bile leakage have been described in several studies.4-9 IBL was very rare and accounted for 0.1%–1% of all hepatectomy cases in some reports.10-13 Risk factors for IBL have not been reported clearly. Types of liver resection in patients with IBL were various, including 22 cases of major hepatectomy and five cases of minor hepatectomy (Table 1). Bile duct anomalies were reported as a risk factor for IBL.14-15 After right-side major hepatectomy, IBL occurred from the bile duct of segment 1, left segmental bile duct, and remnant right-side liver.10,12,15 Some cases in which Spiegel’s lobe was joined to the right posterior section or the common bile duct were reported.13,15,16 Patrono et al reported a biliary anomaly of a connection of the segment 2 duct to the right bile duct.11 After left-side major hepatectomy, IBL occurred from the posterior bile duct because of the damaged right posterior segment bile duct draining into the left duct.11,12,14 Several types of bile duct anomalies were related to IBL.

4 | PREVENTION OF IBL

It is most important to confirm preoperative biliary tree images and perioperative assessment to prevent IBL.17 Gadolinium-ethoxybenzyl-diethylenetriamine penta-acetic acid (Gd-EOBDTPA)-enhanced magnetic resonance (MR) imaging could be used for preoperative evaluation of bile duct anatomy in addition to conventional information on focal hepatic lesions.18 Moreover, intraoperative cholangiography through the cystic duct before ligation of the bile duct is very important to prevent bile duct injury such as posterior segment bile duct drain into the left duct. In several reports, residual segments after hepatectomy may have caused isolated bile duct leakage.10,17 Anatomical resection with meticulous surgical technique is important to prevent IBL such as that from the posterior bile duct after anterior resection.

5 | DIAGNOSTIC METHOD FOR IBL

It is very important to classify the type of bile leakage because the treatment method for each type differs.9 For the detection of biliary leakage, cross-sectional imaging studies, including ultrasound, computed tomography (CT), and magnetic resonance cholangiography, are used.20,21 Endoscopic retrograde cholangiopancreatography (ERCP),22 drip-infusion cholangiography with computed tomography (DIC-CT),23 and Gd-EOB-DTPA-enhanced MR cholangiography24 are very important for detecting the bile leakage point. Fistulograms are also helpful for determining the type of biliary leakage and the degree to which leakage can be controlled by drainage.9 Direct enhancement of the bile duct by ERCP is needed for the diagnosis of IBL to confirm the absence of a connection to the central bile duct.24 Area of the independent bile duct was confirmed by these images. The liver volume causing the bile leakage was measured by CT after injecting the contrast medium. Gd-EOB-DTPA-enhanced MR cholangiography using delayed-phase images was effective for detecting the presence and location of active bile leaks.25 In two recently published studies investigating the value of 20–30 minutes delayed Gd-EOB-DTPA-enhanced MR cholangiography for the detection of biliary complications after hepatobiliary surgery, both groups reported 100% sensitivity of this technique for the diagnosis of bile leakage.24,26

5.1 | Surgical treatment of IBL

The 11 cases that underwent surgical treatment for IBL are summarized in Table 2. Timing of surgical intervention was based on non-responsiveness to external drainage and/or the persistence of intra-abdominal sepsis.13 Surgical procedures were mostly carried out at several months after the first operation. Only one patient underwent the second operation at an early time point after the first operation.11 Before the surgical treatment, percutaneous drainage, PTPE, and TAE were done to treat the IBL. A planned approach was based on the patient’s general status, volume of future liver remnant and liver functional reserve, type and extent of injury, and volume of the causing IBL.13 A previous report mentioned that the decision for reoperation should be made as early as possible, preferably before the development of severe intra-abdominal sepsis and dense adhesions.8 It was difficult to immediately determine whether the IBL was not cured by non-surgical treatment. Surgical procedures were carried out in seven cases of liver resection of the independent liver parenchyma containing the fistula and in four cases of bilioenteric anastomosis.10-13,15,17 Another patient underwent resection with biliary-enteric anastomosis.10,13 Liver resection was done when the
independent liver parenchyma of the bile leakage was segment 1 or segment 4, and there was only one case in segments 6 and 7.

Bilioenteric anastomosis or fistulojejunostomy for IBL from the major bile duct such as posterior segment after left hemihepatectomy was reported in four cases in three reports. A percutaneous transhepatic drain was positioned into the excluded bile duct before operation, with the principal aim of guiding hilar plate dissection and facilitating the location of the excluded duct. Anastomosis between the jejunum and the fistula was created using the drainage catheter as a guide. Patrono et al reported that hepatico-jejunostomy on the excluded bile duct presented the advantage of sparing unnecessary sacrifice of the liver parenchyma origin of the fistula. When the flow of the bile duct is insufficient, patients undergoing bilioenteric anastomosis may be at risk for severe cholangitis and liver abscess after the operation.

Type of surgical procedure was based on the estimated volume of the liver remnant and the functional reserve of the liver and intraoperative factors, such as adhesions, infection, abscess formation, and anatomical distortions caused by regeneration of the remaining liver and anatomical errors of the first operation.
**TABLE 2** Surgical treatment for isolated bile leakage

| Author          | Reported year | Rate of isolated bile leakage | Diagnosis                                                | First operation   | Independent liver segment | Non-surgical treatment before 2nd operation | Period between 1st and 2nd operations | Second operation | Operating time (min) | Blood loss (mL) | Postoperative hospital stay (d) | Complication                      |
|-----------------|---------------|-------------------------------|----------------------------------------------------------|------------------|---------------------------|-------------------------------------------|--------------------------------------|------------------|-------------------------|----------------|--------------------------|-------------------------------|
| Fukuhisa et al  | 2017          | ND                            | HCC                                                      | Right hepatectomy | S1                        | Percutaneous drainage                     | 48 d                   | Resection of S1      | ND             | ND                       | 15               | No                       |
| Fragulidis et al| 2008          | 3/234 (1%)                    | CCC                                                      | Right extended hepatectomy | S1                        | Percutaneous drainage                     | 6 m                    | Resection of S1      | ND             | ND                       | ND               | Uneventful               |
|                 |               |                               | Hydatid cyst                                             | Resection of segment 5 | Posterior                 | Percutaneous drainage                     | 8 m                    | Resection of S6 and S7 | ND             | ND                       | ND               | Uneventful               |
| Honore et al    | 2009          | 3/2409 (0.1%)                 | Hepatic abscess after laparoscopic cholecystectomy       | Right hepatectomy | Remnant S 5/8              | Percutaneous drainage                     | 18 m                   | Resection of S5/8 and hepaticojejunostomy | 401            | 450                      | 30               | Fistula on the bilio-digestive anastomosis |
|                 |               |                               | HCC                                                      | Right hepatectomy | Remnant S 5/8              | Percutaneous drainage                     | 3 m                    | Resection of S5/8     | 310            | 2020                     | 10               | Uneventful               |
| Patrono et al   | 2014          | –                             | Hepatic injury                                           | Left hepatectomy  | S6/7                      | ENBD, PTPE and direct closure             | 12 m                   | Resection of S6       | 405            | 2300                     | 13               | Uneventful               |
| Hoekstra et al  | 2012          | 1/315 (0.3%)                  | Focal nodular hyperplasia                                | Right hepatectomy | Left segmental bile duct  | Early timing Bilioenteric anastomosis |                       | Bilioenteric anastomosis | ND             | ND                       | ND               | Bile leakage             |
| Sakamoto et al  | 2016          | 2/334 (0.6%)                  | Right anterior sectionectomy                             | Posterior         | Percutaneous drainage and PTPE | Fistulojejunostomy                      |                       |                   | ND             | ND                       | 323              | ND                       |

Abbreviations: CCC, cholangiocellular carcinoma; d, days; ENBD, endoscopic nasobiliary drainage; HCC, hepatocellular carcinoma; LDLT, living-donor liver transplantation; m, months; ND, not described; PTCD, percutaneous transhepatic choledocho-drainage; PTPE, percutaneous transhepatic portal vein embolization; S, segment; TAE, transcatheter arterial embolization.
5.2 Non-surgical treatment of IBL

Non-surgical procedures to manage IBL are bile duct ablation, percutaneous PTPE or TAE of the liver segment that produced the bile leak. Non-surgical cases of IBL are summarized in Table 3.

5.2.1 Endoscopic treatment

Generally, endoscopic drainage to the common bile duct is ineffective for IBL. Mutignani et al reported bridging stent treatment for IBL. A transpapillary stent was inserted into the peritoneal cavity to drain the associated bilious collection, and a second stent was inserted into the bile duct to ensure proper biliary drainage for the rest of the liver. Lee et al reported that fluoroscopy-guided transgastric hepaticoantrostomy was carried out for IBL after left hepatic trissectionectomy, and all external drainage catheters were removed. The rendezvous procedure, which combines endoscopic techniques with percutaneous techniques for the treatment of IBL, was reported in only one study. Biliary continuity was successfully restored in two out of the three patients using the rendezvous procedure. These endoscopic treatments for IBL are minimally invasive procedures and cause little damage to liver function. However, there are only a few reports of endoscopic treatment because it is not widely carried out.

5.2.2 Bile duct ablation therapy

Bile duct ablation therapy for IBL was mentioned in 13 case reports. Ethanol was commonly used for bile duct ablation therapy. Acetic acid was used in one case and N-butyl cyanoacrylate in another. Kyokane et al reported that selective intrahepatic biliary ethanol injection destroyed the biliary epithelium, permeated the parenchyma, induced hepatocyte degeneration, and resulted in compensatory hypertrophy of the non-injective hepatic lobe in an animal study. Bile duct ablation therapy should only be done for IBL with no communication with the biliary tree because ethanol results in irreversible damage to the remaining bile ducts. It is necessary to confirm that the leaking bile ducts do not communicate with the biliary tree by carrying out fistulography and ERCP. To prevent the outer bile duct from being exposed to ethanol, some authors used a balloon occlusion catheter. A previous study reported that ethanol injection into the liver parenchyma by a percutaneous transhepatic approach, instead of into the bile duct, destroyed both the biliary epithelium and liver parenchyma. Most cases of IBL that were treated with ethanol ablation therapy involved less than one segment. The largest area of IBL treated with ethanol ablation was the anterior or posterior segment. Sadakari et al reported that bile duct ablation with ethanol to the posterior segment was ineffective. They carried out PTPE in the posterior portal branch. Shimizu et al treated IBL from the anterior bile duct with 23 attempts of bile duct ablation with ethanol. Sakamoto et al reported that they successfully treated a case with posterior bile duct ablation with ethanol as the treatment process gradually decreased the size of the residual posterior segment. When the liver volume is large, or when the amount of leaked bile is high, IBL may often not be cured by ethanol ablation therapy.

5.2.3 Percutaneous transhepatic portal vein embolization

Percutaneous transhepatic portal vein embolization induces atrophy of hepatocytes and decreases the amount of bile duct juice. PTPE was reported in five cases; of these, three cases were successfully treated, whereas the other two cases underwent operation without achieving successful treatment of the bile leakage. PTPE was suitable for IBL from one or more liver segments. PTPE with fibrin glue or ethanol was reported to treat isolated bile duct leakage from the posterior segment. PTPE was used to decrease the amount of bile leakage from a large area of the isolated bile duct when ethanol injection was ineffective. However, some reports have shown that bile leakage was not stopped after PTPE and needed to be treated with surgery. In a previous study, treatment with ethanol injection to the fistula before PTPE failed because of the large amount of bile leakage. Combination therapy with bile duct ablation after PTPE was reported to be useful. PTPE should be done only when patients are in good condition, with sufficient remnant liver function to avoid liver failure.

5.2.4 Transcatheter arterial embolization

Treatment for IBL with TAE was mentioned in only one successfully treated case and in an unsuccessfully treated case. TAE in the anterior segmental artery was carried out to stop the production of bile in the injured part of the anterior segment after simple drainage and ethanol injection treatment failed. The TAE treatment was effective, and the patient was discharged 15 days after TAE. In contrast, Honore et al reported a case in which liver resection was carried out as the definitive treatment because TAE 1 month after PTPE failed to stop bile leakage. Patients with a liver abscess after TAE are at high risk of developing bile duct infection because of liver parenchyma necrosis after TAE. When bile leakage was detected after hepatectomy, almost all cases had abdominal infections. TAE may be adaptable only when the bile leakage area is very small; otherwise, infectious complications may arise.

5.2.5 Fibrin glue

Tanaka et al reported two cases of fibrin glue treatment for IBL. After confirmation that the fistula was free of infection and that
| Author | Reported year | Rate of isolated bile leakage | Diagnosis | First operation | Independent liver segment | Treatment method | Outcome |
|--------|--------------|------------------------------|-----------|----------------|--------------------------|-----------------|---------|
| Kyokane et al | 2002 | ND | Gallbladder carcinoma | Right hepatectomy | S2 | Ethanol injection |
| Sakaguchi et al | 2011 | - | Liver metastasis from GIST | Extended left hepatectomy | S5 + 1 | Ethanol injection |
| Shimizu et al | 2006 | - | HCC | Right posterior sectionectomy | Anterior bile duct | Ethanol injection | Alive |
| Matsumoto et al | 2002 | - | HCC | Right hepatectomy | Caudate lobe | Ethanol injection | Alive |
| Nakagawa et al | 2017 | 1/631 (0.2%) | - | - | - | Ethanol injection |
| Kusano et al | 2003 | - | Liver abscess with intrahepatic stones | Left hepatectomy | S4 | Ethanol injection | Alive |
| Yamashita et al | 2001 | 3/781 (0.4%) | - | - | - | Ethanol injection with balloon catheter occlusion |
| Sakamoto et al | 2016 | 2/334 (0.6%) | - | Right anterior sectionectomy | Posterior | Ethanol injection | Alive |
| Park et al | 2005 | - | Biliary cystadenocarcinoma | Left extended hepatectomy | Posterior | Acetic acid | Alive |
| Kim et al | 2012 | - | HCC | Central bisectionectomy | S8 | N-butyl cyanoacrylate | Alive |
| Kataoka et al | 2011 | - | HCC | S5 segmentectomy | - | Ethanol injection into the liver parenchyma | Alive |
| Kubo et al | 2018 | - | HCC | Partial hepatectomy of S4/5 | S5 + 8 | Combination therapy with ethanol injection and PTPE | Alive |
| Sadakari et al | 2008 | - | Liver metastasis from rectal cancer | Central bisectionectomy | Posterior | PTPE | Alive |
| Hai et al | 2012 | - | HCC | Right anterior sectionectomy | Posterior | PTPE | Alive |
| Ikeda et al | 2015 | - | Gallbladder cancer | Extended cholecystectomy | S5 | TAE |
| Tanaka et al | 2002 | 2/363 (0.6%) | CCC | Left hepatectomy | Caudate branch | Fibrin glue | Alive |
| Mutignani et al | 2017 | - | Cholangiocarcinoma | Right hepatectomy | Left lobe branch | Bridging stent |
| Lee et al | 2015 | - | HCC | Left trisectionectomy | Posterior | Fluoroscopy-guided transcatheter arterial embolization |

Abbreviations: CCC, cholangiocellular carcinoma; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; PTPE, percutaneous transhepatic portal vein embolization; TAE, transcatheter arterial embolization.
the volume was less than 50 mL/day, the fistula was completely sealed with a mixture of fibrin glue and iodized oil (Lipiodol; Kodama Pharmaceutical, Tokyo, Japan). The fistula was immediately closed without any major complications. It was considered that patients were required to have a low volume of bile leakage for treatment with fibrin glue. Treatment with fibrin glue was reported in only two cases, and the treatment effect was limited.

6 | TREATMENT STRATEGY FOR IBL

We summarized the treatment strategy for IBL used in previous reports (Figure 2). IBL was confirmed by the absence of continuity. When the bile duct was connected, drainage and biliary stenting were carried out to control bile leakage. However, how do we choose the optimal treatment method for cases with unconnected bile duct? The most effective and minimally invasive treatment method should be chosen depending on the liver volume causing the bile leakage and liver function. When the liver volume causing bile leakage, as assessed using DIC-CT, fistulograms, and ERCP, is less than one segment, non-surgical treatment with bile duct ablation should be initially considered. Fibrin glue or TAE should be restricted for cases with IBL from a very small region. Some cases reported successful treatment of IBL by liver resection.8,10,13,15

When the liver volume causing the bile leakage is one or more segments, fewer cases are amenable to treatment with bile duct ablation or combination treatment with bile duct ablation and PTPE.23 If the non-surgical method is ineffective, surgical procedures, such as bilioenteric anastomosis, fistulojejunostomy, or liver resection should be carried out. However, adhesions as a result of inflammation make these operations difficult, especially in cases with cirrhosis. Therefore, the operation should be done by experienced surgeons.

One limitation of the present study is that since we only summarized the reports that were available on PubMed, almost all these cases were successfully treated. Thus, there may be publication bias against cases wherein no treatment modality was successful. Further study will be needed to confirm the optimal strategy for the treatment of IBL.
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