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# Ductular Proliferation and Fibrosis as Predictors of Poor Outcome in Patients with Bile Duct Injury

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**Keywords:**

Bile duct injury; Liver fibrosis

## 1. Abstract

### 1.1. Aims

To determine whether the degree of histologic damage to the liver after cholecystectomy bile duct injury (BDI) is correlated with a patient's clinical course.

### 1.2. Methods

A prospective cohort study was conducted at a tertiary level university hospital. Two hundred thirty-seven patients with BDI repair with a minimum follow-up of one year were included. Liver biopsies were performed for histopathology analysis. Histopathologic findings were correlated with McDonald's grading system via univariate and multivariate analyses.

### 1.3. Results

A total of 207 patients (66.5%) were female, with a mean age of 44 +/- 2 years. Histopathologic findings were classified as inflammation, cholestasis, ductular proliferation, or fibrosis. Univariate analysis revealed that ductular proliferation and fibrosis were correlated with BDI progression time and vascular damage (p=0.001). Fibrosis was correlated with the persistence of a McDonald CD grade (p=0.001). Multivariate analysis revealed that ductular proliferation (HR .444, CI 95% .233-848; p=0.014) and fibrosis (HR.280, CI 95% .125-.635; p=0.002) correlated with the duration of BDI (HR.996, CI 95% .993-1.000; p=0.023).

### 1.3. Conclusion

Once BDI repair was performed, clinical and biochemical improvements were observed. Changes in ductular proliferation and fibrosis are correlated with poor clinical evolution. A longer evolution of the lesion correlated with liver fibrosis.

## 2. Introduction

Bile duct injury (BDI) is a rare but very serious event associated with cholecystectomy (CCT). Since the introduction of laparoscopic cholecystectomy, the incidence of iatrogenic BDI has increased from 0.7% to 1.5%, [1-3] however, currently the incidence is estimated to range from 0.4% to 0.6%, and similarity is even beginning to be observed with the incidence of open surgery [4]. This condition can cause a significant deterioration in the health of the affected person and high intra- and extrahospital costs.[5-8] BDI can occur due to disruption of continuity by sectioning or acute obstruction (ligation or stapling) of the bile duct, or by stenosis (the most common late manifestation of iatrogenic injury to the biliary tract), from the sixth week or up to fifteen years after the injury occurs, in the event that it is associated with vascular injury or burn , which is underdiagnosed and evolves slowly even after repair [9]. The time at which the bile duct remains obstructed, partially or completely, and the presence or absence of cholangitis, play important roles in hepatic histological changes (inflammation,

cholestasis, ductular proliferation and fibrosis), which can be accompanied by portal hypertension, subclinical, and clinical manifestations of portal hypertension and liver failure. Patients with bile duct injury have a certain degree of histological liver injury, reaching up to 18% of them with fibrosis and/or secondary biliary cirrhosis, which represents the potential complication of postcholecystectomy bile duct stenosis, with the consequent development of liver failure [10-12]. Even after biliodigestive tract reconstruction. The performance of a liver biopsy at the time of repair is crucial for the recognition of established histological alterations, as is follow-up in the postoperative period and early identification of anomalies, which may impact the selection of diagnostic and therapeutic measures.

The objective of the present study was to use liver biopsy to identify the degree of histological lesion that patients had at the time of biliodigestive reconstruction due to postcholecystectomy bile duct injury and its relationship with clinical evolution.

## 3. Materials and Methods

This was a prospective cohort study of patients who were admitted to the Gastrointestinal Surgery Service at a university hospital and were diagnosed with postcholecystectomy bile duct injury between 1997 and 2020. Patients over 18 years of age with postcholecystectomy bile duct injury were included. Patients with a history of malignant neoplasia of the bile duct or at the bilipancreatic junction, sclerosing cholangitis or primary liver cirrhosis of any origin associated with bile duct injury, and patients with some type of biliodigestive reconstruction due to bile duct injury prior to admission to our service were not included (Figure 1). The service's policy to carry out reconstructive surgery is early, but being a reference hospital, many patients are sent late, even more than six weeks or months, so the repair is performed if the clinical conditions and the patient's nutritional status allow it at the time of admission. For each patient, sex, age previous pathological history, initial diagnosis, type of surgical approach and whether it was urgent or scheduled were recorded; Liver function tests were performed before and after reconstructive surgery (total bilirubin, glutamic pyruvic transaminase, alkaline phosphatase and gamma glutamyl transpeptidase); Hepatobiliary scintigraphy was requested before and after reconstructive surgery. In all cases according to availability, computed tomography angiography and or biliary MRI were performed. A trans-surgical liver biopsy was obtained, which was classified according to the histological activity index: inflammation, cholestasis, ductular proliferation and fibrosis. The liver biopsy was obtained at the time of the biliodigestive reconstruction with a wedge-shaped incision on the liver surface of approximately 1cm3 and a Trucut-type needle from the liver areas previously identified by ultrasound as having greater echogenicity and were sent to the Anatomic Pathological Service where they were fixed with formalin, and embedded in paraffin and the sections were stained with hematoxylin-eosin and Masson's trichrome. Histological characteristics (inflammation, cholestasis, ductular proliferation, and fibrosis) were graded independently by two pathologists via a previously validated scale [13,14]. The grades used were as follows: inflammation (0=absent, 1=mild, 2=moderate and 3= severe); cholestasis (0= absent, 1= mild, 2= moderate and 3= severe); and ductular proliferation (0=absent-mild, 1= moderate and 2= severe) and fibrosis (0= absent, 1= portal and periportal fibrosis, 2= numerous septa and 3= cirrhosis). All patients underwent reconstruction via the Hepp-Couinaud hepatic-jejunum anastomosis technique.

Liver function tests were evaluated during follow-up at 3, 6, and 12 months postoperatively. The following parameters were considered abnormal: total bilirubin (> 1 mg/dL), alanine amino transferase (ALT> 41 U/L), alkaline phosphatase (FA> 129 U/L) and gamma glutamyl transpeptidase (GGT> 480 U/L).

During follow-up, hepatobiliary scintigraphy was performed at 6 and 12 months postoperatively. To identify the morphology of the liver and intra- and/or extrahepatic bile duct, a radiopharmaceutical (Tecnesium 99) was injected, late images were obtained at 4 and 24 hours, and the situation, morphology and size of the liver were observed; The extraction of the radiopharmaceutical, the distribution pattern and its clearance through the bile ducts were assessed during the first 60 minutes of the sequential phase. If the extraction of the radiopharmaceutical and its distribution pattern were altered or had a clearance time greater than 60 minutes, it was considered abnormal.

The degree of obstruction (greater or less than 80% of the residual diameter of the bile duct), type of injury (according to Strasberg's classification) [15]. Whether there was vascular injury (present or absent), mechanism of injury (section, ligation with suture or staple or burn by electrocautery) and time of evolution of the injury, from the time the injury occurred until it was repaired (in days), were also evaluated.

To evaluate the outcome, the McDonald classification was used [16]. Which measures the functional status of the liver, at 3, 6 and 12 months after reconstructive surgery. This classification consists of the following: A, normal biochemical liver function tests and asymptomatic patient; grade B, moderate alteration of biochemical liver function tests and asymptomatic patient; grade C, abnormal biochemical liver function tests and patient with signs of cholangitis; and grade D, the patient requires some type of endoscopic and/or surgical therapy.

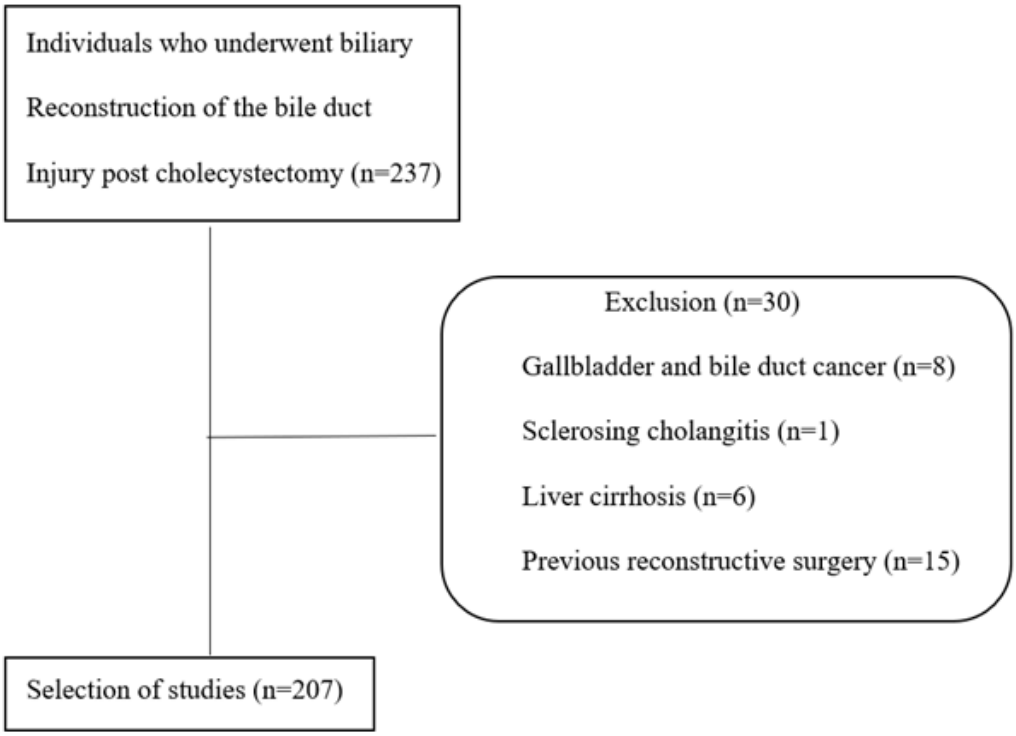


**Figure 1:** Flowchart of the Study Population.

## 4. Data Management and Statistical Analysis

To calculate the sample size, the Freeman formula was used: 10*(k+1), requiring a total of 160 patients when the inflammation-cholestasis group was compared with the ductular proliferation and fibrosis groups, considering a total of 7 variables.

Descriptive analysis was carried out with frequency tables for categorical variables and measures of central tendency and dispersion for numerical variables. The normality of the data was assessed via the Shapiro- Wilk test. To compare proportions, the chi square test or Pearson's exact test was used. To compareordinal or continuous variables between two independent groups, the Mann- Whitney U test was used. For continuous variables between 3 or more groups, the Kruskal- Wallis test was used. To analyze the correlation between continuous variables and the evolution of continuous or ordinal variables, multiple logistic regression analysis was performed.

To calculate the probability of poor outcomes occurring at different times, the Kaplan- Meier analysis was used. To calculate the possibility of poor outcomes according to the histopathological findings, Cox proportional hazards analysis adjusted for the effects of variables such as sex, age, time of evolution, degree of obstruction, degree of vascular injury and mechanism of injury was used.

If a patient presented partial follow-up (due to not attending the appointment or due to failure to perform control studies), it was considered censored data (loss to follow-up).

The IBM SPSS version 21 program was used for statistical analysis. Statistical significance was considered when the value of $p<0.05$.

This work was registered and accepted by the local Ethics and Research Committee of the HE CMN SXXI with folio R2016-3601-16.

## 5. Results

Two hundred and seven patients were included in the present study, sixty-five percent were female, and the average age was 44+- 2 years. Table 1 shows the histopathological findings and their relationships with the baseline characteristics.

The time of evolution was significant for the development of greater severity of histological damage from 61 days of biliary obstruction or damage.

The characteristics of the bile duct lesions and their correlations with the histopathological groups are described in Table 2. Vascular damage was found in 62% of patients with fibrosis (grades 1,2 and 3), whereas it was detected in only 2.2% of those with inflammation (grade 3) (p=0.001). The most severe histological damage, ductular proliferation (grade 2) and fibrosis (grades 1, 2 and 3) was caused by ligation by suture, clipping or burn, in 29.5% and 30.5% of the patients, respectively. This mechanism of injury was referred to the sending note from another hospital or by identification during reconstruction surgery.

When histological damage was correlated with clinical evolution at 3, 6 and 12 months (Table 3), 97.6% of patients with ductular proliferation (grade 2), at 12 months, were registered with McDonald B and 2.4% were registered with McDonald A. In the fibrosis group, 100% of the patients had McDonald C-D at 3 months,70% at 6 months and only 15.8% (grade 3) at 12 months.

When the findings of the hepatobiliary scintigraphy (irregular uptake and radiopharmaceutical elimination time > 60 minutes) were correlated with the type of histological lesion at admission, and at 6 and 12 months (Table 4), in the ductular proliferation group, the irregular uptake rate was 7.9% at 12 months and the elimination time at 12 months persisted for a prolonged duration of 5.3% meanwhile in the fibrosis the irregular uptake rate was 69.4%with an elimination time greater than 60 minutes in 16.7% at 12 months.

Upon admission, all patients presented with clinical and biochemical alterations in liver function.

To calculate the possibility of poor outcomes occurring at different times, the Kaplan- Meier method was used. After bilio-digestive reconstruction, none of the patients in the inflammation group presented alterations from 6 months onward. In the cholestasis group, from 6 months onward only 2% of them were affected. In the ductular proliferation group, at 6 months 20% and at 12 months 2% of the patients presented persistent clinical and biochemical alterations, and in the fibrosis group, at 3, 6, and 12 months, 88%, 50% and 18% of the patients presented persistent alterations, respectively (Figure 2).

Cox proportional hazards analysis to predict the outcome of liver clinical and biochemical dysfunction, at admission and after bilio-digestive tract reconstruction in the cholestasis, ductular proliferation and fibrosis groups, is presented in Table 5. The inflammation group adjusted by age, sex and potential confusion variables (obstruction and lesion degree, vascular lesion, mechanism of lesion and time of evolution) was used as a reference. In terms of the degree of histological lesion, ductular proliferation ($p < 0.014$) and fibrosis ($p < 0.002$) as well as time of evolution ($p < 0.023$), were statistically significant predictors of poor outcomes.

Fourteen patients (6.7%) were excluded because they missed the year appointment; 3 were in the inflammation group, 5 were in the cholestasis group, 4 were in the ductular proliferation group and 2 were in the fibrosis group.

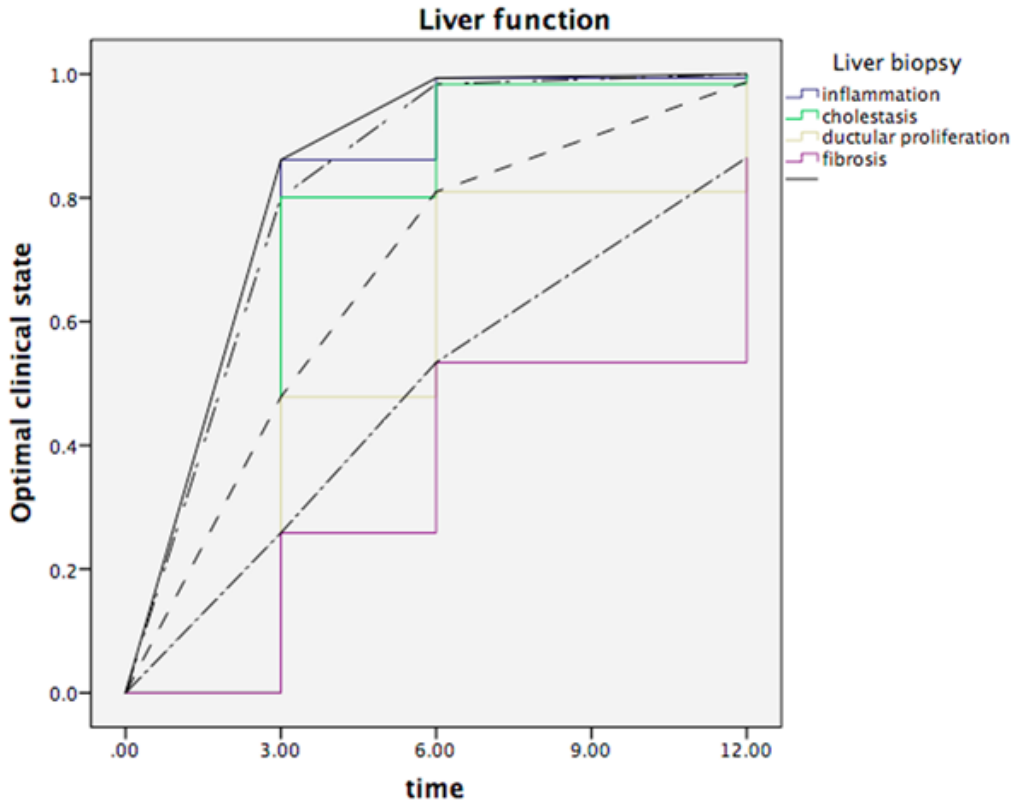


**Figure 2:** The Kaplan- Meier variable-interval method was used. Evolution of the optimal clinical state.

**Table 1:** Demographic Aspects.

| | | INFLAMMATION | CHOLESTASIS | DUCTULAR PROLIFERATION | FIBROSIS | P* |
|---|---|---|---|---|---|---|
| | N | 45 | 77 | 45 | 40 | |
| Age | | 43(25-76) | 46(23-76) | 42(20-76) | 43(21-79) | 0.064 |
| Gender | | | | | | |
| Female | 155 | 37(82.2%) | 60(79.2%) | 32(71.1%) | 26(65%) | |
| Male | 52 | 8(17.7%) | 17(21.8%) | 13(28.9%) | 14(35%) | 0.32 |
| Diagnosis | | | | | | |
| Cholecystitis | 166 | 33(73.3%) | 66(85.7%) | 37(82.2%) | 30(75%) | |
| Hydrocholecysto | 21 | 7(15.5%) | 7(10.3%) | 3(6.6%) | 4(10%) | |
| Pyocholecysto | 20 | 5(11.1%) | 4(5.1%) | 5(11.1%) | 6(15%) | 0.478 |
| Type of surgery | | | | | | |
| Open | 89 | 16(35.5%) | 27(35%) | 26(57.7%) | 20(50%) | |
| Laparoscopic | 118 | 29(64.5%) | 50(65%) | 19(42.3%) | 20(50%) | 0.039 |
| Program | | | | | | |
| Urgent | 79 | 23(51.1%) | 27(35) | 17(37.7%) | 12(30%) | |
| By schedule | 128 | 22(48.9%) | 50(65%) | 28(62.3%) | 28(70%) | 0.154 |
| Bismuth** | | | | | | |
| I | 21 | 8(17.7%) | 9(11.6%) | 4(8.8%) | - | |
| II | 93 | 13(28.8%) | 36(46.7%) | 22(48.8%) | 22(55%) | |
| III | 82 | 21(46.6) | 28(36.3%) | 15(33.3%) | 18(45%) | |
| IV | 11 | 3(6.6%) | 4(5.1%) | 4(8.8%) | - | 0.084 |
| Obstruction/Injury-time | | | | | | |
| <14 days | 49 | 27(60%) | 18(23.3%) | 4(8.8%) | - | |
| 15-60 days | 63 | 17(37.7%) | 41(53.2%) | 5(8.8%) | - | |
| 61-120 days | 14 | 1(2.3%) | 8(10.3%) | 3(6.6%) | 2(5%) | |
| 121-250 days | 68 | - | 10(12.9%) | 29(64.4%) | 29(72.5%) | |
| >250 days | 13 | - | - | 4(8.8%) | 9(22.5%) | 0.001 |
| Comorbidities | | | | | | |
| SAH*** | 56 | 13(2 3.2%) | 28(50%) | 8(14.2%) | 7(12.5%) | 0.08 |
| DM*** | 28 | 4(14.2%) | 17(60.7%) | 6(21.4%) | 1(3.5%) | 0.024 |
| Obesity | 27 | 8(29.6%) | 13(48.1%) | 4(14.8%) | 2(7.4%) | 0.201 |
| COPD*** | 12 | 3(29.6%) | 4(33.3%) | 4(33.3%) | 1(8.3%) | 0.646 |
| Other | 12 | 3(17.6%) | 8(47%) | 3(17.6%) | 3(17.6%) | 0.614 |

*p value: for age we used Student´s t-test and for the remaining variables we used.

The chi-square test.

**According to Strasberg's classification, 100% of type E corresponds to those classified in Bismuth.

***SAH=systemic arterial hypertension, DM= diabetes mellitus, COPD= chronic obstructive pulmonary disease.

**Table 2:** Characteristics of Bile Duct Injury and Histological Damage.

| | | INFLAMMATION | CHOLESTASIS | DUCTULAR PROLIFERATION | FIBROSIS | P* |
|---|---|---|---|---|---|---|
| FACTOR | N | 45 | 77 | 45 | 40 | |
| | | | | | | |
| Strasberg´s classification | | | | | | |
| $E_1$-$E_2$ | 117 | 22(48.8%) | 47(61%) | 26(57.7%) | 22(55%) | |
| $E_3$ | 90 | 23(51.2%) | 30(39%) | 19(42.3%) | 18(45%) | .673 |
| | | | | | | |
| Obstruction degree | | | | | | |
| <80% | 205 | 44(97.7%) | 76(98.7%) | 45(100%) | 40(100%) | |
| >80% | 2 | 1(2.3%) | 1(1.3%) | - | . | .551 |
| | | | | | | |
| Vascular injury | 46 | 1(2.2%) | 7(9%) | 13(16.8%) | 25(62.5%) | .001 |
| | | | | | | |
| Injury Mechanism | | | | | | |
| Cute-off | 76 | 39(86.6%) | 31(40.2%) | 6(13.3%) | - | |
| Ligation with suture | 59 | 4(6.8%) | 18(30.5%) | 18(30.5%) | 19(32.2%) | |
| Ligation with staple | 48 | 2(4.4%) | 24(31.1%) | 13(29%) | 9(22.5%) | |
| Burn (diathermy) | 24 | - | 4(16.6%) | 8(33.3%) | 12(50%) | .001 |

*Pearson's chi-square test.

**Table 3**: Correlation of Histological Damage with the Grading System.

| | McDonald 3 months | | | | McDonald 6 months | | | | McDonald 12 months | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Histological injury | N | A | B | CD** | N | A | B | CD** | N | A | B | CD** |
| | | | | | | | | | | | | |
| Inflammation | 45 (100) | 8 (17.8) | 37 (82.2) | 0 | 45 (100) | 39 (86.7) | 6 (13.3) | 0 | 42 (100) | 42 (100) | 0 | 0 |
| | | | | | | | | | | | | |
| Cholestasis | 77 (100) | 0 | 74 (96.1) | 3 (3.9) | 73 (100) | 17 (23.3) | 56 (76.7) | 0 | 72 (100) | 60 (83.3) | 12 (16.7) | 0 |
| | | | | | | | | | | | | |
| Ductular proliferation | 45 (100) | 0 | 12 (26.7) | 33 (73.3) | 45 (100) | 0 | 37 (82.2) | 8 (17.8) | 41 (100) | 1 (2.4) | 40 (97.6) | 0 |
| | | | | | | | | | | | | |
| Fibrosis | 40 (100) | 0 | 0 | 40 (100) | 40 (100) | 0 | 12 (30) | 28 (70) | 38 (100) | 0 | 32 (84.2) | 6 (15.8) |
| | | | | | | | | | | | | |
| P* | | .001 | | | | .001 | | | | .001 | | |

* Pearson's chi-square test

** Both grades of severity were unified because there were only 3 cases of D.

McDonald A=biochemical tests for normal liver function and asymptomatic patients

McDonald B=moderate of alteration of biochemical tests for liver function and asymptomatic patients

McDonald C=biochemical tests for abnormal liver function and clinical signs of cholangitis

McDonald D=patient requires endoscopic and/or surgical therapy

N=Starting number of patients (%)

**Table 4:** Correlation Between Hepatobiliary Isotope Scanning findings and Histological Damage.

| | **Uptake** | | | **Clearance Time** | | |
|---|---|---|---|---|---|---|
| | **Admission** | **6 months** | **12 months** | **Admission** | **6 months** | **12 months** |
| **Histological Injury** | Irregular | Irregular | Irregular | >60 Minutes | >60 Minutes | >60 Minutes |
| **Inflammation** | 4/45 (8.9) | 1/45 (2.2) | 2/45 (4.9) | 1/45 (2.2) | 0 | 0 |
| **Cholestasis** | 21/77 (27.3) | 5/72 (6.9) | 3/68 (4.9) | 54/77 (70.1) | 3/72 (4.2) | 0 |
| **Ductular Proliferation** | 41/45 (91.1) | 21/45 (46.7) | 3/38 (7.9) | 45/45 (100) | 13/45 (28.9) | 2/38 (5.3) |
| **Fibrosis** | 38/40 (95) | 34/40 (85) | 25/36 (69.4) | 40/40 (100) | 24/40 (60) | 6/36 (16.7) |
| | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 | 0.001 |

*Pearson's chi-square test (expressed as percentages).

**Table 5:** Cox regression model results.

| | **B** | **Wald** | **Sig** | **Exp (B)** | **Inferior** | **Superior** |
|---|---|---|---|---|---|---|
| Cholestasis | 0.146 | 0.459 | 0.498 | 0.864 | 0.567 | 1.318 |
| Ductular | 0.811 | 6.054 | 0.014 | 0.444 | 0.233 | 0.848 |
| **Proliferation** | | | | | | |
| Fibrosis | 1.272 | 9.3 | 0.002 | 0.28 | 0.124 | 0.635 |
| Age | 0.06 | 0.926 | 0.336 | 0.994 | 0.982 | 1.006 |
| Gender | 0.153 | 0.607 | 0.436 | 1.165 | 0.793 | 1.711 |
| **Obstruction** | | | | | | |
| Degree | 0.315 | 0.25 | 0.617 | 0.73 | 0.212 | 2.508 |
| **Strasberg´s** | | | | | | |
| Classification | 0.022 | 0.001 | 0.972 | 0.979 | 0.29 | 3.307 |
| Vascular injury | 0.234 | 0.882 | 0.348 | 0.792 | 0.486 | 1.289 |
| **Injury** | | | | | | |
| Mechanism | 0.123 | 0.129 | 0.719 | 1.13 | 0.58 | 2.205 |
| **Obstruction/** | | | | | | |
| Injury-time | 0.004 | 5.173 | 0.023 | 0.996 | 0.993 | 1 |

## 6. Discussion

We identified patients with bile duct injury and a longer time of evolution, that is, from the moment of the lesion up to biliary repair, more than 60 days, related to lesion mechanisms such as obstruction or diathermy associated with vascular lesions, resulting in more severe histological injury and consequently a poor clinical evolution. Several factors could increase the risk of unsuccessful clinical evolution after surgical repair of bile duct injury such as the location of the lesion, complexity of the lesion, presence of peritonitis, sepsis or local inflammation, vascular damage association or previous repair attempts [ 17,18]. Some morbidities, such as stenosis or secondary biliary cirrhosis, which can lead to long-term disability, can combine with such injury and become late complications after biliary reconstruction [19]. The conventional approach for type E injuries includes controlling sepsis and establishing a controlled biliary fistula, and a definite repair takes more than 6 weeks or even months, depending on the clinical status of the patient. Despite this conventional practice, recent studies point to early bile duct injury repair in a selected group of patients. The result of this early approach is similar to that of the late approach in a steady-state patient in whom abdominal sepsis and vascular injury can be excluded and even more so when surgery is performed by a hepatobiliary specialist. The exact timing of repair to call it early, has not been defined at all, but it is suggested during the first 6 weeks [20,21]. Importantly, the longer the duration of unresolved biliary tract injury, the greater the degree of histological injury in the liver, such as ductular proliferation and fibrosis. Notably patients with diabetes mellitus, compared with those with other comorbidities, had statistically significant differences, for which we did not find any relationship or pathophysiological explanation.

It has been demonstrated that biliary obstruction associated with vascular injury leads to the development of secondary sclerosing cholangitis; in addition, when such obstruction is wide, it obstructs secondary biliary branches which allows portal fibrosis development and consequently, the beginning of a secondary biliary cir-

rhosis [10,22,23,24]. Sikora [12] revealed two important factors related to severe fibrosis and secondary biliary cirrhosis: extended time with injury upon repair and portal hypertension. Addiotionally, in the period 20 weeks after injury, hepatic fibrosis data appear, and injury repair should be performed as soon as possible to avoid irreversible damage. The fact that the clipping or ligation of biliary ducts during cholecystectomy contributes to depriving the tissue, hypoxia and/or necrosis, and consequences of vascular damage are also serious, as this lesion is associated with a decrease in tissue oxygenation as well as a dramatic increase in cholangiocyte proliferation, up to 30% of the total hepatic cell population, compared with the normal 2%, resulting in the secretion of angiogenic factors from cholangiocytes, adaptive proliferation of the vascular supply, the secretion of vascular epithelial growth factor (VEGF) with changes in the peribiliary plexus and the proliferation of biliary ducts [25]. Among our patients with vascular lesions associated with bile duct injury (22%) identified before reconstructive surgery via diagnostic methods, more than 80% developed ductular proliferation and fibrosis confirming that bile duct injury and vascular injury are associated with poor oxygenation and ductular reactions. In the literature, good results of surgical reconstruction of the bile duct are based on anastomotic permeability, in such a way that its dysfunction is translated to clinical manifestations and changes in liver function tests [26,27]. Therefore, two authors Terblanche [28] and McDonald [16] have proposed very similar classifications to assess long term results, and they are widely used to rate patients during follow-up. In the present study, in the ductular proliferation group, 100% of patients with McDonald B and CD at admission, presented good clinical outcomes 12 months later, together with a slight increase in liver enzymes and were asymptomatic. All patients with fibrosis and McDonald CD when admitted, achieved an outcome toward B, twelve months later and, only 16% of them presented with cholangitis. This fact becomes important as despite the severe histological damage identified with clinical and biochemical relevance during biopsy in reconstructive surgery, its status could be better within time, once the obstruction has been released with reconstruction. Importantly, bilirubin depletion depends on primary liver excretion, thus, the decrease in serum bilirubin after the resolution of biliary obstruction mostly depends on the uptake and transport mechanisms of hepatocytes, as well as the permeability of bilioenteric anastomosis. However, serum bilirubin clearance could change if there is significant cholestasis. Similarly, the clearance of alkaline phosphatase after the resolution of biliary obstruction could be modified with fibrosis [29-31]. Negi et al. [32]. Reported that basal values of liver function tests and the degree of fibrosis are independent predictors of abnormal recovery of biochemical test patterns ($p = 0.001$). Fialkowsky et al. [33]. Advised not to use laboratory tests as the only evidence, because only a bilioenteric derivation could induce changes and increase liver function tests due to bilioenteric flow (conditioning the decrease in glucuronic transferase enzyme). Serum changes in liver function tests could prevail for more than 5 years after bile duct reconstruction. Sanchez-Morales et al. [34]. Reported that an increase in alkaline phosphatase (above 323 mg/dL) after the fourth operation week was a predictor of long-term anastomotic dysfunction. Sikora et al. [12]. Reported that the clinical manifestations and biochemical changes presented by patients with functional McDonald´s scale A, B or even C, scores were related to biliary damage associated with secondary biliary cirrhosis more than to anastomosis permeability problems, such that the biochemical changes detected reveal show liver dysfunction more than anastomosis problems. Their study suggested that liver status reported via biopsy is a key factor in clinical evolution and that patients with fibrosis and/or secondary biliary cirrhosis might experience clinical and biochemical changes in the presence of permeable anastomosis.

Biliary scintigraphy allows identification of the bile uptake and excretion ability, of the liver and bile ducts, uses a radiopharmaceutical at a specific time [12,35] and is suitable for identifying hepatocellular damage, biliary kinetics and anastomotic permeability in patients with biliary reconstruction. In our study, most of the patients with ductular proliferation increased radiopharmaceutical intake after repair, unlike the fibrosis group in which a poor intake was observed in approximately 25% of patients after 12 months of admission. With respect to radiopharmaceutical depletion, once derivative surgery was performed, and after 12 months, few patients with ductular proliferation and almost 16% of fibrosis patients continued with delays greater than 60 minutes in radiopharmaceutical depletion, matching the physiological depletion mechanisms already described and found to be changed when an obstructive process has occurred, with a consequent bile histological injury.

In addition, studying the possibility of biochemical or clinical changes or even, any other kind of intervention over time, the results obtained suggest that low histological damage, such as inflammation, cholestasis, and some cases of ductular proliferation would continue with less than 10% of clinical and biochemical changes compared with admission, unlike histological degree fibrosis cases in which abnormal evolution persisted in approximately 18% to 20% of patients. Thus, with a greater histological bile injury, there is a greater possibility of continuing with clinical and biochemical dysfunction within a 12-month period.

With respect to the effect of performing biliary reconstruction and liver biopsy on an unsuccessful outcome, the histological degrees of ductular proliferation, fibrosis and time of evolution were significant compared with those of inflammation and cholestasis when adjusted for sex, age, and potential confounding variables. This model indicates that fibrosis and time of evolution are the main risk factors.

The limitation of the present study is related to the maximum time needed for the clinical and biochemical evaluation of the patients. Information obtained with a longer follow-up time might allow a better assessment of the results of the different correlations. On the other hand, without a new liver biopsy during follow-up, the interpretation of comparative results with the initial biopsy, is restricted. With the advent of new techniques in radiological studies such as magnetic resonance elastography, it can be used to monitor patients with ductal proliferation and fibrosis and does not require a new liver biopsy, which will be the subject of future research [36-38].

## 7. Conclusion

Recognition of liver histological changes such as ductular proliferation and fibrosis, through a biopsy during biliary reconstruction, would allow a correct assessment and interpretation of the clinical status and biochemical studies in patients during follow-up. Those with clinical, histological, and biochemical alterations at the time of biliary reconstruction could continue with such changes during follow-up and even, show unsuccessful clinical evolution depending on the degree of histological lesion.

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