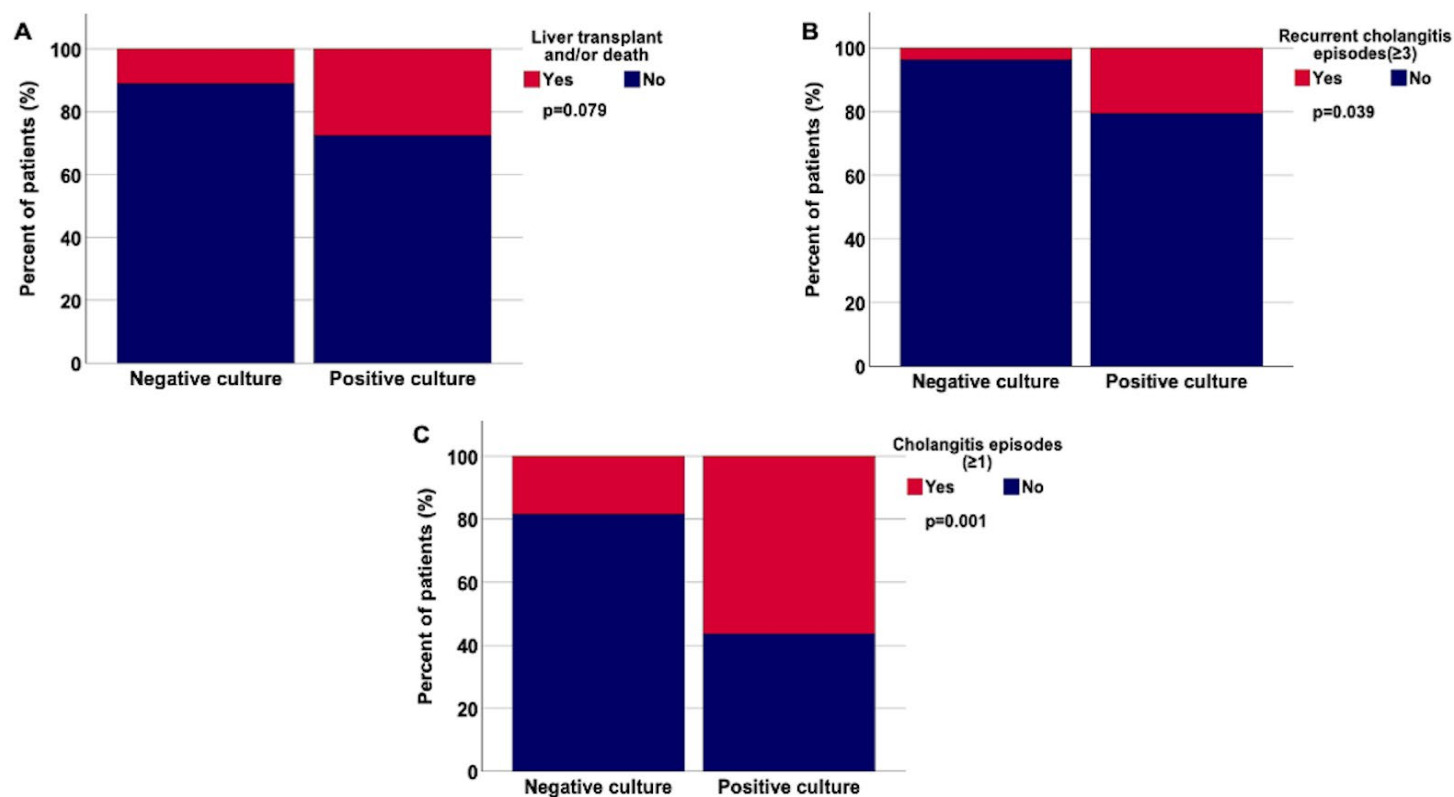
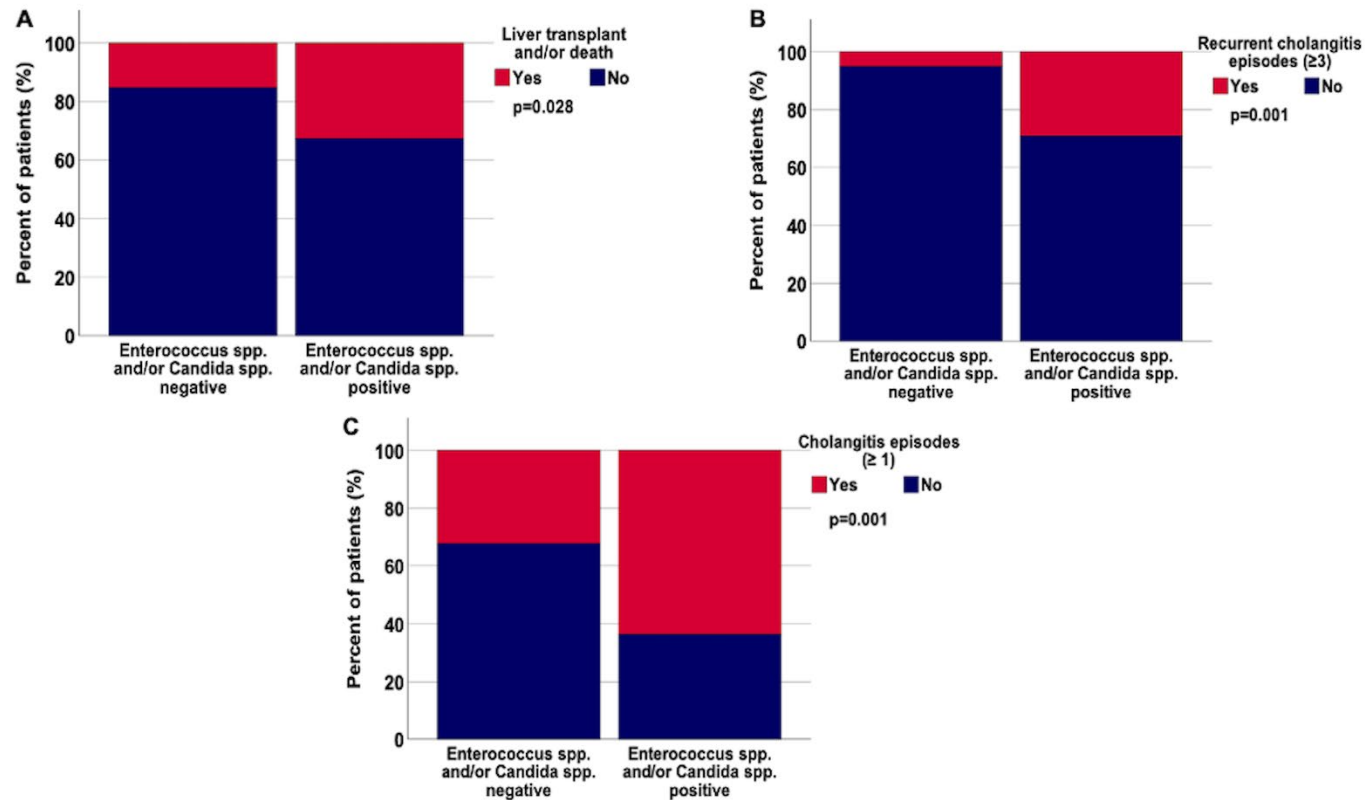


## Supplementary Material



**Supplementary Figure 1 Positive bile cultures are associated with recurrent cholangitis episodes.**

28% (n=24) of patients with positive bile cultures received liver transplantation or died from a liver-related cause, while the proportion in patients with negative culture was 11% (n=3) (OR, 3.048; 95% CI, 0.840-11.061; p=0.079) (**A**). Patients with positive bile culture results suffered significantly more often from recurrent (≥ 3) cholangitis episodes compared to patients with negative bile culture results (n=18 (21%); OR, 6.783; 95% CI, 0.861-53.406; p=0.039) (**B**). 56% of patients with positive bile culture results (n=49) suffered from at least one cholangitis episode (OR 5.674; 95% CI, 1.967-16.367; p=0.001) (**C**). A p-value <0.05 was considered significant.



**Supplementary Figure 2 Candida spp. and/or Enterococcus spp. in bile is associated with a poorer outcome**

Patients positive for *Enterococcus* spp. and/or *Candida* spp. had a more frequent occurrence of liver transplantation and/or liver-related death (OR, 2.703; 95% CI, 1.092-6.688; p=0.028) (**A**). Presence of either *Enterococcus* spp. and/or *Candida* spp. in bile was linked to a higher frequency of developing recurrent cholangitis episodes (≥ 3) (OR, 7.658; 95% CI, 2.089-28.075; p=0.001) (**B**). Moreover, 64% of patients with *Enterococcus* spp. and/or *Candida* developed at least one episode of cholangitis (OR, 3.684; 95% CI, 1.698-7.994; p=0.001) (**C**). A p-value <0.05 was considered significant.

**Supplementary Table 1 Baseline characteristics of Control cohort**

	<b>Control cohort (n=50)</b>
<b>Gender</b>	
▪ Female	▪ 5 (10%)
▪ Male	▪ 45 (90%)
<b>Median age at time of bile sampling (range)</b>	<b>61 (12-71)</b>
<b>Reason for liver transplantation</b>	
▪ Hepatocellular carcinoma	▪ 36 (72%)
▪ Alcohol-related liver disease	▪ 11 (22%)
▪ Nonalcoholic steatohepatitis (NASH)	▪ 3 (6%)
<b>Positive bile cultures</b>	<b>6 (12%)</b>
▪ Enterococcus spp.	▪ 2 (4%)
▪ Streptococcus	▪ 1 (2%)
▪ Candida	▪ 1 (2%)
▪ Other	▪ 2 (4%)

**Supplementary Table 2 Subgroup analysis – Outcome**

	<i>Positive culture n=87</i>			<i>Enterobacteriaceae n=28 (25%)</i>			<i>Enterococcus spp. n=42 (32%)</i>			<i>Candida spp. n=19 (22%)</i>			<i>Candida and/or Enterococcus spp. n=55 (48%)</i>		
	No. of patients (%)	OR (95%CI)	p-value	No. of patients (%)	OR (95%CI)	p-value	No. of patients (%)	OR (95%CI)	p-value	No. of patients (%)	OR (95%CI)	p-value	No. of patients (%)	OR (95%CI)	p-value
<b>Liver transplant and/or death</b>	24 (28%)	3.048 (0.840-11.061)	0.079	7 (25%)	1.100 (0.408-2.963)	0.850	<b>15 (36%)</b>	<b>2.778 (1.147-6.728)</b>	<b>0.021</b>	8 (36%)	2.195 (0.804-5.996)	0.119	<b>18 (33%)</b>	<b>2.703 (1.092-6.688)</b>	<b>0.028</b>
▪ Liver transplant	19 (22%)	2.235 (0.607-8.231)	0.217	6 (21%)	1.193 (0.416-3.422)	0.742	12 (29%)	2.480 (0.963-6.385)	0.055	7 (32%)	2.396 (0.835-6.973)	0.098	14 (26%)	2.177 (0.833-5.691)	0.108
▪ Liver-related death	5 (6%)	-	0.203	1 (4%)	0.759 (0.081-7.090)	0.809	3 (7%)	2.692 (0.431-16.810)	0.272	1 (5%)	1.048 (0.111-9.864)	0.968	4 (7%)	4.549 (0.492-42.026)	0.146
<b>Recurrent cholangitis episodes (≥3)</b>	<b>18 (21%)</b>	<b>6.783 (0.861-53.406)</b>	<b>0.039</b>	8 (29%)	2.727 (0.968-7.683)	0.052	<b>11 (26%)</b>	<b>2.839 (1.037-7.768)</b>	<b>0.037</b>	<b>9 (41%)</b>	<b>5.677 (1.940-16.616)</b>	<b>0.001</b>	<b>16 (29%)</b>	<b>7.658 (2.089-28.075)</b>	<b>0.001</b>
▪ Cholangitis episodes (≥ 1)	<b>49 (56%)</b>	<b>5.674 (1.967-16.367)</b>	<b>0.001</b>	17 (61%)	2.047 (0.857-4.887)	0.103	23 (55%)	1.601 (0.744-3.444)	0.227	<b>21 (96%)</b>	<b>37.545 (4.829-291.891)</b>	<b>&lt;0.001</b>	<b>35 (64%)</b>	<b>3.684 (1.698-7.994)</b>	<b>0.001</b>

Significant results (p<0.05) are shown in bold type. Initial diagnosis (ID); Autoimmune hepatitis (AIH); Endoscopic retrograde cholangiopancreatography (ERCP); Endoscopic retrograde cholangiopancreatography (ERCP); Odds ratio (OR); Confidence interval (CI)

### Supplementary Table 3 Multivariable logistic regression analysis for features associated with positive cultures

Parameter	Multivariable logistic regression	
	p-value	Odds ratio (95% CI)
Gender	0.538	1.394 (0.484-4.018)
Age at initial diagnosis	0.323	1.018 (0.983-1.054)
Inflammatory bowel disease	<b>0.003</b>	<b>4.707 (1.688-13.128)</b>
≥ 2 ERCPs per patient	0.812	0.762 (0.081-7.194)

Significant results (p<0.05) are shown in bold type. Endoscopic retrograde cholangiopancreatography (ERCP); Confidence interval (CI)

### Supplementary Table 4: Clinical characteristics and Odds ratio for patients with specific pathogens in bile samples

	<i>Enterobacteriaceae</i> n=28 (25%)			<i>Enterococcus spp.</i> n=42 (32%)			<i>Other Streptococcus and/or Staphylococcus spp.</i> n=31 (27%)		
	No. of patients (%)	OR (95%CI)	p-value	No. of patients (%)	OR (95%CI)	p-value	No. of patients (%)	OR (95%CI)	p-value
<b>Gender</b>									
▪ Female	6 (21%)	0.565 (0.206-1.550)	0.264	13 (31%)	1.089 (0.475-2.493)	0.841	12 (39%)	1.751 (0.732-4.187)	0.205
▪ Male	22 (79%)			29 (69%)			19 (61%)		
<b>Age at ID (≥ 30 years)</b>	15 (54%)	1.1 (0.467-2.592)	0.827	<b>28 (67%)</b>	<b>2.667 (1.201-5.919)</b>	<b>0.015</b>	15 (48%)	0.828 (0.362-1.897)	0.656
<b>Overlap with AIH</b>	3 (11%)	0.818 (0.211-3.170)	0.771	3 (7%)	0.427 (0.112-1.626)	0.202	4 (13%)	1.081 (0.313-3.740)	0.902
<b>Inflammatory bowel disease</b>	23 (82%)	1.993 (0.683-5.817)	0.201	34 (81%)	1.995 (0.798-4.985)	0.135	23 (74%)	1.102 (0.432-2.813)	0.839
<b>Proton-pump inhibitor use</b>	7 (25%)	0.970 (0.363-2.592)	0.951	10 (24%)	0.872 (0.361-2.107)	0.760	7 (23%)	0.809 (0.306-2.139)	0.669
<b>Relevant stenosis</b>	24 (86%)	0.370 (0.092-1.489)	0.149	37 (88%)	0.435 (0.110-1.721)	0.225	28 (90%)	0.727 (0.170-3.106)	0.666

$\geq 2$ ERCPS per patient	26 (93%)	0.975 (0.185-5.130)	0.976	39 (93%)	0.970 (0.220-4.282)	0.968	29 (94%)	1.130 (0.216-5.920)	0.885
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Significant results (p<0.05) are shown in bold type. Initial diagnosis (ID); Autoimmune hepatitis (AIH); Endoscopic retrograde cholangiopancreatography (ERCP); Odds ratio (OR); Confidence interval (CI)

### Supplementary Table 5 Multivariable logistic regression analysis for features associated with biliary candidiasis

Multivariable logistic regression		
Parameter	p-value	OR (95% CI)
Age at initial diagnosis	0.570	1.011 (0.974-1.050)
Inflammatory bowel disease	0.452	1.595 (0.473-5.381)
Proton-pump inhibitor intake	<b>0.015</b>	<b>3.559 (1.275-9.937)</b>

Significant results (p<0.05) are shown in bold type. Odds ratio (OR); Autoimmune hepatitis (AIH); Model for End-Stage Liver Disease (MELD)