Major hepatectomies for perihilar cholangiocarcinoma: Predictors for clinically relevant postoperative complications using the International Study Group of Liver Surgery definitions

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KEYWORDS
complications; major liver resection; perihilar cholangiocarcinoma

Abstract  Background/aim: Major hepatectomies are widely used in curative-intent surgery for perihilar cholangiocarcinoma, but morbidity rates are high. The aim of the study is to explore potential predictors for clinically relevant complications after major hepatectomies for perihilar cholangiocarcinoma.

Methods: Seventy patients were included. Univariate and multivariate analyses were performed for risk factors of morbidities using the International Study Group of Liver Surgery definitions.

Results: Severe morbidity rate was 36.5%. Clinically relevant posthepatectomy liver failure, bile leak, and hemorrhage rates were 24%, 22%, and 8.5%, respectively. A neutrophil-to-lymphocyte ratio > 3.3 is an independent prognostic factor for severe complications (hazard ratio = 1.258; 95% confidence interval 1.008–1.570; p = 0.042) while the number of blood units > 3 is an independent prognostic factor for clinically relevant liver failure (hazard ratio = 1.254; 95% confidence interval 1.082–1.452; p = 0.003). Biliary drainage and portal vein resection were not statistically correlated with any postoperative complication (p > 0.101). Significantly higher bilirubinemia levels were observed in patients with postoperative hemorrhage (p = 0.023).

Conclusion: Clinically relevant morbidity rates after major hepatectomies for perihilar cholangiocarcinoma are high. Liver failure represents the main complication and is correlated with

Conflicts of interest: None.

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1. Introduction

Perihilar cholangiocarcinoma (PHC) is considered as a cholangiocarcinoma involving the hilar bile duct (i.e., bile duct located between the right side of the umbilical portion of the left portal vein and the left side of the origin of the posterior portal vein). Major hepatectomies with extrahepatic bile duct resection and loco-regional lymphadenectomy represent the standard approach for curative-intent surgery in the largest part of patients with PHC and have been associated with significant improvements for resectability and survival rates. Nowadays, decreased mortality rates after major hepatectomies were observed in referral centers, but for patients with PHC mortality rates are significantly higher compared with other pathologies and ranges from 1.4% to 12%. Major hepatectomies with zero mortality were also reported. Conversely, morbidity rates after major hepatectomies are still high, particularly in patients with PHC because they are more likely to present added potential risk factors such as obstructive jaundice with or without cholangitis. Thus, morbidity rates after hepatectomies for PHC ranges from 43% to 81% and the main complications are represented by liver failure, hemorrhage, and septic complications due to bile leak.

In the literature, there is a broad spectrum of definitions for major liver resections. Recently, it was suggested that resection of four or more liver segments should be considered the standard definition for major hepatectomies. Furthermore, standard definitions and grading systems were proposed in 2011 by the International Study Group of Liver Surgery (ISGLS) for specific complications such as posthepatectomy liver failure, posthepatectomy hemorrhage, and bile leak.

Up to now, there are only several studies investigating potential risk factors for postoperative complications after liver resection for PHC and the studies do not always include patients with only major hepatectomies. Major hepatectomies are differently defined, and the postoperative complications are not standardized according to the ISGLS definitions or Dindo-Clavien classification, except in very few studies. Thus, there are a lack of data regarding potential predictors for clinically relevant complications after major hepatectomies for PHC and a study addressing this issue appears to be of interest.

The aim of the present study is to investigate potential risk factors for clinically relevant postoperative complications after major hepatectomies for PHC in a relatively large, single center experience, using the ISGLS definitions for specific morbidities.

2. Methods

2.1. Study population, inclusion criteria, and primary endpoint

Seventy patients, recruited from 1996 to 2012 at our Department of Surgery, were included. Inclusion criteria were as follows. (1) Final pathological diagnosis of PHC (i.e., hilar cholangiocarcinomas or intrahepatic cholangiocarcinomas invading the biliary convergence). Perihilar cholangiocarcinoma was considered according to the definition provided by Ebata et al. (2) Major liver resections (defined as ≥ four resected liver segments), combined with extrhepatic bile duct resection, and loco-regional lymphadenectomy. (3) Estimated future liver remnant volume ≥ 30%.

The primary end point of the study was the identification of risk factors for clinically relevant postoperative complications that might be potentially useful in clinical decision-making for patients with PHC proposed for major hepatectomies.

The data of the patients were retrospectively assessed from a prospectively gathered electronic database and included pre-, intra-, and postoperative data (available for all patients). The study was approved by the Ethics Committee at our institution.

2.2. Preoperative characteristics of the patients

The median age was 59 years, with male gender predominance (40 patients, 57%). Cardiovascular comorbidities and diabetes mellitus were observed in 19 patients (27%) and five patients (7%), respectively.

Most of the patients presented with jaundice (59 patients, 84%), and 18 patients (26%) showed signs of cholangitis, due to the presence of the disease in eight patients (11%) and related to biliary drainage in 10 patients (14%).

Preoperative biliary drainage was performed for 15 patients (21%): percutaneously (5 patients, 7%), endoscopically (5 patients, 7%), or by previous surgery (5 patients, 7%). Only eight patients (11%) were considered for preoperative biliary drainage in our unit (indicated only in patients with cholangitis with impaired renal function); another five patients (7%) had already received biliary drainage while previous surgical exploration, and two patients (3%) were referred from gastroenterologists with palliation of jaundice. No patient underwent preoperative portal vein embolization.

Preoperative median serum level of bilirubin was 10.5 mg/dL, aspartate-aminotransferase 123 U/L, alanil-
aminotransferase, albumin 3.9 g/dL, urea 39 mg/dL, creatinine 0.8 mg/dL, hemoglobin 12.3 g/dL, leukocytes 8750 µL, lymphocytes 1600 µL, neutrophiles 5800 µL, neutrophil-to-lymphocyte ratio 3.3, thrombocytes 323,000 mmc, thrombocyte-to-lymphocyte ratio 183, and the CA 19-9 serum level was 375 UI/mL. Preoperative bioumoral parameters were assessed no more than 1 week prior to resection.

2.3. Operative characteristics of the patients

All patients underwent extrahepatic bile duct resection, loco-regional lymphadenectomy, and one of the following liver resections, as shown in Table 1.

The median tumor diameter was 3 cm (range, 0.5–10 cm). Portal vein resection was performed in 17 patients (24%) when invasion was suspected at preoperative imaging or intraoperative exploration.

The median intraoperative blood loss was 800 mL, and 53 patients (76%) required per operative blood transfusions. The median operating time was 300 minutes.

2.4. Assessments of postoperative complications

Postoperative complications were assessed with the Dindo-Clavien classification26 and the ISGLS definitions and severity grading for posthepatectomy liver failure,18 bile leak,20 and hemorrhage.19 In patients with more than one postoperative complication, the highest grade of severity was considered. Severe complications were considered Grade III–V Dindo-Clavien while clinically relevant complications were defined as Grades B and C of the ISGLS grading. Postoperative mortality was assessed at 90 days.

2.5. Statistical analysis

The data are expressed as n (%) and median. Univariate analysis for potential risk factors utilized Mann–Whitney U test for continuous variables and Fisher’s exact test for categorical variables. Multivariate analysis used a linear logistic binary regression forward stepwise model to analyze variables with p < 0.10 in univariate analysis, after elimination of intercorrelated factors. Pearson’s correlation coefficient was used for continuous variables, while Spearman’s rho correlation coefficient was used for categorical variables. A p value < 0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Postoperative overall morbidity and mortality

Complications occurred in 44 patients (63%). According to the Dindo-Clavien classification five patients were assessed as Grade I (7%), 13 patients as Grade II (18%), nine patients as Grade IIIa (13%), five patients as Grade IIIb (7%), four patients as Grade IVa (5%), and one patient as Grade IVb (1.5%). Median postoperative hospital stay was 16 days (range, 1–65 days). Relaparotomy for complications was necessary for 14 patients (20%).

Postoperative bile leak was observed in 20 patients (29%): Grade A — four patients (6%), Grade B — 13 patients (18%), and Grade C — three patients (4%). Postoperative liver failure was observed in 20 patients (29%): Grade A — three patients (4%), Grade B — 12 patients (17%), and Grade C — five patients (7%). Postoperative hemorrhage was observed in six patients (8.5%): Grade B — one patient (1.5%), and Grade C — five patients (7%).

The 90-day mortality rate was 10% (7 patients) due to postoperative liver failure (4 patients, 6%), sepsis with multiorgan failure (2 patients, 3%) and hemorrhagic shock (1 patient, 1.5%).

3.2. Predictors for severe postoperative complications

Severe postoperative complications (i.e., Grades III–V Dindo) were observed in 26 patients (36.5%). In univariate analysis, the following factors were identified as predictors for severe morbidity: creatinine serum level, lymphocyte number, neutrophil-to-lymphocyte ratio, CA 19-9 serum level, blood and fresh frozen plasma unit number, and the operative time (Tables 2 and 3). In multivariate analysis the increased neutrophil-to-lymphocyte ratio (> 3.3) has been identified as the single independent prognostic factor for development of severe postoperative complications after major hepatectomies for PHC (hazard ratio = 1.258; 95% confidence interval 1.008–1.570; p = 0.042).

3.3. Predictors for clinically relevant posthepatectomy bile leak using the ISGLS definitions

Posthepatectomy bile leak rate in the present series was 29% with clinically relevant (Grades B and C) fistula rate of 22%. In univariate analysis, urea serum level and neutrophil-to-lymphocyte ratio were identified as predictors for posthepatectomy clinically relevant bile leak (Tables 2 and 3) but no independent risk factors were identified in multivariate analysis.

### Table 1 Operative characteristics in 70 patients with major hepatectomies for perihilar cholangiocarcinoma.

<table>
<thead>
<tr>
<th>Surgical procedure</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EHBDR + left hemi-hepatectomy + caudate lobectomy</td>
<td>34 (49)</td>
</tr>
<tr>
<td>EHBDR + right hemi-hepatectomy + caudate lobectomy</td>
<td>15 (21)</td>
</tr>
<tr>
<td>EHBDR + right hemi-hepatectomy</td>
<td>12 (17)</td>
</tr>
<tr>
<td>EHBDR + right trisectionectomy + caudate lobectomy</td>
<td>6 (9)</td>
</tr>
<tr>
<td>EHBDR + right trisectionectomy</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

* EHBDR — extrahepatic bile duct resection and loco-regional lymphadenectomy (hepato-duodenal ligament, common hepatic artery, posterior surface of the pancreatic head, right side of the celiac trunk).
Table 2  Univariate analysis for predictors of severe complications (i.e., Grade III–V Dindo), posthepatectomy clinically relevant (i.e., Grades B and C International Study Group for Liver Surgery) bile leak, liver failure, and hemorrhage in 70 patients with major hepatectomies for perihilar cholangiocarcinoma (continuous variables).

<table>
<thead>
<tr>
<th>Parameter*</th>
<th>Severe complications</th>
<th></th>
<th>Clinically relevant</th>
<th></th>
<th>Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Ye</td>
<td>p*</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Age (y)</td>
<td>58</td>
<td>61</td>
<td>0.961</td>
<td>57</td>
<td>63</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>11</td>
<td>10.1</td>
<td>0.279</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>122</td>
<td>127</td>
<td>0.365</td>
<td>120</td>
<td>190</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>150</td>
<td>240</td>
<td>0.064</td>
<td>183</td>
<td>147</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>3.9</td>
<td>3.6</td>
<td>0.421</td>
<td>3.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>37</td>
<td>40</td>
<td>0.493</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>12.5</td>
<td>12</td>
<td>0.211</td>
<td>12.5</td>
<td>11.9</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>8 600</td>
<td>9 000</td>
<td>0.772</td>
<td>8 800</td>
<td>8 600</td>
</tr>
<tr>
<td>Leukocytes (µL)</td>
<td>1 700</td>
<td>1 600</td>
<td>0.047</td>
<td>1 600</td>
<td>1 400</td>
</tr>
<tr>
<td>Neutrophil-to-lymphocyte ratio</td>
<td>3.1</td>
<td>5.2</td>
<td>0.004</td>
<td>3.1</td>
<td>5.24</td>
</tr>
<tr>
<td>Neutrophil-to-lymphocyte ratio</td>
<td>308 000</td>
<td>323 000</td>
<td>0.625</td>
<td>323 000</td>
<td>257 000</td>
</tr>
<tr>
<td>Thrombocytes (µL)</td>
<td>169.2</td>
<td>247.8</td>
<td>0.146</td>
<td>171</td>
<td>189.3</td>
</tr>
<tr>
<td>CA 19-9 (U/mL)</td>
<td>165</td>
<td>400</td>
<td>0.031</td>
<td>266</td>
<td>400</td>
</tr>
<tr>
<td>Tumor diameter (cm)</td>
<td>3</td>
<td>3</td>
<td>0.927</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Fresh frozen plasma units</td>
<td>2</td>
<td>4</td>
<td>0.022</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Operative time (min)</td>
<td>280</td>
<td>360</td>
<td>0.008</td>
<td>300</td>
<td>270</td>
</tr>
</tbody>
</table>

Data are expressed as median.
* Mann–Whitney U test.
3.4. Predictors for clinically relevant posthepatectomy liver failure using the ISGLS definitions

Posthepatectomy liver failure rate in the present series was 29% and clinically relevant (Grades B and C) in 24% of the patients. In univariate analysis, the following factors were identified as risk factors for clinically relevant liver failure: albumin serum level, lymphocyte number, neutrophil-to-lymphocyte ratio, thrombocyte-to-lymphocyte ratio, blood and fresh frozen plasma unit number, right trisectionectomy, and caudate lobectomy (Tables 2 and 3). In multivariate analysis, the number of blood units (> 3) has been identified as the single independent prognostic factor for the development of clinically relevant liver failure after hepatectomies for PHC (hazard ratio = 1.254; 95% confidence interval 1.082–1.452; \( p = 0.003 \)).

3.5. Predictors for clinically relevant posthepatectomy hemorrhage using the ISGLS definitions

Posthepatectomy hemorrhage rate in the present series was 8.5%, all clinically relevant (Grades B and C). In univariate analysis, the following factors were identified as predictors for posthepatectomy hemorrhage: bilirubin serum level, aspartate aminotransferase serum level, urea serum level, neutrophil-to-lymphocyte ratio, blood and fresh frozen plasma unit number, male gender, and presence of cholangitis (Tables 2 and 3). No independent risk factors were identified in multivariate analysis.

4. Discussion

The concept of PHC has been demonstrated as valid but the curative-intent surgery for these patients still remains challenging, even in referral centers.\(^5\) In a recent multicentre European study (including only patients with major hepatectomies for PHC), the overall morbidity rate was 68.6%, with severe complication rates of 27.6%, and mortality rates of 10.7%.\(^10\) Similar results were observed in the present series: overall morbidity rate of 63%, severe complication rate of 38.5%, including the mortality rate of 10%. Thus, one might conclude that nowadays such complex surgical procedures are still associated with increased rates of postoperative complications.\(^{27}\) It was suggested as a potential detrimental effect of the postoperative complications on long-term outcomes,\(^9\) but our previous studies failed to sustain this finding after curative-intent surgery for Klatskin tumors.\(^{26}\)

The ISGLS grading system for posthepatectomy specific complications is only retrospectively assessed and is not useful to predict morbidity in early settings, but is of real value for surgical audit. The main studies exploring potential predictors for postoperative complications after surgery for PHC are shown in Table 4.

Most of the patients with PHC present with jaundice at diagnosis but the impact of bilirubin serum level on postoperative outcomes remains controversial. Persistent jaundice is associated with bacterial translocation, impaired coagulation, renal, or liver dysfunctions.\(^{10,27}\) Some studies showed no impact on postoperative complications rates,\(^{5,11,16,21,23}\) while others did.\(^{10,22,29}\) In the present series, preoperative bilirubin serum level had no significant impact on severe or specific posthepatectomy complication rates. However, patients with increased bilirubin serum levels at the time of liver resection appear to have a high risk of developing postoperative hemorrhage, as shown in Table 2.

Routine preoperative biliary drainage of the future liver remnant was proposed to increase the safety of major liver resections for PHC.\(^2,3,30\) However, some surgical teams prefer to selectively use biliary drainage,\(^10,16\) as was the case in the present series. Ascending cholangitis is the most feared complication after biliary drainage; the presence of cholangitis at the time of liver resection has been associated with increased morbidity and mortality rates in some...
<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>Patients resected for PHC (n)</th>
<th>Major liver resections (≥ 4 segments), %</th>
<th>Overall morbidity, %</th>
<th>Liver failure, %</th>
<th>Mortality, %</th>
<th>Independent risk factors for complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nagino et al, 2001</td>
<td>1999–2001</td>
<td>105</td>
<td>84</td>
<td>81</td>
<td>28</td>
<td>9.5</td>
<td>NA</td>
</tr>
<tr>
<td>Sano et al, 2006</td>
<td>2000–2004</td>
<td>102</td>
<td>63</td>
<td>50</td>
<td>0</td>
<td>0</td>
<td>Cholangitis for overall morbidity</td>
</tr>
<tr>
<td>Hasegawa et al, 2007</td>
<td>1990–2003</td>
<td>44</td>
<td>100</td>
<td>47</td>
<td>16</td>
<td>2</td>
<td>Bilirubin serum level, extended hepatectomies for liver failure</td>
</tr>
<tr>
<td>Kennedy et al, 2009</td>
<td>1997–2007</td>
<td>60</td>
<td>100</td>
<td>53</td>
<td>8</td>
<td>10</td>
<td>Absence of biliary drainage, future live remnant volume &lt; 30%, blood transfusions for liver insufficiency and mortality</td>
</tr>
<tr>
<td>Hirano et al, 2010</td>
<td>2001–2008</td>
<td>126</td>
<td>57</td>
<td>44</td>
<td>16</td>
<td>3.4</td>
<td>Operative time for overall complications</td>
</tr>
<tr>
<td>Regimbeau et al, 2011</td>
<td>2008</td>
<td>39</td>
<td>100</td>
<td>72</td>
<td>7</td>
<td>7.6</td>
<td>NA</td>
</tr>
<tr>
<td>Nagino et al, 2013</td>
<td>1977–2010</td>
<td>574</td>
<td>97</td>
<td>57</td>
<td>53</td>
<td>4.7</td>
<td>Cholangitis, liver function, blood loss for mortality</td>
</tr>
<tr>
<td>Farges et al, 2013</td>
<td>1997–2008</td>
<td>366</td>
<td>100</td>
<td>69</td>
<td>5</td>
<td>10.7</td>
<td>Bilirubin serum levels, right hepatectomies for mortality</td>
</tr>
<tr>
<td>Furusawa et al, 2014</td>
<td>1990–2012</td>
<td>144</td>
<td>65</td>
<td>72</td>
<td>32</td>
<td>1.4</td>
<td>Blood loss for overall morbidity</td>
</tr>
<tr>
<td>Sugawara et al, 2013</td>
<td>2001–2011</td>
<td>587</td>
<td>NA</td>
<td>NA</td>
<td>5.7</td>
<td>3.3</td>
<td>Age, body mass index, positive bile culture, operative time, blood loss</td>
</tr>
</tbody>
</table>

Table 4: Studies from literature exploring risk factors for postoperative complications after major hepatectomies for perihilar cholangiocarcinoma.
studies.5,8,11,25 Other studies23,27 failed to identify any correlation with postoperative complications, as was the case in the present study. A recent systematic review associated biliary drainage with increased morbidity but of no benefit prior to resection for PHC.31 Furthermore, prior biliary drainage appears to be associated with increased mortality for left hepatectomies but decreased mortality for right hepatectomies.10 However, in some studies biliary drainage was not associated with increased rates of infectious complications27; synbiotic treatment can reduce infectious morbidity rates.32,33 Absence of biliary drainage in patients with estimated future liver remnant < 30% was found as an independent risk factor for liver insufficiency and mortality.24 Selective use of biliary drainage prior to resection for PHC appears to be the best approach.34,35 Patients with scheduled right hepatectomies and patients with an estimated future remnant liver volume of < 30% are more likely to benefit from preoperative biliary drainage.10,36 The low biliary drainage rate (21%) represents one of the particularities in the present series; biliary drainage was indicated only in patients with cholangitis and impaired renal function. The safety of major hepatectomies without biliary drainage was previously reported in some other high-volume centers.34,35 Based on the results of the present study, a more liberal use of preoperative biliary drainage should be considered, particularly in patients with increased bilirubin (with or without cholangitis) and long-lasting jaundice.

The extent of liver resection was not identified as a risk factor for clinically relevant complications in the present series. Previous studies have shown the same results,5,11,21,23 while others identified left trisectionectomy and right hepatectomies as independent risk factors for mortality after surgery for PHC.6,8–10 Caudate lobectomy appears to reduce morbidity rates in some studies.29

Intraoperative blood loss is a significant predictor for postoperative mortality or morbidity in some studies,5,8,29 including infectious complications27 while others failed to demonstrate any correlation.25 In the present study, intraoperative blood loss does not appear to impact severe or specific posthepatectomy complications rates; however, an increased number of transfused blood units were an independent risk factor for clinically relevant liver failure. Expertise and technical improvements have reduced the intraoperative blood loss and the need for blood transfusions after surgery for PHC.7,37 A decreased need for blood transfusions were associated with low mortality and morbidity rates.7,37

The impact of portal vein resection during major hepatectomies for PHC is controversial. Thus, most of the studies did not associate venous resection with increased mortality or morbidity rates,5,6,9,11,16,23 while others showed increased postoperative complication rates.21 In the present series, portal vein resection did not influence severe or clinically relevant specific posthepatectomy morbidities rates.

Postoperative liver failure represented the most common and feared complication after major liver resections for PHC in most of the studies,2–6,8,10,13 as in the present series. Furthermore, liver failure is considered the main cause of death after major hepatectomies for PHC,27 as was the case in the present series. Data from the literature identify the bilirubin serum level22,24 and extended hepatectomies13,22,24 as independent risk factors for developing liver insufficiency, while no correlation was established with biliary drainage,22 albumin serum level,24 or intraoperative blood loss.22 However, prior biliary drainage was identified as an independent risk factor in one study.24 The same study identified the need for perioperative blood transfusion but not intraoperative blood loss as an

### Table 4 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Period</th>
<th>Patients resected for PHC (n)</th>
<th>Major liver resections (≥ 4 segments), %</th>
<th>Overall morbidity, %</th>
<th>Liver failure, %</th>
<th>Mortality, %</th>
<th>Independent risk factors for complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present series</td>
<td>1996–2012</td>
<td>70</td>
<td>100</td>
<td>63&lt;sup&gt;a&lt;/sup&gt;</td>
<td>29&lt;sup&gt;c&lt;/sup&gt;</td>
<td>10&lt;sup&gt;d&lt;/sup&gt;</td>
<td>loss, pancreateo-duodenectomy for infectious morbidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Neutrophil-to-lymphocyte ratio for severe complications</td>
</tr>
</tbody>
</table>

NA = not available.

<sup>a</sup> Morbidity assessed according to Dindo-Clavien classification.

<sup>b</sup> Posthepatectomy liver failure according to the ISGLS definition.

<sup>c</sup> Mortality assessed as in-hospital.

<sup>d</sup> Mortality assessed at 90 days.
independent risk factor for posthepatectomy liver failure.\textsuperscript{24} The present study showed that although intraoperative blood loss was not a risk factor, the number of perioperatively transfused blood units was an independent predictor for developing clinically relevant liver failure.

Markers of systemic inflammatory response such as neutrophil-to-lymphocyte ratio have been largely investigated as prognostic factors for malignancies.\textsuperscript{38} Our previous studies showed that a neutrophil-to-lymphocyte ratio has a significant impact on long-term outcomes in patients with curative-intent surgery for Klatskin tumors.\textsuperscript{28} Only a few studies explored the predictive value of the inflammatory markers on the development of postoperative complications.\textsuperscript{39–42} Thus, increased neutrophil-to-lymphocyte ratio was previously correlated with the risk of developing postoperative complications after colorectal surgery,\textsuperscript{43} emergency abdominal surgery,\textsuperscript{44} or breast cancer surgery.\textsuperscript{45} A recent study identified increased neutrophil-to-lymphocyte ratio as an independent risk factor for persistent posthepatectomy liver failure (ISGLS definition) in patients with liver resection and Child-Pugh Grade A cirrhosis.\textsuperscript{46} Neutrophil-to-lymphocyte ratio was an independent risk factor for the development of postoperative complications after major hepatectomies for PHC in the present series. Furthermore, patients with increased neutrophil-to-lymphocyte ratio appear to have a high risk of developing clinically relevant posthepatectomy liver failure, bile leak, and hemorrhage, as shown in Table 2. Symbiotics appear to attenuate the systemic inflammatory response.\textsuperscript{47} In patients with perihilar cholangiocarcinoma an increased neutrophil-to-lymphocyte ratio might be a consequence of the infectious/inflammatory complications related to biliary obstruction.\textsuperscript{28} In these patients antibiotics and/or a more liberal approach to preoperative biliary drainage might be considered to reduce postoperative morbidity rates.

In conclusion, clinically relevant morbidity rates after major hepatectomies for PHC are high. Liver failure represents the main complication and is correlated with the number of transfused blood units. A patient with increased bilirubinemia appears to have a high risk of postoperative hemorrhage. Biliary drainage and portal vein resection do not appear to have a detrimental effect on morbidities. Neutrophil-to-lymphocyte ratio is a novel independent predictor for severe morbidity after major hepatectomies for PHC and may contribute to better and informed decision-making.

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References


