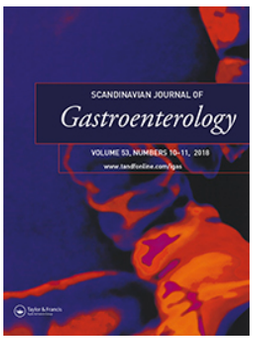

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ORIGINAL ARTICLE



# The impact of post-hepatectomy liver failure on mortality: a population-based study

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**ABSTRACT**

**Background:** Post-hepatectomy liver failure (PHLF) is considered a main reason for death after major hepatectomy. The reported PHLF-related mortality differs largely and the data mainly originate from single centers.

**Aim:** A retrospective, population-based register study was designed to evaluate the impact of PHLF on 90-day mortality after hepatectomy.

**Method:** All patients who underwent liver resection in Sweden between 2005 and 2009 were retrospectively identified using the Swedish Hospital Discharge Registry. 30- and 90-day mortality were identified by linkage to the Registry of Causes of Death. Additional clinical data were obtained from the medical charts in all seven university hospitals in Sweden. PHLF was defined according to Balzan criteria (Bilirubin >50 μg/L and international normalized ratio >1.5) on postoperative day 5.

**Results:** A total of 2461 liver resections were performed (2194 in university hospitals). 30- and 90-day mortality were 1.3% and 2.5%, respectively. 90-day mortality at university hospitals was 2.1% ($n = 46$). In 41% ($n = 19$) of these patients, PHLF alone or in combination with multi-organ failure was identified as cause of death. Between the PHLF and non-PHLF group, there was no significant difference regarding age, sex, American Society of Anesthesiologists-classification, or preoperative chemotherapy. Cholangiocarcinoma as indication for surgery, need for vascular reconstruction and an extended resection were significantly overrepresented in the PHLF-group. Between groups, the incidence of 50:50 criteria differed significantly already on postoperative day 3.

**Conclusion:** Overall mortality is very low after hepatectomy in Sweden. PHLF represents the single most important cause of death even in a population-based setting.

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**KEYWORDS**
Post-hepatectomy liver failure; population-based; major hepatic resection; post-operative mortality; hepatectomy; liver dysfunction

## Introduction

Today, liver resections are performed with low overall morbidity and mortality [1,2]. In a previous, population-based study we found an overall 90-day mortality after hepatectomy of 3.1% with great variance depending on the extent of performed liver resection and underlying diagnosis [3].

However, despite an improvement of hepatectomy related patient-outcome over the last decades [1,4,5], post-hepatectomy liver failure (PHLF) still is a feared complication after major and extended hepatectomy. In recent decades, much effort has been undertaken to better understand, define, and prevent PHLF [6,7]. In two recent multi-center analyses the incidence for PHLF still was 5–9% [8,9]. Depending on severity and the used definition of PHLF, the perioperative mortality still ranges between 40% and 60% in several studies over the past 15 years [5,10,11]. Thus, PHLF still represents the single most important reason for death after major and extended hepatectomy [12]. However, the majority of the data originate from single- or multi-center experiences, but little is known about the impact of PHLF on mortality related to liver resections in a population-based setting.

Thus, the aim of this study was to evaluate the incidence and the impact of PHLF on mortality after liver surgery in a nation-wide perspective.

## Patients and methods

All patients who underwent hepatectomy in Sweden during a 5-year period (2005–2009) and have been registered in the Swedish Hospital Discharge Registry were included in this retrospective register study. The obtained data were partially published before [3].

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The Swedish Hospital Discharge Registry includes all in-hospital patient contacts which can be followed-up by the patients' national registration number. In this registry, both medical data (e.g., diagnosis, comorbidity, and procedure code) and general patient-related data (e.g., age and sex) can be found. Another registry, the National Cancer Registry, collects cancer-related data such as tumor site, histological type of cancer, and date of diagnosis. In addition, the Registry of Causes of Death contains the individuals' death certificates with information such as underlying disease and date of death. All registers are endorsed and maintained by the Swedish Board of Health and Welfare.

In order to validate the population-based approach, we identified in a first step all patients in the Hospital Discharge Register matching a procedure code for liver resection according to the Tenth Revision of the International Classification of Diseases and Procedures, (ICD 10 codes JJB00, JJB10, JJB20, JJB30, JJB40, JJB50, JJB53, JJB60, JJB71 and JJB96). Second, the personal national registration number was used for cross-linkage with the Registry of Causes of Death in order to identify patients who died within 90-days from surgery. In addition, the Registry of Domestic and International relocations was used for censoring in the event of a cohort member emigrating. Based on the discharge record, patients were allocated to the following diagnoses: metastases (ICD10 code C78.7), hepatocellular cancer (HCC, ICD10-code C22.0), intra- (ICC, ICD10-code C22.1) and extrahepatic bile duct cancer (ECC, ICD10-code C24.0) were gathered in the group 'cholangiocarcinoma', gallbladder cancer (GBC, ICD10-code C23.9), and others/unclear. The patients with unclear diagnoses were then cross-linked with the National Cancer Register in order to obtain a definite diagnosis. Those who were identified with a cancer diagnosis were allocated to the corresponding group of patients. A diagnosis of colorectal cancer in the discharge record (ICD10-codes C18.0–C18.9, C19.9 and C20.9) along with a procedure code for liver resection was allocated to the colorectal liver metastasis (CRLM)-group. All patients who were not allocated to a cancer diagnosis were categorized as either benign or unclear diagnosis. The individual patient's comorbidity was analyzed according to the Charlson score [13], excluding malignancy from contributing to the score. The score was categorized into three groups: no comorbidity (Charlson score 0), Charlson score 1 and Charlson score $\geq$2. All liver resections were stratified according to three groups: minor ($\leq$2 Couinaud segments), major (3–4 Couinaud segments) and extended (>4 Couinaud segments). We did not discriminate for laparoscopic and open liver resection. Biopsies, ablations and de-roofing of liver cysts were excluded from the analysis. For comparison, hospitals were allocated to university and non-university hospitals (7 university and 33 non-university hospitals), respectively. Data from these registries were obtained anonymized and did not contain the personal identification number. Therefore, based on these data we could not identify patients in the local hospital registries.

According to data from the in-hospital registry, over the study period 90% of all hepatectomies were performed at university hospitals. As a consequence, we screened in a second step all patient charts at local hospital registries in order to identify patients who died within 90 days after scheduled or emergency hepatectomy at one of the seven university liver units. For the patients identified, Charlson score, diagnosis and extend of hepatectomy were analyzed similar to the analysis of registry data explained above. Additional clinical data were obtained related to three different time points in order to identify relevant risk factors; pre-, intra- and post-operatively. Pre-operatively, BMI ($\geq$30, yes or no), smoking habits (active, yes or no), alcohol (not included due to poor data quality), diabetes (with medication, yes or no), hypertension (with medication, yes or no), hepatitis (any type of virus hepatitis), American Society of Anesthesiologists score ($\geq$2, yes or no), pre-operative chemotherapy (any type of neoadjuvant treatment), portal vein embolization (yes or no) and cholestasis at time of surgery (elevated bilirubin above normal values) were analyzed. Intra-operatively, we were able to assess Pringles maneuver and total vascular exclusion (both yes or no) along with information regarding other procedures at the time of liver resection (resection of extrahepatic bile ducts, vascular reconstruction, ablation and resection of extra-hepatic disease) and if there was extensive intra-operative bleeding. Data on operating time were unfortunately not obtainable in a quality allowing for statistical analysis and this variable was therefore excluded. Post-operatively, we could assess histological features such as cirrhosis, steatosis and fibrosis (presence of any stage). In regard to blood samples, we analyzed Bilirubin and international normalized ratio (INR) both on post-operative day (POD) 3 and POD 5 along with platelets and creatinine at POD 5 only (due to poor data quality on POD 3). In the post-operative course, data regarding transfusion of blood products, bile leakage (defined by bilirubin 3 times higher in percutaneous drainage compared to blood), surgical intervention (any kind of surgery related to the index operation), percutaneous-transhepatic-cholangiography/endoscopic retrograde cholangiopancreatography (yes or no), infection (any kind with need for antibiotic treatment), portal thrombosis (according to radiologic findings) and the presence of encephalopathy (any Westhaven grade I–IV [14]).

PHLF was either defined by the 50:50 criteria [10] if considered primary, or based on clinical observations when PHLF occurred in the later post-operative course and appeared secondarily to post-operative complications.

The Regional Research Ethics Committee of Stockholm approved the study protocol (DN 2010/1872-31/2).

### Statistical analysis

Data were calculated as means ± standard deviations for continuous variables, and proportions for categorical variables. In order to identify significant differences, the distribution of several variables in the entire background cohort was compared with those positive for 90-day mortality. In addition, the group with 90 day mortality was further analyzed, divided in a PHLF and non-PHLF group. Chi-square and Fisher's exact test were used to compare proportions where appropriate and $p$-values $<$ .05 were considered to be statistically significant.

Statistical analyses were performed using SPSS Version 20 for Windows (SPSS, Inc., Chicago, IL, USA).

## Results

During 2005–2009, a total of 2461 liver resections were performed in 2241 patients (220 re-resections) with an age of 61.6 (13.6) years (mean, std) in all Swedish hospitals. 1322 patients (53.7%) were male and 1490 patients (60.5%) underwent hepatectomy due to CRLM, 150 (6.1%) due to HCC, 88 (3.5%) due to CCC, 129 (5.2%) due to GBC and 604 (24.5%) due to other or benign diagnosis. 2194 (89%) hepatectomies were performed in 1993 patients (201 re-resections) at one of the seven university hospitals. Of these patients, 1546 (62.8%) were subjected to minor hepatectomy, 718 (29.2%) to major and 197 (8.0%) to extended liver resection. 267 liver resections were performed in non-university hospitals and 30-day mortality was 1.5% and 90-day mortality was 3.0%. Overall 30- and 90-day mortality were 1.4% and 2.7%, respectively and did not differ from mortality observed in university hospitals (1.4% and 2.6%, respectively). All patients positive for 90-day mortality at non-university hospitals underwent minor resections only, two for metastasis and the remaining six concomitant to other procedures. According to the in-patient's registry, we identified 56 patients who died within 90 days from surgery in one of the seven university hospitals. In the local registries, we identified 46 patients (80.7%) positive for 90-day mortality who were subjected to elective hepatectomy and thereby accessible for further data acquisition. Additional information regarding the study population, both the background population of liver resections and those positive for 90-day mortality, is shown in Table 1. In the group with 90-day mortality, there is a significant overrepresentation of patients with Charlson score 1 and ≥2, diagnosis of cholangiocarcinoma and GBC as well as major and extended hepatectomy. In contrast, minor resections and patients with Charlson score 0 are significantly underrepresented in the PHLF group. Subdividing all patients with 90-day mortality in a PHLF and non-PHLF group, 19 patients (41%) were assigned to the PHLF group. Of those, 16 patients fulfilled the 50:50 criteria. The remaining three patients were allocated due to PHLF developed in the later course as a consequence of secondary complications. In all patients, PHLF was considered to be the main reason for death, whether alone or in combination with multi-organ failure. In the non-PHLF group, we allocated 27 patients (59%). In this group, the most common reason for death was post-operative hemorrhage ($n = 9$). Other reasons, whether alone or in combination, were anastomotic insufficiency/bowel perforation ($n = 5$), cancer progress ($n = 4$), aspiration/respiratory failure ($n = 3$), sepsis/multi-organ failure ($n = 3$), ischemic heart disease ($n = 2$), pulmonary embolism ($n = 1$) and unclear reasons in three patients. Comparing the baseline characteristics in the PHLF and non-PHLF group, there were significantly greater proportions of patients with CCC ($p = .01$) and after extended hepatectomy ($p = .019$) in the PHLF group. On the other hand, in the non-PHLF group there were more patients after minor resections ($p < .001$). Additional data are shown in Table 2. When comparing pre-operative variables, we could not identify any significant difference between the PHLF and non-PHLF groups. Data are detailed in Table 3. Intra-operatively, we found a statistically significant higher proportion of patients with vascular reconstructions in the PHLF group ($p = .026$). Other variables did not differ significantly and details are shown in Table 4. Analyzing a compilation of variables related to the post-operative course of patients, we found several significant differences between the PHLF and non-PHLF groups. Bilirubin >50 μg/L and INR >1.5 were significantly more often found in the PHLF compared to the non-PHLF group already on POD 3 (all $p < .001$). In the post-operative course, encephalopathy of any grade was also found more frequently in the PHLF group than in the non-PHLF group ($p < .001$). In contrast, transfusion of blood products was found more often in the non-PHLF group ($p = .036$). No other significant differences were found and all post-operative variables are compiled in Table 5.

**Table 1.** Demographic and clinical data of all patients in Sweden between 2005 and 2009 who underwent hepatectomy compared to the group of patients positive for 90-day mortality.

| | Hepatectomies | | 90-day mortality | | |
|---|---|---|---|---|---|
| | *N* | % | *N* | % | *p** |
| Total | 2461 | | 46 | | |
| Age (mean, std) years | 61.6 (13.6) | | 67.4 (8.1) | | n.s. |
| Male sex | 1322 | 53.7 | 33 | 71.7 | n.s. |
| Comorbidity Charlson score | | | | | |
| 0 | 1671 | 67.9 | 10 | 21.7 | <.001 |
| 1 | 700 | 28.4 | 26 | 56.5 | <.001 |
| ≥2 | 90 | 3.7 | 10 | 21.7 | <.001 |
| Diagnosis | | | | | |
| CRLM | 1490 | 60.5 | 22 | 47.8 | n.s. |
| HCC | 150 | 6.1 | 3 | 6.5 | n.s. |
| CCC | 88 | 3.5 | 10 | 21.7 | <.001 |
| GBC | 129 | 5.2 | 11 | 23.9 | <.001 |
| Benign or other | 604 | 24.5 | 16 | 34.8 | n.s. |
| Type of resection | | | | | |
| Minor | 1546 | 62.8 | 16 | 34.8 | <.05 |
| Major | 718 | 29.2 | 13 | 28.3 | n.s. |
| Extended | 197 | 8.0 | 17 | 37.0 | <.05 |

CRLM: colorectal liver metastasis; HCC: hepatocellular cancer; CCC: cholangiocarcinoma; GBC: gallbladder cancer; n.s.: non-significant.
*p**: comparison of proportions in the hepatectomies/90-day mortality group (chi-square).

**Table 2.** Data from medical charts on resected patients who died within 90 days at university hospitals, stratified for PHLF and non-PHLF.

| | PHLF-group ($N = 19$) | | Non-PHLF-group ($N = 27$) | | |
|---|---|---|---|---|---|
| | *N* | % | *N* | % | *p* |
| Age (mean, std) years | (67.5, 7.1) | | (67.7, 8.7) | | n.s |
| Male sex | 13 | 68.4 | 19 | 73.1 | n.s |
| Comorbidity | | | | | |
| Charlson 0 | 3 | 15.8 | 6 | 22.2 | n.s |
| Charlson 1 | 10 | 52.6 | 16 | 59.3 | n.s |
| Charlson ≥2 | 6 | 31.6 | 4 | 14.8 | n.s |
| Diagnosis | | | | | |
| CRLM | 7 | 36.8 | 14 | 53.8 | n.s |
| HCC | 2 | 10.5 | 1 | 3.8 | n.s |
| CCC | 8 | 42.1 | 2 | 7.7 | =.01* |
| GBC | 2 | 10.5 | 9 | 34.6 | n.s |
| Type of resection | | | | | |
| Minor | 1 | 5.3 | 15 | 57.7 | <.001** |
| Major | 9 | 47.4 | 7 | 26.9 | n.s |
| Extended | 9 | 47.4 | 4 | 15.4 | =.019** |

CRLM: colorectal liver metastasis; HCC: hepatocellular cancer; CCC: cholangiocarcinoma; GBC: gallbladder cancer; n.s.: non-significant.
*Fisher's exact test; **chi-square test.

**Table 3.** Pre-operative data on PHLF and non-PHLF patients.

| | PHLF-group (*N* = 19) | | Non-PHLF-group (*N* = 27) | | |
|---|---|---|---|---|---|
| | *N* | % | *N* | % | *p* |
| BMI ≥30 | 4 | 21 | 4 | 15 | n.s |
| Smoking | 1 | 5 | 3 | 11 | n.s |
| Diabetes | 6 | 32 | 3 | 11 | n.s |
| Hypertension | 6 | 32 | 12 | 44 | n.s |
| Hepatitis | 0 | 0 | 3 | 11 | n.s |
| ASA ≥2 | 16 | 84 | 20 | 74 | n.s |
| Pre-operative chemotherapy | 3 | 16 | 5 | 18 | n.s |
| Cholestasis at time of surgery | 7 | 37 | 5 | 19 | n.s |
| PVE | 3 | 16 | 1 | 4 | n.s |

BMI: body mass index; ASA: American Society of Anesthesiologists score; PVE: portal venous embolization; n.s.: non-significant.

**Table 4.** Intra-operative data on PHLF and non-PHLF patients.

| | PHLF-group (*N* = 19) | | Non-PHLF-group (*N* = 27) | | |
|---|---|---|---|---|---|
| | *N* | % | *N* | % | *p* |
| Pringle | 7 | 37 | 10 | 37 | n.s |
| TVE | 1 | 5 | 0 | 0 | n.s |
| Resection of extrahep bile ducts | 8 | 42 | 6 | 22 | n.s |
| Vascular reconstruction | 4 | 21 | 0 | 0 | =.026* |
| Combination with other surgery | 0 | 0 | 4 | 15 | n.s |
| Combination with ablation | 0 | 0 | 4 | 15 | n.s |
| Operative bleeding >2000 mL | 8 | 42 | 8 | 30 | n.s |

TVE: total vascular exclusion; extrahep: extra-hepatic; n.s.: non-significant.
*Fisher's exact test.

**Table 5.** Post-operative data on PHLF and non-PHLF patients.

| | PHLF-group (*N* = 19) | | Non-PHLF-group (*N* = 27) | | |
|---|---|---|---|---|---|
| | *N* | % | *N* | % | *p* |
| Cirrhosis | 4 | 21 | 3 | 11 | n.s |
| Steatosis | 4 | 21 | 10 | | n.s |
| Fibrosis | 5 | 26 | 3 | 11 | n.s |
| POD 3 | | | | | |
| Bilirubin ≥50 μg/L | 15 | 79 | 3 | 11 | <.001** |
| INR >1.5 | 15 | 79 | 1 | 4 | <.001** |
| POD 5 | | | | | |
| Platelets <100 × 10(9)/L | 5 | 26 | 2 | 7 | n.s |
| Creatinine >120 μmol/L | 7 | 37 | 3 | 11 | n.s |
| Post-operative transfusion | 5 | 26 | 15 | 55 | =.036** |
| Bile leakage | 2 | 11 | 7 | 26 | n.s |
| Surgical intervention | 5 | 26 | 10 | 37 | n.s |
| PTC/ERCP | 2 | 11 | 2 | 7 | n.s |
| Infection | 6 | 32 | 14 | 52 | n.s |
| Aspiration | 1 | 5 | 3 | 11 | n.s |
| Portal thrombosis | 5 | 26 | 1 | 4 | n.s |
| Encephalopathy | 8 | 42 | 0 | 0 | <.001* |

n.s.: non-significant; POD: post-operative day; INR: international normalized ratio; PTC: percutaneous-transhepatic-cholangiography; ERCP: endoscopic retrograde cholangiopancreatography.
*Fisher's exact test; **chi-square test.

## Discussion

Our study confirms that PHLF is the main reasons for post-operative short-term mortality even in a population-based setting. As shown previously, certain risk factors significantly contribute to death in the PHLF group compared to those patients with 90-day mortality due to other reasons than PHLF.

PHLF is considered a serious complication following hepatectomy with frequently dismal outcome [6,15]. However, there are several remaining problems in the understanding and description of PHLF. The maybe most important limitation is found in the problem of defining PHLF as this massively influence the incidence of PHLF. In the year 2005, Balzan et al. were the first to publish a risk score, a combination of bilirubin value and INR on POD, to predict mortality following hepatectomy [10] and the accuracy of this so called 'Balzan' or '50:50' criteria was prospectively confirmed later on [16]. However, several reports could not confirm the accuracy of the 50:50 criteria but proposed other variables in order to define PHLF and predict patient outcome. The most important ones are represented by the International Study Group of Liver Surgery (ISGLS) criteria [17], the Mullen or 'peak-bilirubin' criteria [5] and the Hyder score [18]. Recent reports focused on validating especially the ISGLS criteria [9,19] but on the other hand, even the '50:50' criteria as well as the Mullen criteria are still used in current publications [20,21]. In a recently published Swedish single-center study on extracorporeal liver support in patients with PHLF, the 50:50 criteria were found to serve as valid inclusion criteria [22]. Therefore, the 50:50 criteria have been used to define PHLF in the current study, too.

In recent years, several reviews have summarized the available literature regarding PHLF and discussed important issues such as definition and prevention, risk factor analysis, management and outcome of patients with PHLF [6,15,23,24]. Compared to the reviewed reports, our study provides several advantages. A major benefit is represented by the study design with a population-based approach, covering all hepatectomies in Sweden over a 5-year period. This is a unique methodology in the evaluation of PHLF and implicates improvement of data quality as they do not contain any selection bias compared to single-center data [11,25,26]. Another advantage is the large number of patients included in the study which increases the statistical power of the results. As we have observed in a previous study, mortality following hepatectomy is lower in Sweden [3] compared to other population-based data [1,2]. All university hospitals in Sweden apply national, evidence-based guidelines for patient selection prior to surgery. However, patient mix/characteristics with lower number of patients with, for example, cirrhosis and a more conservative patient selection in regard to, for example, age or disease burden might contribute to a lower short-term mortality in Sweden. Despite these differences in terms of patient selection, also in the present study, PHLF contributes to or is the single cause in more than 40% of all deaths within 90 days from surgery. At non-university hospitals, we identified eight patients positive for 90-day mortality. All of them underwent minor resections and, in consequence, the risk for PHLF as cause of death should be very low in these patients.

On the other hand, there are several limitations in the present study. Due to the retrospective study design, it might be assumed that quality of the obtained data is not as good as compared to prospective collected data and several variables had to be excluded from analysis due to this problem. Another issue could be seen in the time period for data

collection. However, an earlier publication addressing the outcome after liver surgery in Sweden between 2002 and 2011 [3] raised several scientific questions which we were able to address in the present study. In addition, from 2009 onwards, there was a new registry, the national liver registry, sweliv introduced in Sweden. Data from this registry might be, after validation, available in the near future for a follow-up study of the present report. Another problem was the mismatch of cases positive for 90-day mortality in the Swedish Hospital Discharge Registry compared to local hospital registries. A possible explanation might be wrong coding in the Swedish Hospital Discharge Registry, or even more likely, liver resections have been performed by other specialties than liver units, for example, trauma units, colorectal surgeons or urologists and therefore the cases have not been identified in the local hospital registries where data on elective hepatectomies were available exclusively. As major and extended hepatectomies and thereby the risk for PHLF are more unlikely to be missed in this situation, there could be an underestimation of deaths due to other causes in our final patient population and thus, the impact of PHLF could be overestimated for the whole population. Finally, due to the study design, we are not able to present the incidence of PHLF in the entire population as these data, mainly blood samples, are not available in the used nation-wide registries.

In summary, PHLF represents a major risk for short-term mortality even in a population-based setting and measures have to be taken to improve both, avoidance and treatment, of patients with PHLF.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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