Pulmonary Infection after Hepatic Resection: Associated Factors and Impact on Outcomes

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Original article

Abstract

Background and aims: Postoperative pulmonary complications are frequent after hepatectomy. The aim of this retrospective study was to use preoperative and intraoperative data to establish specific factors associated with post-hepatectomy pneumonia (PHPN).

Methods: Patients underwent minor or major hepatectomy for cancer or non-cancer treatment. Surgical procedure was performed by laparoscopy or laparotomy. PHPN was defined as a new radiologic finding associated with fever, leucocytosis and purulent bronchial secretions. The incidence, associated factors and prognosis of PHPN were investigated.

Results: In 399 patients undergoing planned hepatectomy, 49 (12.3%) developed pneumonia. Of 81 patients (20.3%) with cirrhosis, 77 were Child-Pugh A and 4 were Child-Pugh B. Hepatectomy indication was cancer in 331 patients (of which metastasis in 213). Laparoscopy rate was 31.3%. In multivariate analysis, the main factors statistically associated with PHPN were: chronic obstructive pulmonary disease (COPD) (odds ratio [OR]=4.17; 95% confidence interval [CI], 1.60–10.84; P=0.003), intraoperative blood transfusion (OR=2.46; 95%CI 1.01–5.70; P=0.001), laparotomy (OR=3.01; 95%CI 1.09–8.27; P=0.03), and nasogastric tube maintained at day 1 (OR=2.09; 95%CI 1.03–4.22; P=0.04). Length of stay was significantly different between groups without PHPN (10.2 days) versus with PHPN (26.4 days; P<0.001). Intra-hospital and one-year mortality were greater in the PHPN group than the pneumonia-free group (8.16 vs 0% and 18.4 vs 3.4%, respectively; P<0.001).

Conclusions: COPD, transfusion and laparotomy (versus laparoscopy) are factors associated with PHPN and impaired survival.

Keywords: pneumonia, liver surgery, risk factors, laparoscopy, blood transfusion

Abbreviations:

PHPN: post-hepatectomy pneumonia

COPD: chronic obstructive pulmonary disease

PPC: postoperative pulmonary complications

PTC: portal triad clamping

TVEL: total vascular exclusion of the liver

RBCT: red blood cell transfusion

AST: aspartate aminotransferase

ALT: alanine transaminase

PT: prothrombin time (expressed as a percentage)

Introduction

Liver resection is an increasingly common surgery and remains the first-line treatment for metastatic colorectal disease and hepatocarcinoma [1]. Despite technical advances and high experience with liver resection in specialized centers, hepatic resection is still burdened by relatively high rates of postoperative morbidity and mortality [2]. Postoperative pulmonary complications (PPC) were the most frequent complication in these series, reaching a prevalence of up to 50% of patients [3-7].

Many risk factors for PPCs have already been identified, such as advanced age, tobacco, history of chronic obstructive pulmonary disease (COPD), ASA classification and incision site [8]. These factors have been established for general elective surgery or upper abdominal procedures. However, fewer studies have specifically analyzed factors associated with PPC after hepatectomy for cancer [4].

PPCs are a broad set of complications including pleural effusion, pulmonary embolism atelectasis, and pneumonia. When we enlarged the definition to encompass patients needing oxygen therapy > 3L O2/min on postoperative day 2 (capillary oxygen saturation in ambient air < 90%), the incidence reached 34% [9]. Ischemia-reperfusion and hemodynamic phenomena, primarily located in the liver but targeting secondary lungs, could be implicated in these pathologies. Previous research [4] has demonstrated that risk factors differ depending on type of pulmonary complication.

Because pulmonary complications after liver surgery is such a vast group encompassing different entities with different causes [4], we decided to only study pulmonary infections with narrower criteria. Moreover, the evolution of surgery, with more than 30% of procedures now performed by laparoscopy in some expert centers, mean that previous studies are now outdated. In ~~y~~our own centre, after our study on the causes of pulmonary complications [9], the rate of continuous hepatic clamping (continuous portal triad clamping (PTC) or total vascular exclusion of the liver (TVEL) decreased from 56% to 37% in the interval between our first study and the present study. Furthermore, perioperative management of patients in these studies was either not standardized or, when standardized, only very partially reported.

For this reason, and because anesthetic and surgical techniques have evolved over the past decade towards more laparoscopic surgery and shorter liver clamping, we used our prospective database to analyze the risk factors specifically for post-hepatectomy pneumonias (PHPN)

Materials and Methods

This retrospective study was approved by the institutional review board of Paris Descartes University (№ 2018-19, approved March 6, 2018) that did not require written informed consent. Our database (HEPATODATA) was declared with the French data privacy authority (CNIL) (report number № 1947002 v0, April 22, 2016).

Patient population

All adult patients who were candidates for elective liver surgery between January 2015 and December 2017 at our center were considered eligible for this study. There were no exclusion criteria. Data were prospectively collected from our hospital database (MetaVision® Suite, Clinical Information System - version 5.47, Europe-iMDsoft GmbH, Germany).

Primary endpoint

The primary endpoint of the study was onset of pneumonia from the postoperative day (POD) 1 until POD 7. A priori criteria used for diagnosis of pneumonia [10] were as follows: recent radiologic pulmonary infiltrates (routine chest radiography or computed tomography) associated with at least two of the following criteria:

- leukocytosis or leukopenia
- fever > 38°C
- purulent bronchial secretions

Secondary endpoints

The secondary endpoints were:

- postoperative mortality, one-year mortality, hospital length of stay, and ICU length of stay,
- bacteriologically-proven infections

- onset of acute respiratory distress syndrome (ARDS) defined by the Berlin criteria requiring invasive or non-invasive mechanical ventilation [11]

- medical or surgical postoperative complications classified by Clavien-Dindo criteria [12].

Anesthetic procedure

Each patient had an arterial catheter routinely placed in the radial artery, and two 16G venous catheters or a central venous catheter routinely placed in the right internal jugular vein. Fluid management and hemodynamic monitoring (systolic ejection volume by esophageal Doppler) were left to the anesthetists' discretion depending on hemodynamic condition. Target mean arterial pressure (MAP) was > 60 mmHg in the absence of comorbidity and > 70 mmHg for patients with cardiac risk. Blood transfusion was performed if intraoperative hemoglobin level (measured with Hemocue®) was < 8–9 g/dL depending on the patient's comorbidities. All patients received protective ventilation, defined by an end-tidal volume of 7–8 mL/kg, PEEP 5, FiO2 40%–50%, and recruitment maneuvers were executed if needed. Nasogastric tube was inserted just after the anesthetic induction and retrieved usually in the recovery room, unless medical imperatives required otherwise. The tube was left in place if patients required associated surgery (stomach, bowel, nodular carcinoma). If a patient vomited, the tube was put back in place. Non-invasive mechanical ventilation was only performed in cases of suspected atelectasis or in obese patients.

All patients received antibiotic prophylaxis as per French Society of Anesthesiology recommendations, i.e. Cefazolin, 2 g intravenously, 30 min before the incision, and Clindamycin + Gentamycin in case of allergy to beta-lactam antibiotics.

Surgical procedure

Liver resection was performed through abdominal incision or by laparoscopy, either without any clamping, with PTC (intermittent or continuous) or with TVEL (i.e. continuous clamping of the portal triad and infrahepatic and suprahepatic inferior vena cava). TVEL was preceded by a test of a few minutes of clamping to evaluate hemodynamic tolerance and adapt the procedure accordingly [13].

Postoperative management and data handling

Patients were admitted to either the ICU or the surgical ward according to their surgery and comorbidities. A daily subcutaneous injection of low-molecular-weight heparin sodium was started as a prophylactic against deep venous thrombosis on POD 1 or when prothrombin time reached more than 50% according to medical-surgical team decision.

Biological parameters such as a liver function tests (aspartate aminotransferase (AST) and alanine transaminase (ALT), total bilirubin, alkaline phosphatase and gamma-glutamyltransferase), blood creatinine, coagulation profile (prothrombin time (PT)(%), V factor), and blood cell counts were recorded on POD 1, 3, 5 and 7. Postoperative chest X-ray was performed if pulmonary complications were suspected. A thoraco-abdomino-pelvic CT scan was performed to confirm signs of postoperative abdominal or pulmonary complications. Patients were monitored for postoperative complications, mortality, and length of postoperative stay.

Definitions

Chronic obstructive pulmonary disease (COPD) was diagnosed by spirometry [14].

History of thromboembolic episodes was considered when there was a history of deep venous thrombosis or when pulmonary embolism had been confirmed by specific imaging. Cardiac disease included history of myocardial infarction, angina, coronary arterial stent insertion or cardiac surgery and/or history of congestive heart failure.

Major hepatectomy was defined as resection of three or more hepatic segments.

Hepatopathy was defined as the presence of steatosis >30% and/or suspicion of cirrhosis on preoperative imagery confirmed with direct intraoperative analysis and histology.

The definitions intraoperative complications are summarized in Table 1

Hepatic ischemia: PTC was either continuous or with alternating periods of 10 minutes clamping and 5 minutes declamping.

Inadequate analgesia was defined as visual analogic scale > 3 at least two times during the first 24 hours after discharge from surgery.

Postoperative mortality was defined as death within 30 days after surgery or during the hospital stay, and 1-year mortality was also studied.

Statistical analyses

Categorical variables were reported as counts and percentages, and quantitative variables were reported as mean and standard deviation. First, univariate analyses using logistic regression were performed to investigate associations between patient characteristics, pre- and intraoperative factors, and absence of pulmonary infection. Then, all factors with a P-value < 0.10 in the univariate analysis were included in a multivariate logistic regression model. After performing a stepwise procedure, the model with the lowest Akaike information criterion (AIC) score was selected as the final model.

We computed the unadjusted odds ratios (OR) after univariate analysis and the adjusted OR after multivariate analyses (using absence of pulmonary complication as the reference) along with the 95%-level confidence intervals (95%CI).

A log-rank test was used to compare survival curves between patients with and without PHPN.

The level of significance was set at P<0.05. All statistical analyses were performed using R 3.0.2 [15].

Results

Laparoscopic surgery was performed in 125 patients (31.3%), giving a total of 274 laparotomies. There were 169 (42%) major hepatectomies and 230 (58%) minor hepatectomies. Intermittent PTC was performed in 249 patients, continuous PTC was performed in 73 patients, no clamping was performed in 76 patients, and TVEL was performed in 14 patients. Time of continuous clamping was 41±21 min. Time of TVEL was 60 ± 15 min. All patients undergoing TVEL (except one with cirrhosis: ischemia time =38 min) had normal liver parenchyma. Hepatic ischemia time was > 60 min in 6 patients, for which we performed a cooled 20°C perfusion of the liver and veno-venous bypass.

General patient characteristics

The demographic and clinical characteristics of the population used to develop the multivariate logistic regression model are reported in Table 2.

Indications for surgery were benign tumor in 59 patients and cancer in 331 patients. In a further 9 patients, hepatic resection was performed for biliary lithiasis in liver disease and chronic angiocholitis following trauma to the bile ducts. Cancers included 85 hepatocarcinoma (HCC), 33 cholangiocarcinoma, and 213 metastatic tumors. Of 81 (20.3%) patients with cirrhosis, 77 were Child-Pugh A and 4 were Child-Pugh B. Meld score was 8.2 ± 2.5. The origin of cirrhosis was: alcohol (n=27), hepatitis B or C virus (without replication at the time of surgery; n=32), NASH cirrhosis (n=17), hemochromatosis (n=4), and autoimmune hepatitis (n=1). Another 35 patients had serologic evidence of viral hepatitis without biological, clinical, radiologic or histologic signs. For cirrhotic patients, biologic data were: ALT=45±52, AST=54±60, total bilirubin=10±9, alkaline phosphatase=96±45, gamma-glutamyltransferase=162±267, TP=86±12, and blood creatinine=87±29.

Operative time was 267 ± 108 min. Intraoperative blood loss was 289 ± 265mL, and 41 (10%) of patients received red blood cell transfusion (RBCT). Mean intraoperative fluid load was 7.7 ± 4 mL/kg/h, and 79 (20%) patients presented hemodynamic complications requiring vasopressors drugs.

In the immediate postoperative period, a nasogastric tube was in place on POD 1 in 113 patients (28%), and visual analog scale was scored > 3 at least once in 285 patients (71%).

In total, 49 patients (12.3%) presented postoperative pneumonia. Median day of onset was POD 3 [2-6]. Pneumonia was confirmed by bacteriologic samples in 31 patients (63%): 18 cases were oropharyngeal flora, 8 cases (16%) were gram-negative bacillus, 2 cases (4%) were *Staphylococcus aureus*, 2 cases (4%) were *Hemophilus Influenzae*, and 1 case (2%) was *Streptococcus* spp.

Four patients (1%) died during the immediate postoperative period, and 17 (4%) patients died during the first year post-surgery.

Hospital length of stay was 11.9 ± 12.1 days, and ICU length of stay was 7.4 ± 8.1 days.

Factors associated with onset of PHPN (Primary endpoint)

The univariate analysis identified the risk factors associated with occurrence of PHPN (Table 3). This analysis identified two preoperative factors, i.e. age and COPD, as higher in patients with PHPN (p<0.001). Intraoperative parameters associated with PHPN were operative time, type of surgery (laparotomy vs laparoscopic), associated non-hepatic cancer surgery, and blood loss. Postoperative parameters associated with PHPN were presence (or re-insertion) of a nasogastric tube at POD 1 and inadequate pain relief. Table 2 reports the comparison of characteristics two-by-two, i.e. by presence or absence of PHPN. Ventilation parameters (PEP level, FiO2), systolic ejection fraction and fluid and electrolytic loading during surgery were did not differ between groups.

Multivariate analysis was then performed by including all the significant ($P < 0.10$) preoperative and intraoperative factors associated with presence of PHPN. After a stepwise model selection process (see Statistical analysis), the final multivariate analysis retained 5 parameters independently associated with PHPN, i.e. COPD, laparotomy, intraoperative RBCT , nasogastric tube at POD 1, and age (Figure 1).

Secondary endpoints

Eight patients presented ARDS, 108 (27%) presented pleural effusion, 111 presented atelectasis (28%), 17 presented pulmonary embolism (4.3%). Non-invasive ventilation was performed in 66 patients (16.5%), and 10 patients (2.5%) required re-intubation.

The need for non-invasive or mechanical ventilation was higher in patients with PHPN than without PHPN, i.e. 61.2 *vs* 10.3 (P<0.001) and 18.4 *vs* 0.3% (P<0.001), respectively.

Clavien-Dindo score was < 3 in 304 (76%) patients. Postoperative liver insufficiency was higher in patients with PHPN than without (26.5% vs 4.8%, P<0.001). Postoperative ascites and jaundice were also higher in patients with PHPN (22.4% and 26.5% *vs* 8.6 and 9.1, respectively; P<0.001).

Table 3 reports postoperative and 1-year mortality rates and hospital and ICU length of stay.

Three patients that had early postoperative liver insufficiency died postoperatively in hospital. A fourth returned to the operative room for portal thrombosis, then presented PHPN and died in a clinical picture of multi-visceral failure resistant to all treatment. Of the 17 other patients who were dead at one-year follow-up, 16 underwent associated surgery and died of cancer recurrence, and one had been liver-transplanted and died early after the transplantation. One-year survival curves for patients with and without PHPN are reported in Figure 2.

Discussion

This three-year cohort study identified five independent parameters associated with PHPN after hepatic resection, *i.e.* COPD, laparotomy, and intraoperative RBCT, nasogastric tube, and age. Age is not discussed here as the OR was very close to 1, which rules out certain clinical significance. PHPN was also associated with longer hospital and ICU stays and higher postoperative and 1-year mortality.

The pneumonia incidence rate was very similar here to Nobili et al. [4] (12.3 versus 12.8%) with criteria very similar criteria. The association of PHPN occurrence with longer hospital stay was also similar in both series. Multivariate analysis in both studies identified intraoperative blood transfusion as an independently associated parameter. Atrial fibrillation was the only other associated parameters evidenced by Nobili et al. whereas we found COPD and laparotomy but not atrial fibrillation as associated parameters. An explanation for the discordance between the our two studies on COPD could be the difference in disease severity: COPD is considered as a qualitative parameter (yes/no) whereas COPD can be classified on a gradient of many classes (16). However, COPD is more frequently found to be associated with pulmonary complication than atrial fibrillation [17], and although Nobili et al. recognized atrial fibrillation as a risk factor for pulmonary complications, it was only for pleural effusion, and not for pneumonia.

The most important point differentiating our study from Nobili et al. is that here we were able to also factor in laparoscopic operations, which were still infrequent in the late 2000s. Recent meta-analyses [18,19] have shown lower risks for total complications and shorter hospital stays in patients undergoing laparoscopic surgery. Upper-abdominal laparoscopic surgery [20] is probably superior to laparotomy, especially for liver resection [21], and we systematically use laparoscopy in our center unless the procedure is ruled impossible or dangerous. A recent retrospective study [22] focussing on pulmonary complications after liver resection used propensity score matching to compare laparoscopic surgery against laparotomy and found that pulmonary complications (pneumonia, pleural effusion) were more frequent in patients undergoing laparotomy and that postoperative hospital stay was significantly shorter in the matched laparoscopic group.

Intraoperative blood transfusion is the third independent parameter associated with pneumonia in our study. Bleeding is a major cause of post-surgery morbidity and is often managed using RBCT, especially in patients presenting preoperative anemia. Intraoperative blood loss is highly correlated with RBCT but much harder to measure reliably and prone to inaccuracy [23], which is why we opted to test RBCT rather than blood loss in our multivariable analyses. In the literature, the reported proportions of patients who receive RBCT following hepatectomy vary widely (25%–57%) but are decreasing strongly over time [24], likely due to the decrease in the target hemoglobinemia (Hb) threshold for considering RBCT and to the better availability of intravenous iron in perioperative patient management. RBCT is known to negatively impact several short-term outcomes following hepatectomy, such as acute lung injury and 30-day morbidity and mortality [25,26]. One cause may be immunomodulatory effects of RBCT resulting in greater susceptibility to infection [27]. However, the trend towards higher mortality in patients receiving RBCT after hepatectomy is not seen in all studies [27]. Other factors than RBCT per se, such as preoperative anemia or iron deficit, may be implicated in the higher morbidity of transfused patients, and so a more restrictive transfusion strategy in hepatectomies should probably be combined with early preoperative detection of anemia and intravenous iron administration [28].

Another key finding of this study is that pneumonia is statistically associated with one-month and one-year mortality. PHPN was strongly associated with overall postoperative complications, and all 4 patients that died postoperative had developed pneumonia. The time of diagnosis at POD 3 was in agreement with results reported in the EOLE study in general surgery [29]. Pneumonia was confirmed bacteriologically in 60% of cases. This rate, which is rarely reported in the literature, may be considered low but nevertheless reflects current practice: only patients with severe PHPN admitted to critical care and mechanically ventilated systematically benefit from bacteriological sampling. There is no relationship between between PHPN and mortality in clinically-healthy living liver donors [30], but PHPN has a disproportionately large contribution to surgical mortality in emergency general surgery patients [31]. The association found here between PHPN and one-year mortality may mean that PHPN is more a signal of patients in severe medical condition than a direct cause of mortality. Indeed, all four patients that died postoperatively in hospital presented severe hepatic complications. In short, patients die with PHPN rather than 'because of' PHPN. PHPN may be an aggravating factor and should therefore be addressed as a priority by targeted surgical improvement initiatives. Laparoscopic surgery, early withdrawal of nasogastric intubation, early postoperative patient mobilization, and preoperative respiratory physiotherapy in COPD are all key strategies that could be developed to decrease the length of hospital stay. However, 1-year follow-up data shows that patients with PHPN have more advanced cancer.

Interestingly, we, like Nobili et al. [4], found that PHPN was not significantly associated with cirrhosis, major hepatectomy, and age. A plausible explanation could be the stringent screening performed by the surgical teams in charge of patients with associated comorbidities. Diabetes mellitus, which was found as a risk factor in Nobili et al. but not here, is a different case. Diabetes mellitus, like tobacco use, renal insufficiency and cardiac insufficiency, is probably not characterizable by a straightforward dichotomous 'yes or no': the risk factor for a patient with well-controlled diabetes that started one year ago will be different from a patient who has struggled with hard-to-manage diabetes mellitus for over 30 years. This reduction of complex parameters to a dichotomous ‘yes/no’ is the first limitation of our study, and could explain why some of our results diverge from other studies.

A second limitation concerns the diagnosis of pneumonia. We defined the diagnosis of pneumonia in our center according to American Thoracic Society guidelines [10], but our database did not collect each criterion. We trust the physicians in charge of the patient to comply with the diagnosis criteria, but we could not double-check the process *a posteriori*. Another limitation of our study is that many factors had to be rejected from the multivariate analysis despite being statistically significant in the univariate analysis, because the sample of 49 PHPN out of a total population of 399 patients meant that the multivariate models could only include a small number of parameter variables.

The findings reported here come from a single-center analysis but are probably generalizable enough to inform all future efforts to reduce PHPN. This study has three implications for anesthetic practice:

- practitioners should aim to make more use of laparoscopic surgery in liver resection;
- practice should systematically include preoperative detection of anemic patients, early intravenous iron administration, and Hb < 7.5g/dL for RBCT in hemodynamically-normal patients
- better detection, evaluation and preoperative management of patients with COPD.

Declaration of competing interests

The authors declare that they have no competing interests.

Financial support

None

Author contributions

Study design: DE, YL

Coordination**:** YL, LL, DE

Data acquisition: YL, NT, LL, OS

Data interpretation: DL, ES, DE, BG, YL

Writing–Original draft: DE, YL, JCV

Writing–Review & Editing: DE, ES, DL, JCV

All authors read and approved the final manuscript.

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Table 1 – Definitions of intraoperative complications

Intraoperative complications	**Definitions**
Hemorrhage	Intraoperative bleeding > 500 ml
Hemodynamics	Need for catecholamine support
Air embolism	Sudden onset of SpO_2 < 90%, associated with MAP < 60 mmHg and $EtCO_2$ < 20 mmHg.
Pneumothorax or diaphragmatic effraction	Intraoperative or postoperative radiologic findings

MAP: mean arterial pressure

Table 2 – Characteristics of the population and comparison between patients with and without PHPN
Odds ratios in univariate analysis

	All	No PHPN	PHPN	OR [95%CI]	PValue
	n=399	n=350	n=49		
Age (yrs), mean (SD)	61.4 (13.1)	60.7 (13.1)	66.6 (12.0)	1.04 [1.01–1.07]	0.004
Women (n, %)	174 (43.6%)	157 (44.9%)	17 (34.7%)	0.66 [0.34–1.22]	0.181
BMI, mean (SD)	25.4 (4.80)	25.5 (4.82)	24.6 (4.64)	0.96 [0.89–1.02]	0.182
ASA score > 2 (n, %)	164 (41.1%)	138 (39.4%)	26 (53.1%)	1.73 [0.95–3.19]	0.071
Arterial hypertension (n, %)	167 (41.9%)	140 (40.0%)	27 (55.1%)	1.84 [1.00–3.39]	0.047
Cardiac disease (n, %)	35 (8.77%)	34 (9.71%)	1 (2.04%)	0.22 [0.01–1.05]	0.110
Atrial fibrillation (n, %)	26 (6.52%)	22 (6.29%)	4 (8.16%)	1.36 [0.38–3.80]	0.619
History of venous thromboembolic disease (n, %)	37 (9.27%)	31 (8.86%)	6 (12.2%)	1.46 [0.52–3.51]	0.446
Tobacco (n, %)	182 (45.6%)	156 (44.6%)	26 (53.1%)	1.40 [0.77–2.58]	0.265
Alcohol use (n, %)	49 (12.3%)	42 (12.0%)	7 (14.3%)	1.24 [0.48–2.80]	0.648
COPD (n, %)	29 (7.27%)	18 (5.14%)	11 (22.4%)	5.33 [2.27–12.1]	<0.001
Obstructive sleep apnea (n, %)	17 (4.26%)	13 (3.71%)	4 (8.16%)	2.36 [0.62–7.09]	0.159
CRI (grade 3-4-5) (n, %)	41 (10.3%)	34 (9.71%)	7 (14.3%)	1.57 [0.60–3.60]	0.327
Diabetes (n, %)	50 (12.5%)	45 (12.9%)	5 (10.2%)	0.79 [0.26–1.94]	0.600
History of abdominal surgery (n, %)	260 (65.2%)	225 (64.3%)	35 (71.4%)	1.38 [0.73–2.75]	0.327
Cirrhosis (n, %)	81 (20.3%)	72 (20.6%)	9 (18.4%)	0.88 [0.38–1.83]	0.720
Cholestasis (n, %)	66 (16.5%)	53 (15.1%)	13 (26.5%)	2.03 [0.98–4.02]	0.047
NASH (n, %)	35 (8.77%)	30 (8.57%)	5 (10.2%)	1.24 [0.40–3.14]	0.706
Tumor (n, %)					0.038
Benign tumor (n, %)	59 (15.1%)	59 (16.7%)	2 (4.2%)	Ref.	
Cancer (n, %)	331 (84.9%)	285 (83.3%)	45 (95.8%)	4.29 [1.27–28.8]	
Type of surgery					0.192
Minor surgery (n, %)	230 (57.6%)	206 (58.9%)	24 (49.0%)	Ref.	
Major surgery (n, %)	169 (42.4%)	144 (41.1%)	25 (51.0%)	1.49 [0.81–2.73]	
Radiofrequency or microwave ablation (n, %)	23 (5.76%)	21 (6.00%)	2 (4.08%)	0.71 [0.10–2.56]	0.592
Associated cancer surgery (n, %)	44 (11.0%)	32 (9.1%)	12 (24.5%)	3.23 [1.48–6.72]	0.002
Operative time (min), mean (SD)	267 (108)	261 (107)	312 (108)	1.00 [1.00–1.01]	0.002
Cumulative clamping time (min), mean (SD)	43.5 (31.6)	43.4 (32.4)	44.6 (25.4)	1.00 [0.99–1.01]	0.582
Type of surgery					0.004
Laparoscopic surgery (n, %)	125 (31.3%)	119 (34.0%)	6 (12.2%)	Ref.	
Laparotomy, (n, %)	274 (68.7%)	231 (66.0%)	43 (87.8%)	3.60 [1.60–9.78]	
Blood transfusion (n, %)	41 (10.3%)	31 (8.86%)	10 (20.4%)	2.65 [1.15–5.70]	0.020
Blood loss (mL), mean (SD)	289 (265)	267 (226)	450 (421)	1.00 [1.00–1.00]	<0.001
Presence of nasogastric tube at day 1 (n, %)	113 (28.3%)	89 (25.4%)	24 (49.0%)	2.81 [1.52–5.19]	0.001
Inadequate analgesia during the first 24 hours	285 (72%)	241 (69%)	44 (90%)	3.50 [1.50–9.60]	0.005
Intraoperative complication (n, %)	102 (25.6%)	82 (23.4%)	20 (40.8%)	2.25 [1.19–4.19]	0.010

PHPN: post-hepatectomy pneumonia; BMI: body mass index; NASH: nonalcoholic steatohepatitis; CRI: chronic renal insufficiency, defined as creatinine clearance < 60 mL/min calculated by the Cockroft formula. Odds ratios (OR) were estimated by logistic regression analysis using "no pneumonia" as reference category.

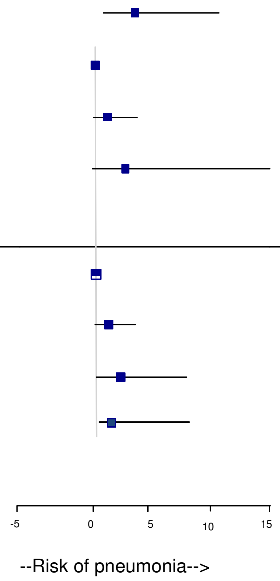
Table 3 – ICU and hospital length of stay and postoperative and one-year mortality year in patients with and without PHPN

	All patients (n= 399)	No PNPH (n= 350)	PNPH (n= 49)	P-value
Hospital length of stay (days, n ± SD)	12.2 ± 13.1	10.2 ± 9.5	26.4 ± 23	<0.001
ICU length of stay (days, n ± SD)	8.78 ± 10.9	6.27 ± 5.4	18.2 ± 18.6	<0.001
Postoperative deaths (n)	4 (1%)	0	4 (8.16%)	<0.001
One-year mortality (n)	21 (5.26%)	12 (3.4%)	9 (18.4%)	<0.001

PHPN: post-hepatectomy pneumonia

Figure 1 – Multivariate analysis: risk factors for PHPN

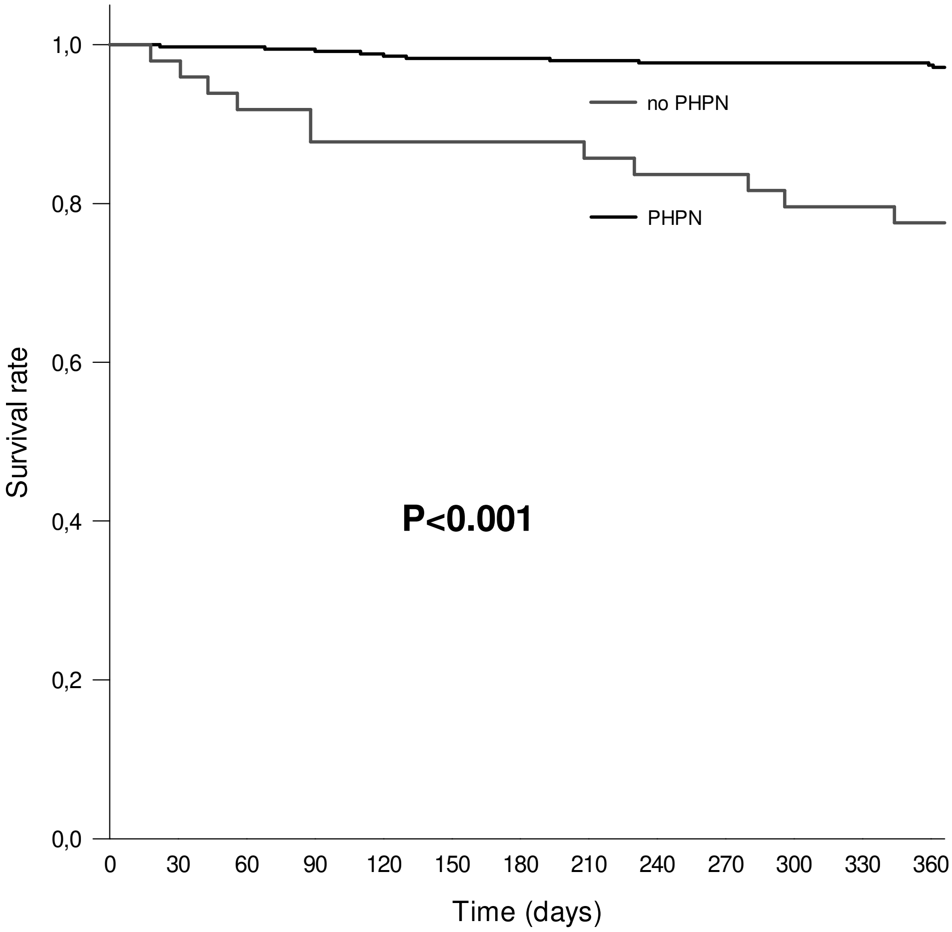
	OR	95%CI	P-value
Patient characteristics			
COPD	4.17	[1.60–10.84]	0.003
Age	1.04	[1.01–1.08]	0.008
Cholestasis	2	[0.92–4.33]	0.08
Cancer	3.43	[0.75–15.58]	0.11
Intraoperative factors			
Operative time	1	[1.00–1.01]	0.04
Nasogastric tube	2.09	[1.03–4.22]	0.04
Laparotomy	3.01	[1.09–8.27]	0.03
Intraoperative blood transfusion	2.46	[1.01-5.70]	0.001



PHPN: post-hepatectomy pneumonia

COPD: chronic obstructive pulmonary disease

Figure 2 – Survival curve for patients with and without postoperative pulmonary pneumonia



Number at risk

No PHPN	350	349	349	348	346	345	345	344	343	342	342	341	338
PHPN	49	47	45	44	44	44	44	43	42	42	41	41	40

PHPN: post-hepatectomy pneumonia