Research Article

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Pulmonary embolism after elective liver resection: A prospective analysis of risk factors

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Background & Aims: Impairment of clotting factors after liver resection (LR) is considered to protect from the risk of pulmonary embolism (PE). We aimed at formally investigating the risk of PE after elective LR.

Methods: From 2007 to 2009, 410 consecutive patients were prospectively analyzed to assess the risk of postoperative PE after LR with a thoracic CT scan, with or without a CT pulmonary angiography (CTPA). All patients were on a standardized thromboprophylaxis regimen.

Results: PE was diagnosed in 24 (6%) patients within the first 10 postoperative days. Comparison between the PE group (n = 24) and the non-PE group (n = 386) showed a similar rate of metastatic liver disease (25 *vs.* 31%, $p = 0.308$) but higher rates of BMI $\geqslant 25$ kg/m^2 (75 *vs.* 46%, $p = 0.006$), major LR (79 *vs.* 45%, $p = 0.003$) and normal or minimally fibrotic liver parenchyma (92 *vs.* 73%, $p = 0.05$). No patients with PE had inherited or acquired coagulation disorders. The 90-day mortality rate was similar in the two groups (4% *vs.* 3%, $p = 0.77$), but the median hospital stay was longer in the PE group (20(IQR 16–27) *vs.* 11(IQR 8–16) days, $p = 0.001$). On multivariate analysis, the independent predictors for PE were a BMI $\geqslant 25$ kg/m^2 (adj. OR 5.27), major LR (adj. OR 3.13) and normal or minimally fibrotic liver parenchyma (adj. OR 4.21).

Conclusions: In addition to patient characteristics (high BMI), major resection and normal liver parenchyma increase the risk of PE after LR. This suggests that specific thromboembolic mechanisms are involved in liver regeneration and advocates more aggressive thromboprophylaxis in the high-risk groups.

Keywords: Pulmonary embolism; Thromboembolism; Computed tomography; Liver resection.

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Abbreviations: ABG, arterial blood gas analysis; PE, pulmonary embolism; LR, liver resection; MSCT, multislice computed tomography; CTPA, computed tomography pulmonary angiography; LMWH, low molecular weight heparin; BMI, body mass index; PVE, portal vein embolization; POD, postoperative day.

Introduction

Major surgery is associated with a postoperative hypercoagulable state related to the surgical trauma that may lead to thromboembolic complications [1]. Well-known risk factors associated with such complications after surgery include: prolonged immobilization, malignancy, obesity, smoking, and inherited or acquired thrombophilia [2]. This risk is particularly well studied after gastrointestinal (GI) surgery with a reported incidence from 1% to 6% [3–9]. However, the data available after liver surgery are scarce and lack standardization. Thromboembolism after liver resection (LR) has been considered as a rare event, since removal of a considerable hepatic mass during LR impairs hepatic synthesis of clotting factors [10], increasing the risk of bleeding after resection and hence protecting patients from PE. In this setting, the anticoagulants are rarely used or applied with caution [5,11,12]. To our knowledge, the rate of PE after liver surgery is reported in only two retrospective series and ranges from 1% to 6.3% [13,14]. Of note, these series included a non-standardized thromboprophylaxis regimen. The systematic screening of all postoperative events following LR in living donors showed that PE is not rare, despite the use of prophylaxis with low molecular weight heparin (LMWH) [15]. These clinical findings are sustained by thromboelastogram monitoring, showing a hypercoagulable state after LR as a result of an imbalance in the interplay of coagulation proteins [16–18].

These findings led us to pay more attention to the risk of PE after LR and to perform a prospective study that aims at detecting the clinical risk factors associated with the development of PE after elective liver surgery.

Patients and methods

Study design

From July 2007 to December 2009, we prospectively collected all demographic, clinical, and radiological data of patients who underwent an elective LR in our department. "Elective LR" defined stable patients with a first or second hepatic resection and with no contraindication to major surgery. The thromboprophylaxis protocol included compression stockings and early mobilization associated with single daily subcutaneous LMWH injection (Nadroparin 2.850 IU/day (0.3 ml) or 3.850 IU/day (0.4 ml) in obese patients) started on the night before LR and continued until the patient was discharged from the hospital [19]. The local ethics committee for clinical research approved the design of this study aimed at analyzing the incidence and risk factors of PE after elective LR.

Table 1. Preoperative data.

	PE group n = 24 (%)	Non-PE group n= 386 (%)	*p* values	Odds ratio	95% CI
Age					
≥65 yr	5	116	0.49	1.63	0.59-4.48
<65 yr	19	270			
Gender (Male/female)	16/8 (33/66)	215/171 (55/44)	0.29	0.75	0.32-1.77
ASA score					
1-2	23 (95)	362 (94)	0.38	1.52	0.19-11.76
3-4	1 (5)	24 (6)			
Body Mass Index					
<25 kg/m^2	6 (25)	210 (54)	0.006	0.33	0.14-0.76
≥25 kg/m^2	18 (75)	176 (46)			
Co-morbidities					
COPD	2 (9)	17 (4)	0.29	1.97	0.43-9.08
Renal insufficiency	0	4 (1)		n.a.	n.a.
Cardiac insufficiency	1 (5)	9 (2)	0.49	1.82	0.22-14.99
Hypertension	5 (24)	100 (26)	0.83	0.75	0.27-2.07
Coronary disease	1 (5)	20 (5)	0.93	0.79	0.1-6.19
Diabetes mellitus	3 (14)	39 (10)	0.54	1.27	0.36-4.45
Preoperative chemotherapy	3 (12)	79 (20)	0.34	0.55	0.16-1.9
Portal vein embolisation	1 (4)	39 (10)	0.35	0.38	0.05-2.94
Preoperative portal vein thrombosis	1 (4)	5 (1)	0.30	0.18	0.03-0.94
Indications to surgery					
Primary liver tumor*	7 (29)	147 (38)	0.31	0.49	0.21-1.13
Liver metastases*	6 (25)	120 (31)			
Benign lesion**	11 (46)	119 (31)			

*Hepatocellular carcinoma, colorectal liver metastases, endocrine liver metastases.
**Hepatocellular adenomas, primary sclerosing cholangitis, polycystic liver disease.
n.a., not attributable.

Table 2. Intra-operative data.

	PE group n = 24 (%)	Non-PE group n = 386 (%)	*p* values	Odds ratio	95% CI
Median operative time in minutes (IQR)	360 (300-420)	300 (240-370)	0.07	-	-
Major hepatectomy (≥3 Couinaud's segments)	19 (79)	173 (45)	0.003	0.21	0.08-0.58
Additional surgery	4 (17)	76 (20)	0.70	2.72	0.62-11.76
Total venous exclusion	2 (8)	16 (4)	0.29	2.1	0.45-9.72
Pedicular clamping (Pringle)	14 (61)	212 (57)	0.71	1.01	0.43-2.38
Patients requiring PRBC* transfusion	5 (21)	77 (20)	0.91	1.06	0.38-2.91

*Packed red blood cells.

This study follows the guidelines for reporting observational studies (STROBE statement [20]) and is registered at http://www.clinicaltrials.gov (identification number: NCT01486511).

Patient characteristics

All recorded demographic data are listed in Table 1. BMI was classified as <25 kg/m^2 (normal body weight) and ⩾25 kg/m^2 (overweight 25–29.9 kg/m^2; obese ⩾30 kg/m^2) as proposed by the World Health Organization classification [21]. Patients with previous history of PE, thromboembolic events or thrombophilia were excluded from this study.

Surgical procedure

Parenchyma transection was done using crushing clamp technique or ultrasonic dissector under intermittent pedicle clamping in case of bleeding. Haemostasis was achieved with bipolar coagulation; small vascular or biliary pedicles were clipped or ligated. The extent of liver resection was defined as major if resection consisted of ⩾3 Couinaud's segments [22]. Intra-operative data recorded are listed in Table 2. Significant portal hypertension (>10 mmHg), assessed by the presence of oesophageal varices, splenomegaly with thrombocytopenia less than 100,000/mm^3, and portosystemic shunts was considered as a contra-indication to major liver resection [23].

Computed tomography

Since we showed that the systematic use of postoperative multi-slice computed tomography (MSCT) of the chest in liver living donor detects a high rate of PE after LR [15], all patients from this study (except those with early hospital discharge, i.e., <5 days) had a conventional abdominal and chest MSCT with contrast media between postoperative days (POD) 5 and 10.

The conventional MSCT aimed at detecting the presence of postoperative intra-abdominal collection, portal or hepatic veins thrombosis, liver volume changes after major LR, and postoperative pulmonary complications, including PE. This was performed with a 64–detector row CT scanner (LightSpeed VCT,

GE Medical Systems) from the lung apices to the pelvis (Supplementary Table 1). Patients with clinical signs and/or conventional MSCT indicating a possible PE underwent a CT pulmonary angiography (CTPA) to confirm the diagnosis of PE. The latter was performed with the same CT unit on the same day (Supplementary Table 1). In patients with a confirmed PE, lower limbs Doppler ultrasound was done to exclude deep vein thrombosis (DVT).

Definition of pulmonary embolism

Only pulmonary veins thrombi confirmed on CTPA were defined as a PE. In addition, two categories of PE were defined: (a) symptomatic PE, when associated with respiratory chest pain, dyspnoea/tachypnoea (>20 cycles per minute), and/or supra-ventricular tachyarrhythmia (>100/minute) that developed after LR; (b) asymptomatic PE, when it was incidentally detected on postoperative conventional MSCT and confirmed on CTPA.

Laboratory investigations

The following hematological tests for inherited or acquired thrombophilia were collected prospectively (before starting heparin therapy) and analyzed retrospectively in patients with a postoperative PE: antithrombin deficiency, antiphospholipid antibodies and *Lupus* anticoagulant screening, protein S and C deficiency, activated protein C resistance (APC), Factor V Leiden and Factor II (Prothrombin G20210A) mutation [24]. ABG analysis was performed in all symptomatic patients with a suspicion of PE and in asymptomatic patients, after PE was diagnosed on postoperative CTPA [23]. The following parameters were then calculated: PaO_2/FiO_2 ratio and arterial/alveolar oxygen tension ratio (a/ApO_2). The latter ratio has demonstrated efficacy for prognosis of acute PE and was calculated as previously described [24].

Anticoagulation therapy after PE

Once a PE was diagnosed, we started intravenous (iv) heparin therapy and anti-Xa activity measurement was used for monitoring [25]. All doses and rates were calculated based on total body weight. Once the bleeding risk was lowered (usually after 48 h with no bleeding in drains) patients were put on a therapeutic dose of sc LMWH (according to body weight).

Assessment of surgical complications

Postoperative abdominal complications were recorded and graded according to the method described by the Clavien-Dindo classification [26]. Grade III to IV complications were categorized as severe. Postoperative mortality (i.e., grade V) was defined to include any death during postoperative hospitalization or within 90 days after LR.

Assessment of liver specimen

An experimented hepato-biliary pathologist analyzed all liver specimens. According to 2 well-established scoring systems [27,28], the liver parenchyma was defined as normal or minimally fibrotic when fibrosis score was no more than F2 with a macro- or micro-vesicular steatosis of less than 30% [29].

Statistical analysis

Student t, one-way ANOVA, and Mann–Whitney U tests were used to compare continuous variables where appropriate. The difference among proportions was determined using the Fisher exact test. Binary logistic regression model was used to identify independent predictors (age, sex, BMI, ASA score, portal vein embolization, preoperative chemotherapy, type of liver vascular clamping, indication for surgery, liver parenchyma, additional surgery and major LR) of postoperative PE after LR. The latter factors were included in multivariate analysis based on their clinical significance and regardless of their statistical significance in univariate analysis [30,31]. Statistical analyses were performed with the SPSS software (Version 18, SPSS Inc, Chicago, Illinois). Statistical significance was accepted with $p \leqslant 0.05$ (2-sided tests).

Results

During the study period, a total of 480 patients underwent a LR. As showed in Fig. 1, 70 patients were excluded from the study, leaving 410 consecutive patients, which formed the study group. Of note, patients with an early hospital discharge (n = 12) were systematically seen in our outpatient clinic, up to one month after surgery and they were all alive, without symptoms of PE at that time.

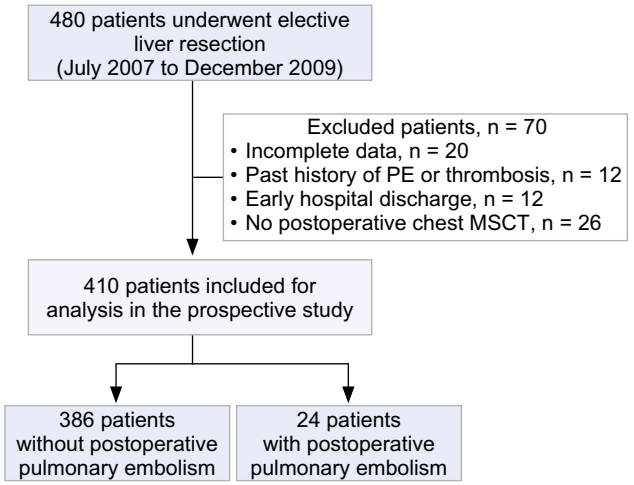

Fig. 1. Study population.

In the study group, median age was 54 years (range 18–88), and median BMI was 24 kg/m^2 (range 16–44). Indication for LR included primary malignant liver tumor in 154 patients (38%), liver metastases in 126 patients (31%), and eighty-two had preoperative chemotherapy. Only 4/410 patients underwent a second hepatic resection for metastatic colorectal or neuroendocrine tumor. Among the remaining 125 patients with benign diseases, none were operated for liver procurement in the study period.

Pulmonary embolism characteristics

Twenty-four patients (6%) presented with a postoperative PE in a mean time of 5 days (range 1–10 days). Among the 32 patients (8%) with symptoms of a possible PE after LR, 16 (50%) had a PE confirmed on CTPA. In eight cases (2%), PE was asymptomatic and detected incidentally on conventional chest MSCT. The following symptoms were recorded in the PE group: dyspnoea/tachypnoea (n = 7), tachyarrhythmia (n = 4), and/or chest pain (n = 5). All diagnosed PE were located peripherally in different pulmonary lobes/segments, and five were bilateral. Lower limbs DVT was found in only four patients.

Characteristics of patients with or without PE

As listed in Table 1, the pre-operative characteristics were similar except for the median BMI values (28 in the PE group *vs.* 24 kg/m^2 in the non-PE group, $p = 0.001$). In the PE *vs.* non-PE group, 7 (29%) *vs.* 147 (38%) patients were operated for primary liver tumor, and 6 (25%) *vs.* 120 (31%) for metastatic colorectal (CRC) or neuroendocrine (NE) tumor ($p = 0.308$). Analysis of intra-operative characteristics (Table 2) showed a significant higher rate of major LR in the PE group (79% *vs.* 45%, $p = 0.003$) with a majority of right hepatectomy (79% *vs.* 32%, $p < 0.001$) compared to the non-PE group. In patients with preoperative PVE, the extent of liver resection was significantly higher in the PE group compared

Table 3. Postoperative data.

	PE group n = 24 (%)	Non-PE group n = 386 (%)	*p* values	Odds ratio	95% CI
Major abdominal complications*	3 (12)	63 (16)	0.62	0.73	0.21-2.52
Median hospital stay (d)	20 (IQR 16-27)	11 (IQR 8-16)	0.001		
Median ICU stay (d)	1 (IQR 0-4)	2 (IQR 0-5)	0.183		
90-day mortality rate	1 (4)	12 (3)	0.77	1.35	0.17-10.88
Liver fibrosis score					
F0-F2	22 (92)	297 (77)	0.04	3.3	0.76-14.28
F3-F4**	2 (8)	89 (23)			
Liver steatosis					
≥30%	0	22 (6)	0.64		
<30%	24 (100)	363 (94)			
Normal or minimally fibrotic liver parenchyma	22 (92)	282 (73)	0.05	0.24	0.06-1.06

*Grade III to IV according to Dindo *et al.* classification [21].
**F4 corresponds to cirrhotic patients.

Table 4. Overall arterial blood gas (ABG) analysis in patients with/without PE at the time of suspicion of PE.

	PE group	Non-PE group	Normal range	*p* value
pH	7.44 (IQR 7.4-7.48)	7.35 (IQR 7.33-7.42)	7.34-7.44	0.017
Sat O_2 (%)	96 (IQR 93-98)	99 (IQR 98-100)		<0.001
PaO_2 (mmHg)	72 (IQR 60-82)	178 (IQR 136-230)	75-100	<0.001
$PaCO_2$ (mmHg)	37 (IQR 33-42)	36 (IQR 32-38)	35-45	0.399
PaO_2/FiO_2 ratio	285 (IQR 240-325)	477 (IQR 419-593)	300-500	<0.001
a/APO_2 ratio§	0.56 (IQR 0.41-0.64)	0.81 (IQR 0.72-1.03)	0.77-0.82	<0.001

§Alveolar/arterial ratio.

to the non-PE group (median liver volume resected of 75% (IQR 71–77) *vs.* 67% (IQR 61–74), $p = 0.017$). Postoperative outcome analysis was similar between the two groups (Table 3). No death was related to complications from PE. The only fatality in the PE group occurred in a patient who developed multiple septic complications from a severe chest infection leading to multiple organ failure.

Only two obese patients developed acute lung injury (ALI) with multi-lobar bilateral lung emboli (8%) that required artificial respiratory support. The other patients with PE were managed with non-invasive respiratory support (i.e., oxygen therapy with chest physiotherapy). The median hospital stay was significantly longer after PE (14.5 (range 7–58) *vs.* 11 (range 6–68) days, $p = 0.001$), while the median ICU stay was similar (Table 3). Liver parenchyma (Table 3) was more often normal or minimally fibrotic in the PE group (92% *vs.* 73%, $p = 0.05$). Only one patient (4%) had cirrhosis (i.e., Metavir score F4) in the PE group *vs.* 42 (11%) in the non-PE group ($p = 0.351$).

Arterial blood gas analysis and laboratory investigations

Table 4 lists the ABG measurements of patients with PE and without PE. Except for PCO_2 levels, all ABG values were decreased in the PE group. Of note, in the two patients that required ARS, ABG measurements at the time of PE diagnosis showed a PaO_2/FiO_2 ratio of 280 and 240 and an a/ApO_2 ratio of 0.48 and 0.39 (normal range: 0.7–0.8), respectively. According to ROC curve analysis and Yuden's index (which gives equal weight to sensitivity and specificity), PaO_2 of 124 mmHg, PaO_2/FiO_2 ratio of 372, and a/APO_2 ratio of 0.70 were the cut-off values defining PE in symptomatic patients (Fig. 2A–E).

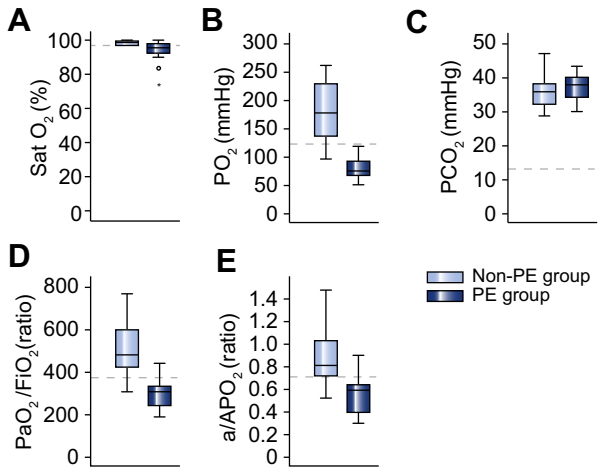

Fig. 2. Arterial blood gas (ABG) analysis in symptomatic patients with suspected postoperative PE. (A) Percentage of O_2 saturation, (B) partial pressure of oxygen (PO_2), (C) partial pressure of CO_2 (PCO_2), (D) partial pressure of O_2 to inspired fraction of O_2 ratio (PaO_2/FiO_2), (E) arterial/alveolar O_2 pressure ratio (a/APO_2). The dashed line represents the cut-off value for each parameter discriminating symptomatic patients at risk of PE. The two outliers in (A) correspond to the two patients that required artificial respiratory support.

Table 5. Antithrombin, protein C, protein S, and prothrombin G20210A (Factor II) activity in patients with PE after hepatectomy (n = 22/24).

	Mean (± SD)	Normal range
Antithrombin activity[1]	91 ± 18%	80-120%
Protein C activity[2]	110 ± 31%	70-140%
Protein S activity[3] (antigen)	94 ± 20%	75-140%
Factor II (prothrombin G20210A) activity[4]	112 ± 35%	75-110%

[1]Automated amidolytic method (Behring reagent).
[2]Coagulation method (Stago® reagent).
[3]Stago-Liatest® method.
[4]Coagulation method.

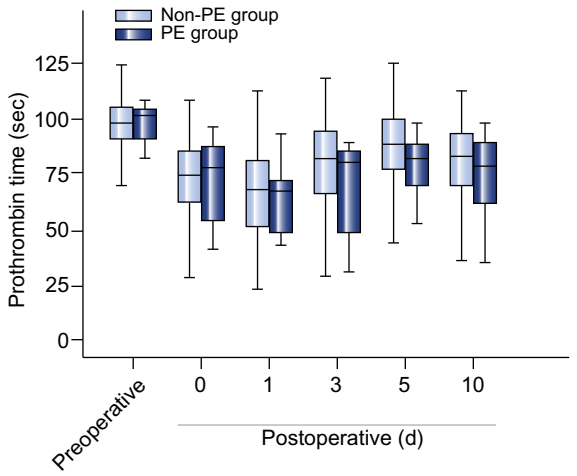

Fig. 3. Prothrombin time according to the postoperative day (POD) in the PE and non-PE groups. Values are expressed as median and interquartile range. Difference was significant only at POD 5 ($p = 0.044$).

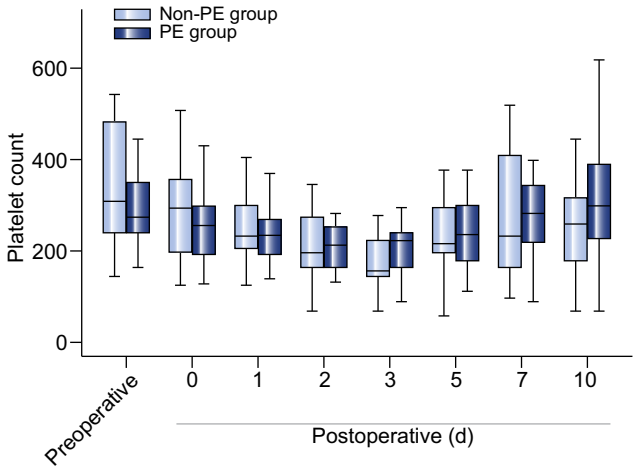

Fig. 4. Platelet count (PLT) according to the postoperative day (POD) in the PE and non-PE groups. Values are expressed as median and interquartile range. PLT tended to be higher in the PE group between POD 2 and 10 (not significant).

In the PE group, the analysis of inherited or acquired thrombophilia tests was performed in 22 of 24 patients (92%). The antithrombin, protein C, protein S, and prothrombin G20210A (Factor II) activity was in the normal range (Table 5). The screening for *Lupus* anticoagulant, antiphospholipid antibody syndrome, Factor II (prothrombin G20210A) mutation, APC resistance, and Factor V Leiden mutation was negative in all cases.

As showed in Figs. 3 and 4, the analysis of postoperative platelet count (PLT) and prothrombin time (PT) showed normocoagulability in the PE and non-PE groups. Although not significant, PLT tended to be higher in the PE group between POD 3 and 10. The median PT was lower after major resection between POD 1 to 5 (from 61 (IQR 47–71) to 87 (IQR 73–94) seconds, $p < 0.001$), while PLT counts tended to be higher after major LR at POD 0 and 1 (Supplementary Fig. 1).

Multivariate analyses (Table 6) showed that BMI values $\geqslant 25$ kg/m^2 (adj. OR 5.82) and major LR (adj. OR 3.13) were independently associated with the risk of PE after an elective LR, while resections in a normal or minimally fibrotic liver parenchyma nearly reach significance (adj. OR 4.21, $p = 0.058$).

Discussion

This is the first prospective study, to our knowledge, reporting the risk of PE after elective LR. Despite the systematic use of a standardized thromboprophylaxis protocol, we observed a 6% incidence of PE, similar to the high rates reported after gastrointestinal surgery without prophylaxis [3–7,13,14]. In addition to well-known risk factors (i.e., high BMI and major surgery), our study suggests that major liver resection in a normal parenchyma is a new independent risk factor for PE.

The extensive use of CTPA in this homogenous series led us to more precisely characterize symptoms and factors linked to the presence of PE after LR. The vicinity of the liver to the diaphragm explains why liver surgery is associated with a high prevalence of pulmonary complications, including pleural effusions, atelectases and pneumonia [15,32]. PE symptoms are often confounded with other postoperative respiratory events, and are then probably undetected and left untreated. The specific design of this study allowed the detection of 2% asymptomatic PE, which is in accordance with the rate detected in hospitalized patients [33–35]. The delay between LR and diagnosis of PE (mean time of 5 days) correlated well with the observations from other surgical series [33]. The low rate of severe respiratory or cardiac complications secondary to PE could be explained by the peripheral pattern of the emboli, which are unlikely to cause severe complications compared to the more centrally located ones [33]. Indeed, PE was non-fatal and it affected only the length of hospital stay [36]. Of note, PE after LR had a minimal impact on ABG analysis and only 8% of patients with PE required artificial respiratory support due to acute lung injury (ALI).

As described by others [12], we found a low rate of venous peripheral thrombosis in patients with a PE after LR. This may suggest that the thrombi responsible for PE arise from the operative site [37]. Although the routine use of MSCT failed to detect new thrombi in the main trunk of the portal or hepatic veins adjacent to the dissection plan, migration of small clots from the hepatic sinusoids could not be excluded. Of note, a recent study has suggested that inferior vena cava clamping during LR is a risk factor for postoperative PE [38]. In our series, this more

Table 6. Risks factors of postoperative pulmonary embolism in multivariate analysis.

		Number		*p* value	Odds ratio	95% CI	
		PE group	Non-PE group			Lower	Upper
Age group	>65 yr ≤65 yr	5 19	116 270	0.812	1.16	0.35	3.85
Sex	Male Female	16 8	215 171	0.833	1.11	0.42	2.89
BMI value	≥25 kg/m^2 <25 kg/m^2	18 6	176 210	0.001	5.27	1.89	14.71
ASA score	1-2 3-4	23 1	362 24	0.780	1.39	0.14	13.86
PVE	Yes No	1 23	39 347	0.987	1.01	0.20	5.08
Preoperative chemotherapy	Yes No	3 21	79 307	0.830	1.2	0.22	6.7
Total venous exclusion	Yes No	2 22	16 370	0.492	1.82	0.33	10.12
Pringle maneuver	Yes No	14 10	212 174	0.623	1.27	0.49	2.68
Primary liver tumor	Yes No	7 17	147 239	0.352	2.2	0.42	11.64
Liver metastases	Yes No	6 18	120 266	0.608	1.54	0.29	7.98
Normal or minimally fibrotic liver	Yes No	22 2	282 104	0.058	4.21	0.95	18.66
Additional surgery	Yes No	4 20	76 310	0.357	2.05	0.44	9.52
Major hepatectomy*	Yes No	19 5	173 213	0.046	3.13	1.02	9.57

* >3 Couinaud's segments.

"mechanical influence" was not confirmed since neither Pringle maneuver nor total venous exclusion of the liver was associated with the risk of PE.

Most hospitalized patients have one or more risks of PE, and these risks are generally cumulative [39]. We found three factors that were independently associated with the risk of postoperative PE after liver resection: (a) BMI values $\geqslant$25 kg/m^2, (b) major LR, and (c) normal or minimally fibrotic liver parenchyma.

Overweight, obesity, and metabolic syndrome (MS) predispose to thromboembolism events [40–42]. In these settings, the coagulation factors VIII, IX, and XI are increased [43]. Those metabolic disorders are of primary concern for the hepatic surgeon, since an increasing number of patients with high BMI and/or MS develop benign or malignant liver disease that requires liver surgery [44,45]. In addition, the visceral obesity promotes a chronic inflammatory state, which can potentially account for the risk of PE [46].

The coagulation cascade involves a complex interplay of protein with numerous factors and it is well established that the surgical trauma initiates the coagulation pathway through the inflammatory process [2]. The risk of thromboembolism after LR is considered being low due to a decrease in the synthesis of some clotting factors [13]. However, our results show that the prevalence of PE after elective LR should not be underestimated. None of the patients with PE had inherited or acquired thrombophilia and there is accumulating evidence that the balanced system of coagulation is perturbed in favor of a procoagulant state, early after hepatectomy in a normal parenchyma [16,17]. Interestingly, we found that PE occurred more often in patients with major LR, since nearly 80% of our patients with PE had a formal right hepatectomy with more than 70% of the total liver volume resected. These findings corroborate the results of a study showing that major liver surgery has a higher risk of developing a thromboembolism event compared to other major abdominal surgeries [47]. This risk is indeed one time lower after pancreatic surgery [47]. These results are supported by the thromboelastographic (TEG) analysis showing a hypocoagulability state after pancreatic surgery and a hypercoagulability after major liver surgery [10,16,17]. This suggests that specific thromboembolic mechanisms take place during extensive LR and hence during liver regeneration. We provide new evidence to support this hypothesis, since we show for the first time that a normal liver is an independent factor predisposing to PE after hepatectomy. It is clearly established that the non-damaged liver parenchyma has the highest capacity for regeneration [48–50]. This could dramatically influence the clotting cascade after LR to promote a procoagulant state.

One of the limitations of this study is that TEG analysis in the postoperative period is missing. On the other hand, prothrombin time analysis showed normocoagulability in the PE and non-PE groups, while it was slightly lower after major LR. Platelet counts tended to be higher in the PE group in the early postoperative period. However, the PT does not assess all the factors of the coagulation system. There is strong evidence that hypercoagulability may develop after partial hepatectomy in a normal liver [16,17]. It is known that partial hepatectomy in animal models results in an increase in FVIII and vWF plasma levels [51,52]. A previous study from our group showed that, in humans, vWF

plasma levels increased continuously from day 1 to 5 after partial liver resection [16]. The expression of protein ADAMTS 13 (produced by the hepatic stellate cells), which is a vWF cleaving enzyme essential for preventing excessive thrombotic events in the body (i.e., platelet aggregation), is significantly decreased early during liver regeneration [53]. In addition, ADAMTS 13 activity decreases after major LR in humans [54]. Interestingly, a recent study has shown that after major LR, the vWF to ADAMTS13 ratios are extremely high in patients with thrombotic complications [55]. Since we showed that normal or minimally fibrotic liver and major LR are independent risk factors for PE, one hypothesis for the underlying mechanism of PE could be that LR and regeneration act synergistically to promote a procoagulant state. However, this hypothesis needs to be confirmed in further prospective studies. It is noteworthy that according to the available evidence, ADAMTS 13 activity decreases immediately after LR and remains low up to POD 14 [54,55]. This time period corresponds exactly to the period at risk of PE in our series. Further prospective trials investigating the relationship between ADAMTS 13 activity and the risk of PE in the early postoperative period are warranted, as it may be a useful tool to detect patients at risk of PE after hepatectomy.

The results of this prospective study allowed the identification of a subgroup of patients with a high risk of PE after elective liver resection. Although BMI >25 kg/m^2 and major resection are well-known independent risk factors for PE after surgery, the presence of a normal liver parenchyma is a new factor that needs to be considered in the risk assessment for PE prior to LR. This suggests that specific thromboembolic mechanisms are involved in liver regeneration and advocates a more aggressive thromboprophylaxis in the high-risk groups.

Cancer

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhep.2012.08.004.

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