Association between splenectomy and portal hypertension in the development of pulmonary hypertension

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Abstract
Both portal hypertension and splenectomy are risk factors for pulmonary hypertension. However, the interactions between portal hypertension and splenectomy in the development of pulmonary hypertension remain unclear. Twelve newly diagnosed pulmonary hypertension patients with a previous history of splenectomy induced by portal hypertension were recruited between November 2008 and May 2017. We compared their clinical features, hemodynamics, and prognosis with idiopathic pulmonary arterial hypertension patients, who were matched by cardiac index, mean pulmonary arterial pressure, and pulmonary vascular resistance. We also compared the clinical characteristics of portal hypertension-post-splenectomy-pulmonary hypertension patients with eight portopulmonary hypertension patients. Compared with the matched idiopathic pulmonary arterial hypertension patients, the portal hypertension-post-splenectomy-pulmonary hypertension patients showed significantly wider red blood cell distribution width (16.7 ± 2.8% versus 13.3 ± 1.7%, p = 0.004), higher total bilirubin concentration (31.0 ± 13.8 µmol/l versus 18.9 ± 10.0 µmol/l, p = 0.010), and higher lactate dehydrogenase concentration (321.5 ± 41.2 IU/l versus 229.2 ± 69.4 IU/l, p = 0.001). Kaplan–Meier survival analyses showed that the portal hypertension-post-splenectomy-pulmonary hypertension patients tended to have poorer prognosis than the matched idiopathic pulmonary arterial hypertension patients (log-rank test: p = 0.010). Compared with the portal hypertension-post-splenectomy-pulmonary hypertension patients, the portopulmonary hypertension cohort appeared to exhibit poorer clinical conditions, including significantly lower mixed venous oxygen saturation (62.9 ± 8.0% versus 73.9 ± 6.5%, p = 0.004) and a significantly higher proportion of pericardial effusion (75.0% versus 8.3%, p = 0.004), even though the two cohorts showed similar hemodynamics. The mean intervals from diagnosis of portal hypertension to pulmonary hypertension in portopulmonary hypertension patients were significantly shorter than the intervals from splenectomy to diagnosis of pulmonary hypertension in portal hypertension-post-splenectomy-pulmonary hypertension patients (5.5 ± 5.2 years versus 13.1 ± 5.9 years, p = 0.008). Splenectomy might be involved in the initiation and development of pulmonary hypertension in patients with portal hypertension, although the precise mechanisms involved remain unknown. Portal hypertension-post-splenectomy-pulmonary hypertension patients might have poorer prognosis even with mild hemodynamics.

Keywords
spleenectomy, portal hypertension, pulmonary hypertension

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Introduction
Splenectomy is a relatively common surgical procedure performed for various medical and surgical conditions. However, this procedure is associated with both postoperative and long-term complications. Previous studies have found that patients after splenectomy can develop pulmonary hypertension (PH) with histopathological changes

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similar to pulmonary arterial hypertension (PAH) and chronic thromboembolic PH. One retrospective study has found a 10% incidence of pulmonary thromboembolic disease in 150 post-splenectomy patients. Splenectomized patients developing PH in the setting of hemolytic disorders, trauma, sickle cell disease, and Gaucher’s disease were formerly included in the World Health Organization (WHO) group 5 definition of PH.

The development of pulmonary vasculopathy after splenectomy involves complex pathophysiological mechanisms, some of which remain unclear. However, studies have suggested that PH after splenectomy predominantly occurs via thromboembolic involvement of the pulmonary microvasculature through increased thrombus formation; this mechanism has been proposed to be key to thrombogenicity and delayed thrombus resolution.

Although the association of splenectomy and PH was first discussed in 1999, the nature of the actual relationship between splenectomy and PH remains a matter of controversy. In the recent clinical classification of PH, the sixth World Symposium of PH recommended that splenectomy should be considered a risk factor for PH instead of a specific classification. However, evidence relating to the specific clinical characteristics of PH associated with splenectomy remains very limited, and further investigations are required.

In China, some patients with portal hypertension (PHT) may receive splenectomy to relieve the symptoms of hypersplenism. However, because PHT and splenectomy are both risk factors for PH, the interactions between PHT and splenectomy in the development of PH remain unclear. In the present study, we selected a cohort of patients who developed PH with underlying PHT after splenectomy (PHT-post-splenectomy-PH), from a large multicenter PH registry study in China (NCT01417338). We aimed to identify specific clinical and hemodynamic characteristics of PHT-post-splenectomy-PH patients who had received right-sided heart catheterizations (RHCs) and to compare their long-term prognosis with matched idiopathic pulmonary arterial hypertension (IPAH) patients. We also explored whether splenectomy might lead to severe PH and whether splenectomy might promote the initiation and development of PH in patients with PHT.

Methods
We prospectively recruited post-splenectomy patients who were diagnosed with PH for the first time between November 2008 and May 2017 in Fuwai Hospital. The diagnosis of PH was made in accordance with standard guidelines. Clinical history; symptoms; signs; hematological, biochemical, and serological tests; electrocardiography; chest X-ray; transthoracic echocardiography; pulmonary function tests; computed tomography angiography of the chest; ventilation/perfusion scintigraphy lung scanning; and pulmonary angiography (if necessary) were assessed to clarify the clinical groups. The hemodynamic criteria for PH included mean pulmonary arterial pressure (mPAP) $\geq 25$ mmHg measured at rest by RHCs. Patients were excluded if they declined to participate in the study. A total of 17 post-splenectomy patients with newly diagnosed PH were enrolled in this study. Among these patients, PHT ($n = 12$) was the main cause of splenectomy. Other etiologies included trauma ($n = 1$), idiopathic thrombocytopenia ($n = 1$), Hodgkin’s disease ($n = 1$), Epstein–Barr virus associated lymphoproliferative disease ($n = 1$), and an unknown disease ($n = 1$).

Patients were classified into a PHT group or non-PHT group according to the underlying cause of splenectomy. All PHT-post-splenectomy-PH patients were matched to IPAH patients by cardiac index (CI), mPAP, and PVR; these matched patients were recruited in a ratio of 2:1. PHT-post-splenectomy-PH patients and matched IPAH patients were diagnosed and treated simultaneously. We also included patients with portopulmonary hypertension (POPH) who had no prior history of splenectomy and had received RHCs during the study period. (Details relating to the recruitment of IPAH and POPH patients are shown in the supplemental material.)

Written informed consent was obtained from all patients enrolled in this study. This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Fuwai Hospital (ethical approval number: 402).

Clinical evaluation
Exercise capacity was evaluated by the WHO functional class. The 6 min walk test was performed according to American Thoracic Society guidelines.

Endpoint and follow-up
Each patient was followed up by telephone, outpatient assessment, or in-hospital examinations at six-month intervals. Patients were included in this study from the date at which they provided signed and informed consent and were removed if they reached a primary endpoint. The designed primary endpoints included all-cause mortality, worsening WHO functional class, a $\geq 15\%$ reduction in 6 min walk distance (6MWD), or all-cause hospitalization (including transplantation, atrial septostomy, or the introduction of a parenteral prostacyclin analog for any reason). No patients were lost to follow-up during the study period.

Statistical analysis
Continuous data are expressed as mean ± standard deviation or quartile (Q1, Q3). Categorical data are expressed as frequencies with percentage (%). Differences between two groups were analyzed with unpaired Student’s t-test for
Results
Baseline demographic, clinical and hemodynamic characteristics of PHT-post-splenectomy-PH patients

As shown in Table 1, 12 newly diagnosed PHT-post-splenectomy-PH patients were ultimately enrolled in this study. Their mean age was 43.6 ± 9.5 years, and 66.7% were females. The mean age at the time of splenectomy was 30.4 ± 8.8 years. The mean interval from splenectomy to the diagnosis of PH was 13.1 ± 5.9 years. Among the patients, 58.3% were in WHO-FC III–IV, with a mPAP of 48.3 ± 9.7 mmHg, a PVR of 546.6 ± 213.9 dyns/cm², and a CI of 4.0 ± 1.21/min/m².

| Variables | PHT | Non-PHT |
|-----------|-----|---------|
| Patient number | 12 | 5 |
| Age (years) | 43.6 ± 9.5 | 40.0 ± 10.1 |
| Female, n (%) | 8 (66.7%) | 3 (60.0%) |
| WHO-FC I-II, n | 5 | 2 |
| WHO-FC III-IV, n | 7 | 3 |
| 6MWD (m) | 413.5 ± 32.3 | 408.3 ± 86.1 |
| Age at splenectomy (years) | 30.4 ± 8.8 | 26.8 ± 10.6 |
| Interval from splenectomy to the diagnosis of PH (years) | 13.1 ± 5.9 | 9.9 ± 7.1 |

| Hemodynamic characteristics by RHCs | PHT | Non-PHT |
|-----------------------------------|-----|---------|
| Mixed SvO₂ (%) | 73.9 ± 6.5 | 66.9 ± 7.2 |
| mRAP (mmHg) | 6.4 ± 4.7 | 6.2 ± 2.3 |
| RVSP (mmHg) | 76.2 ± 15.9 | 84.5 ± 21.4 |
| RVEDP (mmHg) | 10.7 ± 5.1 | 10.4 ± 4.8 |
| mPAP (mmHg) | 48.3 ± 9.7 | 52.6 ± 11.3 |
| PAWP (mmHg) | 11.1 ± 4.3 | 7.0 ± 5.6 |
| CO (l/min) | 7.1 ± 1.9 | 4.0 ± 1.0 |
| CI (l/min/m²) | 4.0 ± 1.2 | 2.4 ± 0.8 |
| PVR (dyns/s/cm²) | 546.6 ± 213.9 | 1203.8 ± 416.8 |

CI: cardiac index; CO: cardiac output; mRAP: mean pulmonary artery pressure; m: metre; RVSP: mean right atrial pressure; PAWP: pulmonary artery wedge pressure; PH: pulmonary hypertension; PHT: portal hypertension; PVR: pulmonary vascular resistance; RHC: right heart catheterization; RVEDP: right ventricle end diastolic pressure; RVSP: right ventricle systolic pressure; 6MWD: 6 min walk distance; SvO₂: venous oxygen saturation; WHO-FC: World Health Organization functional class.

Comparisons between PHT-post-splenectomy-PH and matched IPAH patients

To better illustrate the clinical characteristics of PHT-post-splenectomy-PH, we selected matched IPAH patients and focused on mPAP, PVR, and CI. During this process, two PHT-post-splenectomy-PH patients were excluded from our analysis, owing to high pulmonary artery wedge pressure (20 mmHg) or incomplete RHC data. Finally, we recruited 10 PHT-post-splenectomy-PH patients and 20 matched IPAH patients (Table 2).

At baseline, compared with the matched IPAH patients, PHT-post-splenectomy-PH patients had significantly lower levels of hemoglobin (HGB, 125.7 ± 25.9 g/l versus 146.3 ± 20.2 g/l, p = 0.024), wider red blood cell distribution width (RDW, 16.7 ± 2.8% versus 13.3 ± 1.7%, p = 0.004), lower albumin (ALB, 35.6 ± 5.9 g/l versus 44.2 ± 6.1 g/l, p = 0.001), higher total bilirubin (TBil, 31.0 ± 13.8 mmol/l versus 18.9 ± 10.0 mmol/l, p = 0.010), and higher lactate dehydrogenase (LDH, 321.5 ± 41.2 IU/l versus 229.2 ± 69.4 IU/l, p = 0.001). Comparisons also showed that PHT-post-splenectomy-PH patients had lower levels of complement 3 (C3, 0.7 ± 0.2 g/l versus 0.9 ± 0.3 g/l, p = 0.024) and complement 4 (C4, 0.1 ± 0.0 g/l versus 0.2 ± 0.1 g/l, p = 0.032), and lower activity of plasma protein C (60.6 ± 13.4% versus 100.9 ± 22.8%, p = 0.001), plasma protein S (50.2 ± 12.0% versus 95.2 ± 26.1%, p = 0.001), and antithrombin-III (60.8 ± 30.1% versus 103.4 ± 16.0%, p = 0.001).

The mean follow-up periods for PHT-post-splenectomy-PH and IPAH patients were 40.1 ± 34.4 and 41.8 ± 32.1 months, respectively. During the study period, all patients received supportive therapy, and specific drug therapy included calcium channel blockers or PAH targeted therapy. At the end of the study, one PHT-post-splenectomy-PH patient died because of right heart failure, and another two PHT-post-splenectomy-PH patients showed clinical deterioration (worsening WHO functional class). None of the IPAH patients reached the primary endpoint. Kaplan–Meier survival analyses further showed that the PHT-post-splenectomy-PH patients might have had poorer prognosis than matched IPAH patients (log-rank: p = 0.010, Fig. 1).

Comparisons between PHT-post-splenectomy-PH and POPH patients

To further explore the interactions underlying the relationship between PHT and splenectomy in PH, we investigated a cohort of eight POPH patients who received RHC examinations in our center during the study period (Table 3). Almost 58% of the PHT-post-splenectomy-PH patients had hepatitis B as the background disease. Baseline comparisons between PHT-post-splenectomy-PH and POPH patients showed that the POPH cohort had poorer clinical conditions, because this group of patients included a higher...
Table 2. Comparisons of baseline demographic, clinical and hemodynamic characteristics between PHT-post-splenectomy-PH and matched IPAH patients.

| Variable                          | PHT-post-splenectomy-PH | IPAH         | P   |
|-----------------------------------|-------------------------|--------------|-----|
| Patient number                    | 10                      | 20           | NA  |
| Age (years)                       | 42.7 ± 9.4              | 36.1 ± 11.7  | 0.130|
| Female, n (%)                     | 7 (70.0%)               | 16 (80.0%)   | 0.657|
| WHO-FC I-II, n                    | 5                       | 12           | 0.705|
| WHO-FC III-IV, n                  | 5                       | 8            |     |
| 6MWD (m)                          | 413.5 ± 32.3            | 474.1 ± 77.6 | 0.091|
| Follow-up period (months)         | 40.1 ± 34.4             | 41.8 ± 32.1  | 0.898|
| Targeted-drugs, yes               | 12                      | 20           | NA  |
| Deceased patient, n               | 1                       | 0            | NA  |
| Patient with primary endpoint, n  | 3                       | 0            | NA  |
| Hemodynamic characteristics by RHCs|                         |              |     |
| Mixed SvO2 (%)                    | 73.8 ± 6.9              | 75.0 ± 4.6   | 0.567|
| mRAP (mmHg)                       | 5.4 ± 3.9               | 4.7 ± 3.6    | 0.630|
| RVSP (mmHg)                       | 76.8 ± 16.6             | 76.6 ± 13.8  | 0.965|
| RVEDP (mmHg)                      | 10.0 ± 4.8              | 7.0 ± 4.3    | 0.101|
| mPAP (mmHg)                       | 49.4 ± 10.2             | 46.9 ± 8.0   | 0.461|
| PAWP (mmHg)                       | 10.2 ± 3.3              | 8.1 ± 3.8    | 0.140|
| CI (l/min/m²)                     | 3.7 ± 0.8               | 3.8 ± 1.0    | 0.972|
| PVR (dyn s/cm⁵)                   | 583.2 ± 185.5           | 643.3 ± 164.5| 0.373|
| Echocardiography                  |                         |              |     |
| RVEDD/LVEDD                       | 0.7 ± 0.2               | 0.7 ± 0.2    | 0.284|
| Pericardial effusion, n (%)       | 1 (10.0%)               | 0 (0.0%)     | 0.333|
| Laboratory tests                  |                         |              |     |
| RBC (10¹²/l)                      | 4.2 ± 0.6               | 4.7 ± 0.7    | 0.072|
| HGB (g/l)                         | 125.7 ± 25.9            | 146.3 ± 20.2 | 0.024*|
| RDW (%)                           | 16.7 ± 2.8              | 13.3 ± 1.7   | 0.004*|
| PLT (10⁹/l)                       | 256.9 ± 152.0           | 221.2 ± 62.0 | 0.491|
| PDW (%)                           | 15.5 ± 3.2              | 14.7 ± 3.1   | 0.571|
| ALB (g/l)                         | 35.6 ± 5.9              | 44.2 ± 6.1   | 0.001*|
| ALT (IU/l)                        | 35.9 ± 21.6             | 26.2 ± 15.6  | 0.169|
| AST (IU/l)                        | 39.3 ± 10.8             | 23.4 ± 6.8   | 0.001*|
| ALP (IU/l)                        | 86.6 ± 15.6             | 74.8 ± 27.0  | 0.212|
| TBil (µmol/l)                     | 29.0 ± 12.7             | 18.9 ± 10.0  | 0.034*|
| DBil (µmol/l)                     | 6.7 ± 3.2               | 4.8 ± 7.1    | 0.473|
| DBil/TBil (%)                     | 22.9 ± 3.6              | 22.1 ± 18.1  | 0.899|
| Creatinine (µmol/l)               | 56.4 ± 13.1             | 69.0 ± 11.1  | 0.010*|
| BUN (mmol/l)                      | 4.3 ± 1.2               | 5.2 ± 1.7    | 0.139|
| UA (mmol/l)                       | 292.1 ± 62.6            | 377.7 ± 115.3| 0.038*|
| LDH (IU/l)                        | 321.5 ± 41.2            | 229.2 ± 69.4 | 0.001*|
| PT (s)                            | 15.0 ± 1.0              | 13.3 ± 1.0   | <0.001*|
| APTT (s)                          | 37.4 ± 5.2              | 38.6 ± 6.3   | 0.644|
| D-Dimer (µg/ml)                   | 1.5 ± 1.9               | 0.4 ± 0.2    | 0.009*|
| INR                               | 1.2 ± 0.1               | 1.0 ± 0.1    | 0.014*|
| ESR (mm/h)                        | 10.4 ± 9.8              | 5.1 ± 4.7    | 0.152|
| NT-proBNP, pg/ml (Q1, Q3)         | 131.9 (26.3,331.0)      | 192.6 (81.8,451.3) | 0.271|
| Endothelin (ng/l)                 | 0.4 ± 0.2               | 0.4 ± 0.3    | 0.662|
| PO₂ (mmHg)                        | 77.3 ± 11.5             | 80.4 ± 10.7  | 0.498|

(continued)
proportion of WHO-FC III–IV patients (87.5% versus 50%), lower mixed venous oxygen saturation (SvO₂, 62.9±8.0% versus 73.9±6.5%, p = 0.004), and a higher proportion of patients with pericardial effusion (75.0% versus 8.3%, p = 0.004). Comparisons also showed that in POPH patients, the mean intervals from the diagnosis of PHT to PH were significantly shorter than the intervals from receiving splenectomy to the diagnosis of PH in PHT-post-splenectomy-PH patients (5.5±5.2 years versus 13.1±5.9 years, p = 0.008). Hemodynamic characteristics, as measured by RHCs, did not show any significant differences between the two cohorts.

Discussion

POPH is a subcategory of pulmonary artery hypertension, which must be diagnosed in the setting of PHT. A very rare disease, POPH occurs in only 4.5–8.5% of eligible liver-transplantation candidates. Because hypersplenism is one of the main complications of PHT, splenectomy is typically carried out to alter the clinical course or provide symptomatic relief in patients with hypersplenism. However, splenectomy increases the risk of some cardiovascular events, such as myocardial infarction, stroke, and PH.
Table 3. Comparisons of baseline demographic, clinical and hemodynamic characteristics between PHT-post-splenectomy-PH and POPH patients.

| Variable                                      | PHT-post-splenectomy-PH | POPH                  | P      |
|-----------------------------------------------|-------------------------|-----------------------|--------|
| Patient number                                | 12                      | 8                     | NA     |
| Age, years                                    | 43.6 ± 9.5              | 45.3 ± 14.0           | 0.753  |
| Female, n (%)                                 | 8 (66.7%)               | 7 (87.5%)             | 0.603  |
| WHO-FC I II, n                                | 6                       | 1                     | 0.158  |
| WHO-FC III-IV, n                              | 6                       | 7                     |        |
| Combined PE, n (%)                            | 0 (0.0%)                | 1 (12.5%)             | 0.400  |
| Background disease: Hepatitis B, n (%)        | 7 (58.3%)               | 2 (25%)               | 0.157  |
| Intervals form the onset of risk factor to PH (years) | 13.1 ± 5.9 a            | 5.5 ± 5.2 b           | 0.008 a|
| Hemodynamic characteristics by RHCs           |                         |                       |        |
| Mixed SvO₂ (%)                                | 73.9 ± 6.5              | 62.9 ± 8.0            | 0.004 a|
| mRAP (mmHg)                                   | 6.4 ± 4.7               | 8.0 ± 6.1             | 0.517  |
| RVSP (mmHg)                                   | 76.2 ± 15.9             | 77.3 ± 22.3           | 0.904  |
| RVEDP (mmHg)                                  | 10.0 (5.0, 16.0)        | 10.0 (5.0, 16.0)      | 0.860  |
| mPAP (mmHg)                                   | 48.3 ± 9.7              | 49.3 ± 14.0           | 0.852  |
| PAWP (mmHg)                                   | 11.1 ± 4.3              | 8.4 ± 3.7             | 0.378  |
| CI (l/min/m²)                                 | 4.0 ± 1.2               | 3.2 ± 0.9             | 0.127  |
| PVR (dyn s/cm⁵)                               | 546.6 ± 213.9           | 655.1 ± 364.4         | 0.425  |
| Echocardiography                              |                         |                       |        |
| RVEDD/LVEDD                                   | 0.7 ± 0.2               | 0.8 ± 0.2             | 0.398  |
| Pericardial effusion, n (%)                   | 1 (8.3%)                | 6 (75.0%)             | 0.004 a|
| Laboratory tests                              |                         |                       |        |
| HGB (g/l)                                     | 123.5 ± 25.4            | 108.4 ± 16.6          | 0.156  |
| RDW (%)                                       | 16.7 ± 2.7              | 16.9 ± 3.5            | 0.888  |
| PLT (10⁹/l)                                   | 236.5 ± 144.6           | 102.8 ± 99.6          | 0.036 a|
| PDW (%)                                       | 13.8 ± 5.4              | 16.7 ± 2.3            | 0.270  |
| ALB (g/l)                                     | 34.9 ± 6.4              | 34.9 ± 5.4            | 0.986  |
| ALT (IU/l)                                    | 34.6 ± 22.0             | 29.6 ± 22.0           | 0.628  |
| AST (IU/l)                                    | 40.5 ± 16.5             | 33.3 ± 21.4           | 0.404  |
| ALP (IU/l)                                    | 84.4 ± 15.2             | 106.9 ± 88.7          | 0.396  |
| TBil (µmol/l)                                 | 35.2 ± 20.9             | 35.0 ± 27.2           | 0.983  |
| DBil, µmol/l (Q1, Q3)                         | 9.1 ± 8.8               | 8.7 ± 6.1             | 0.901  |
| Creatinine (µmol/l)                           | 69.4 ± 41.0             | 63.3 ± 16.6           | 0.697  |
| BUN (mmol/l)                                  | 5.0 ± 3.0               | 5.9 ± 1.9             | 0.432  |
| UA (mmol/l)                                   | 306.7 ± 128.4           | 344.7 ± 72.2          | 0.459  |
| LDH (IU/l)                                    | 328.6 ± 79.5            | 320.3 ± 119.4         | 0.853  |
| PT (s)                                        | 16.3 ± 4.3              | 16.8 ± 2.9            | 0.757  |
| APTT (s)                                      | 42.2 ± 7.4              | 44.8 ± 8.2            | 0.478  |
| INR                                           | 1.3 ± 0.5               | 1.4 ± 0.3             | 0.869  |
| D-Dimer, µg/ml (Q1, Q3)                       | 0.7 (0.3, 3.6)          | 1.3 (0.5, 1042.6)     | 0.356  |
| ESR, mm/h (Q1, Q3)                            | 5.5 (2.5, 19.5)         | 9.0 (7.0, 23.0)       | 0.244  |
| NT-proBNP, pg/ml (Q1, Q3)                     | 131.9 (27.7, 445.1)     | 319.5 (174.1, 673.0)  | 0.108  |
| Endothelin, ng/l (Q1, Q3)                     | 0.4 ± 0.1               | 0.7 ± 0.3             | 0.634  |
| PO₂ (mmHg)                                    | 72.5 ± 15.7             | 88.5 ± 15.9           | 0.080  |
| PCO₂ (mmHg)                                   | 30.1 ± 9.5              | 30.9 ± 1.3            | 0.849  |
| SaO₂ (%)                                      | 92.6 ± 5.2              | 95.0 ± 2.4            | 0.552  |
| C3 (g/l)                                      | 0.7 ± 0.2               | 0.7 ± 0.3             | 0.986  |
| C4 (g/l)                                      | 0.1 ± 0.0               | 0.1 ± 0.0             | 0.331  |

(continued)
number of papers relating to splenectomy and PH. Furthermore, only one study has attempted to describe the relationship between splenectomy and POPH.\textsuperscript{13}

Segraves et al. have considered both PHT and splenectomy to be risk factors for PH, and hypothesized that POPH patients with a previous history of splenectomy would have more severe POPH. However, their results revealed that POPH patients with or without a previous history of splenectomy showed no significant differences in pulmonary hemodynamics.\textsuperscript{13} One limitation of that previous study is that it was a retrospective chart review; thus, POPH patients with or without splenectomy were not strictly matched. Therefore, the generalizability of the results was very limited. In the present study, matched IPAH patients on cardiovascular disease, and only those POPH patients with or without a previous history of splenectomy were analyzed to make the comparisons more reasonable. Our follow-up study showed that PHT-post-splenectomy-PH patients tended to have poorer prognosis (log-rank: $p = 0.010$) despite having similar cardiopulmonary hemodynamics, WHO functional class, and 6MWD. Because PHT-post-splenectomy-PH is very rare, thus hindering large scale studies, we did not analyze the univariate and multivariate Cox proportional hazards in the present study. Therefore, we determined only the Kaplan–Meier curves to compare the approximate occurrence of endpoints in each cohort. Further comparisons showed that, at baseline, PHT-post-splenectomy-PH patients had wider RDWs and that this observation could be used as an important prognostic predictor for IPAH.\textsuperscript{14,15} Furthermore, PHT-post-splenectomy-PH patients had poorer liver function than IPAH patients. The differences between these patients in terms of ALB, TBil, LDH, and PT, all of which reached clinical significance, might have been predominantly due to the underlying liver disease in the PHT-post-splenectomy-PH patients. Therefore, we speculated that in PHT-post-splenectomy-PH patients, underlying liver diseases might be the main reason for their poorer prognosis.

Liver function impairment would not only lead to the decreased expression of C3 and C4,\textsuperscript{16} but also result in lower synthesis of anti-coagulation factors, including plasma protein C, protein S, and antithrombin-III. Furthermore, splenectomy itself would lead to a loss of splenic filtering function and result in the accumulation of abnormal erythrocytes in circulation, thus potentially exposing phosphatidylserine on cell surfaces and activating coagulation.\textsuperscript{4} Therefore, PHT-post-splenectomy-PH patients have a strong pro-coagulant tendency. However, we found no evidence of venous thromboembolism in PHT-post-splenectomy-PH patients in this study. In addition, liver dysfunction might lead to abnormal iron metabolism\textsuperscript{17} which is mainly mediated by hepcidin, a liver peptide that ultimately leads to iron deficiency anemia. The loss of splenic filtering function and iron deficiency anemia would contribute to lower levels of HGB and wider RDW in PHT-post-splenectomy-PH patients.

In this study, we also studied a cohort of eight POPH patients who had received RHCs during the study period. The number of POPH patients was very small because POPH is a very rare disease, and RHC is not routinely performed for PHT in China. In addition, many POPH patients had abnormal coagulation function as a result of the underlying liver diseases; consequently, these patients could not receive invasive cardiac catheterization. Therefore, the number of POPH patients confirmed by RHCs was very limited. However, our center is a hospital that specializes in cardiovascular disease, and only those POPH patients with severe heart dysfunction are likely to come to our hospital. This aspect might be the main reason why the POPH cohort in this study showed poorer clinical conditions, with a higher proportion of patients in WHO-FC III–IV (87.5% versus 50%), lower mixed $\text{SvO}_2$ (62.9 ± 8.0% versus 73.9 ± 6.5%, $p = 0.004$), and a higher proportion of patients with pericardial effusion (75% versus 8.3%, $p = 0.004$), which is commonly regarded as a strong predictor of poorer prognosis.\textsuperscript{9}

Notably, in cases with PHT, prior splenectomy appears to delay the time required for this condition to develop into PH. In a previous study, Kawut et al.\textsuperscript{18} found that splenectomy did not affect the risk of POPH. In the present study,
the mean interval from receiving splenectomy to the diagnosis of PH in PHT-post-splenectomy-PH patients was 13.1 ± 5.9 years, which was significantly longer than that required for patients with PHT to develop POPH (5.5 ± 5.2 years, p = 0.008). In another study, Segraves et al. have reported a time interval between splenectomy and the development of POPH ranging from 8.8 to 43 years. Prior to the present study, it seemed quite reasonable to speculate that splenectomy in PHT patients would lead to early onset of PH. However, for unknown reasons, splenectomy appeared to postpone the development of PH. Further research on a larger POPH cohort is now required to validate these results.

Our study has several limitations that must need to be considered. First, this study examined patients who were referred to a single tertiary center, thus possibly introducing referral bias. Second, our center is a specialized hospital for cardiovascular diseases. Therefore, we were unable to recruit a large POPH patient cohort, because most POPH patients are referred to other general hospitals with gastroenterology departments. Only those POPH patients who had developed severe PH were likely to be referred to us for RHCs. Thus, the clinical features of our POPH cohort cannot accurately represent the general POPH population. Third, the study population of PHT-post-splenectomy-PH was limited and may reflect only a relatively small sample of the entire PHT-post-splenectomy-PH population. Given that cases of PHT-post-splenectomy-PH are very rare, conducting large scale studies would be highly challenging. Fourth, owing to the limited number of study patients, we were unable to perform univariate and multivariate Cox proportional hazard analysis. Therefore, we determined only Kaplan–Meier curves to compare the approximate occurrence of endpoints in each cohort. Fifth, we did not study the therapeutic effects of specific drugs in PHT-post-splenectomy-PH patients. Little is known about specific drugs for treating this cohort of patients, and a larger study is now needed to address this lack of knowledge.

Conclusions

PHT-post-splenectomy-PH patients had distinct clinical features from those of IPAH patients or POPH patients. PHT-post-splenectomy-PH patients might have a poorer prognosis than matched IPAH patients because of their underlying liver diseases, even with mild hemodynamics. Splenectomy may therefore be related to the process of PH in patients with PHT, although the mechanisms involved remain unknown.

Authors’ contributions

Contributing to the conception and design: QG and JH. Data collection, analysis, and interpretation: LH, WL, TY, CX, and XN. Drafting the article: LH and QG. Revising the article: QG and JH. Approving the final version to be published: all authors.

Conflict of interest

The author(s) declare that there is no conflict of interest.

Ethical approval

This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Fuwai Hospital (the ethical approval number: 402).

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Supplemental material

Supplemental material for this article is available online.

References

1. Jaïs X, Ios V, Jardim C, et al. Splenectomy and chronic thromboembolic pulmonary hypertension. Thorax 2005; 60: 1031–1034.
2. Coltheart G and Little JM. Splenectomy: a review of morbidity. Aust NZ J Surg 1976; 46: 32–36.
3. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014; 35: 3033–3069, 3069a–3069k.
4. Frey MK, Alias S, Winter MP, et al. Splenectomy is modifying the vascular remodeling of thrombosis. J Am Heart Assoc 2014; 3: e000772.
5. Hoepner MM, Niedermeyer J, Hoffmeyer F, et al. Pulmonary hypertension after splenectomy? Ann Intern Med 1999; 130: 506–509.
6. Simonneau G, Montani D, Celermager DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J 2019; 55:1801913.
7. Katz SC and Pachter HL. Indications for splenectomy. Am Surg 2006; 72: 565–580.
8. Wells J, Runo JR and Lucey MR. Portopulmonary hypertension. Hepatology 2008; 48: 13–15.
9. Gallié N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Eur Respir J 2015; 46: 903–975.
10. Frost AE, Badesch DB, Miller DP, et al. Evaluation of the predictive value of a clinical worsening definition using 2-year outcomes in patients with pulmonary arterial hypertension: a REVEAL Registry analysis. Chest 2013; 144: 1521–1529.
11. Gomberg-Maitland M, Bull TM, Saggar R, et al. New trial designs and potential therapies for pulmonary artery hypertension. J Am Coll Cardiol 2013; 62: D82–D91.
12. Raevens S, Colle I, Reytjens K, et al. Echocardiography for the detection of portopulmonary hypertension in liver transplant candidates: an analysis of cutoff values. Liver Transpl 2013; 19: 602–610.
13. Segraves JM, Cartin-Ceba R, Leise MD, et al. Relationship between portopulmonary hypertension and splenectomy:
Mayo Clinic experience and review of published works. *Hepatol Res* 2018; 48: E340–E346.

14. Rhodes CJ, Wharton J, Howard LS, et al. Red cell distribution width outperforms other potential circulating biomarkers in predicting survival in idiopathic pulmonary arterial hypertension. *Heart* 2011; 97: 1054–1060.

15. Hampole CV, Mehrotra AK, Thenappan T, et al. Usefulness of red cell distribution width as a prognostic marker in pulmonary hypertension. *Am J Cardiol* 2009; 104: 868–872.

16. Zhu C, Song H, Xu F, et al. Hepatitis B virus inhibits the expression of complement C3 and C4, in vitro and in vivo. *Oncol Lett* 2018; 15: 7459–7463.

17. Sangkhare V and Nemeth E. Regulation of the iron homeostatic hormone. *Adv Nutr* 2017; 8: 126–136.

18. Kawut SM, Krowka MJ, Trotter JF, et al. Clinical risk factors for portopulmonary hypertension. *Hepatology* 2008; 48: 196–203.