The clinical characteristics and long-term prognosis of pulmonary arterial hypertension associated with hereditary hemorrhagic telangiectasia

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Abstract
Pulmonary arterial hypertension (PAH) is a severe complication of hereditary hemorrhagic telangiectasia (HHT); however, little is known about its clinical characteristics and prognosis. Nine newly diagnosed HHT-PAH patients were prospectively recruited between October 2007 and January 2016 and were followed up every half-year. Eighteen idiopathic pulmonary arterial hypertension (IPAH) patients, matched with HHT-PAH patients on mean pulmonary arterial pressure, pulmonary capillary wedge pressure, pulmonary vascular resistance, cardiac index, and World Health Organization (WHO) functional class (FC), were recruited. The clinical characteristics of HHT-PAH patients were described and the prognosis of these two cohorts were compared. Of HHT-PAH patients, 55.56% were WHO FC III. Kaplan–Meier survival analysis showed one- and three-year survival rates of HHT-PAH patients were 77.8% and 53.3% respectively, which were worse than matched IPAH patients (log rank: $P = 0.047$). HHT-PAH patients had higher red cell distribution width (14.88 ± 2.93% versus 13.19 ± 0.83%, $P = 0.031$), larger right ventricular anteroposterior diameter (34.67 ± 6.67 mm versus 28.56 ± 6.35 mm, $P = 0.029$), and lower mean corpuscular hemoglobin concentration (317.38 ± 17.71 g/L versus 335.72 ± 14.68 g/L, $P = 0.011$) than matched IPAH patients. Multivariate Cox proportional hazards regression analyses showed baseline total bilirubin independently predicted the mortality of HHT-PAH after adjusting by age, cardiac index, mixed venous oxygen saturation, or serum uric acid. HHT-PAH patients may have a worse prognosis than matched IPAH patients. Baseline total bilirubin may be a promising predictor for the long-term prognosis in HHT-PAH patients.

Keywords
hereditary hemorrhagic telangiectasia, pulmonary arterial hypertension, clinical characteristics, prognosis

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Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber syndrome, is a rare autosomal dominant vascular disorder. It is characterized by the presence of multiple arteriovenous malformations. HHT is reported to be caused by mutations in the genes codifying for transforming growth factor β signaling receptors and its estimated global prevalence was one patient per 5000–8000
Table 1. Curaçao criteria for the clinical diagnosis of hereditary hemorrhagic telangiectasia (HHT).

Curaçao criteria

(1) spontaneous and recurrent epistaxis
(2) multiple telangiectasia at characteristic sites
(3) visceral lesions
(4) a first-degree relative with HHT

A definite diagnosis of HHT needs to meet at least three criteria; meeting two criteria is considered as a clinical “possible” HHT; only meeting one or no criterion makes the diagnosis “unlikely.”

Patients who were diagnosed with HHT-PAH for the first time between October 2007 and January 2016 in Fuwai Hospital were prospectively recruited. The diagnosis of HHT was made according to the four Curaçao criteria (Table 1).4 Clinical history, symptoms, signs, electrocardiogram (ECG), chest X-ray, transthoracic echocardiogram, pulmonary function test, high-resolution computed tomography (CT) of the chest, ventilation/perfusion scintigraphy, and CT and ultrasonography of the abdomen, were performed to exclude other forms of PAH. Exclusion criteria included: (1) patients with other clinical types of PH; (2) patients who declined to participate in the study. For all HHT-PAH patients, matched IPAH patients, on cardiac index, mPAP, PVR, PCWP, and World Health Organization (WHO) functional class (FC), were recruited at the ratio of 2:1 (details about the recruitment of IPAH patients are shown in the supplementary material). Written informed consent was obtained from all enrolled patients. This study complied with the Declaration of Helsinki and was approved by the Institutional Review Board of Fuwai Hospital (ethical approval no. 402).

Clinical evaluation

Exercise capacity was evaluated by the WHO FC. The 6-min walk test was performed according to American Thoracic Society guidelines.10 The algorithm incorporated 11 evaluable elements that were used to calculate REVEAL risk scores (RRS).11 Data for diffusing capacity of the lung for carbon monoxide were not available for some of our patients; however, the RRS only requires 7/12 evaluable elements to maintain significant predictive power and calibration.11 In this algorithm, calculated risks core could be in the range of 1 (lowest risk) to 21 (highest risk). For analysis of risk strata, patients were stratified into low (score 1–7), average (score 8) and higher stratum (score ≥ 9), based on their RRS, due to the small number of study patients. HHT-PAH and IPAH patients were also classified into low-risk, intermediate-risk, or high-risk groups according to European Respiratory Society (ERS) risk assessment.9

Right heart catheterization

Hemodynamic parameters including mean right atrial pressure (mRAP), mPAP, and PCWP were recorded during RHC. Cardiac output (CO) was measured by the thermodilution method (the mean value of three-time measurements). Body surface area (BSA) was calculated according to the Du Bois formula, i.e. BSA = 0.07184 × weight0.425 × height0.725.12 Cardiac index was calculated as CO/BSA. Pulmonary vascular resistance (PVR) was calculated using the following equation: PVR = (mPAP–PCWP)/CO. Diastolic pressure gradient (DPG) = diastolic PAP–mean PCWP. Pulmonary vasoreactivity testing was performed inhaling Iloprost. A positive acute response is defined as a reduction of mPAP ≥ 10 mmHg to reach an absolute value of mPAP ≤ 40 mmHg with an increased or unchanged CO.

Endpoint and follow-up

Each patient was followed up by telephone, outpatient, or in-hospital examinations in a six-month interval. They were included in this study from the date of signing informed consent.
Results

Baseline demographic, clinical, and hemodynamic characteristics of HHT-PAH patients

A total of 13 newly diagnosed HHT patients, who met the hemodynamic criteria of PAH, were recruited for this study. However, four HHT had increased cardiac index (≥4.0 L/min/m²). Among these four patients, three had confirmed hepatic arteriovenous malformations (AVMs), which may lead to post-capillary PH because of high CO. Therefore, in order to be more precise and exclude the possibility of post-capillary PH, we decided to remove the four HHT patients with high CI. In the end, nine HHT patients with PAH were finally enrolled, including seven women and two men. Their mean age was 33.89 ± 10.00 years and 55.56% of them were WHO FC III. Among them, seven patients had a definite HHT diagnosis and two patients had a possible HHT diagnosis (Suppl. Table S1).

The baseline characteristics of HHT-PAH patients are shown in Table 2. All the enrolled patients had confirmed PAH, with mPAP 61.22 ± 19.73 mmHg, PCWP 8.89 ± 3.26 mmHg, and PVR 848.17 ± 378.34 dyn.s.cm⁻⁵. Interestingly, one patient had a positive result of acute vasoactivity test, which had rarely been reported before. Pericardial effusions were detected by echocardiography in three patients. Six patients received PAH-specific drugs combined with conventional therapy as soon as their PAH diagnoses were confirmed. However, the other three patients only received conventional supportive therapy including diuretics, oxygen, and digoxin because of financial issues. The median follow-up time of HHT-PAH patients was 2.70 years (range = 0.77–7.70 years). During this period, five patients died because of right heart failure. Compared with survivors, deceased HHT-PAH patients had a lower ratio of direct and total bilirubin (D/TBil, 21.11 ± 4.72 versus 14.54 ± 2.26, P = 0.046).

Comparisons between HHT-PAH and matched IPAH patients

A total of 18 matched IPAH patients were enrolled in this study and their median follow-up time was 4.36 years (range = 1.79–7.90 years). During this period, three of them died because of right heart failure. Kaplan–Meier survival analyses showed that HHT-PAH patients had a worse prognosis than matched IPAH patients (log rank: P = 0.047; Fig. 1). Comparisons between these two cohorts showed that HHT-PAH patients had higher RRS score (8.67 ± 2.29 versus 7.11 ± 1.57, P = 0.048), worse 6MWD (385.00 ± 59.5 m versus 469.27 ± 62.39 m, P = 0.011), larger right ventricular anteroposterior diameter (RVAPD; 34.67 ± 6.67 mm versus 28.56 ± 6.35 mm, P = 0.029), wider red cell distribution width (RDW; 14.88 ± 2.93% versus 13.19 ± 0.83%, P = 0.031), and lower mean corpuscular hemoglobin concentration (MCHC; 317.38 ± 17.71 g/L versus 335.72 ± 14.68 g/L, P = 0.011) than matched IPAH patients (Table 2).

Reassessment of HHT-PAH patients after long-term specific drug therapy

Four HHT-PAH patients had detailed clinical reassessments after receiving PAH-specific drug therapy (Suppl. Table S2). Among them, two received Sildenafil, one received Bosentan, and one had Diltiazem because of positive pulmonary vasoreactivity result. After treatment, one patient had improved WHO FC; two remained in the same condition, and one had deteriorated WHO FC. As for
|                               | HHT-PAH | IPAH   | P     |
|-------------------------------|---------|--------|-------|
| Patients (n)                  | 9       | 18     | N/A   |
| Age (years)                   | 33.89+/C6 10.00 | 32.06+/C6 9.18 | 0.638 |
| Female (%)                    | 7 (77.78) | 13 (72.22) | N/A   |
| Body mass index (kg/m²)       | 21.62+/C6 3.51 | 21.85+/C6 3.69 | 0.876 |
| WHO FC I/II                   | 4       | 8      | N/A   |
| WHO FC III/IV                 | 5       | 10     |       |
| 6MWD (m)                      | 385.00+/C6 59.5 | 469.27+/C6 62.39 | 0.011* |
| REVEAL risk score             | 8.67+/C6 2.29 | 7.11+/C6 1.57 | 0.048* |
| Low risk (n)                  | 3       | 11     | 0.417 |
| Average risk (n)              | 2       | 3      |       |
| High risk (n)                 | 4       | 4      |       |
| ERS risk group, low risk (n)  | 2       | 5      | 0.951 |
| Intermediate risk (n)         | 6       | 11     |       |
| High risk (n)                 | 1       | 2      |       |
| PAH-specific drug, yes (n)    | 6       | 17     | 0.093 |
| No (n)                        | 3       | 6      |       |
| Follow-up period (years) (Q1–Q3) | 2.70 (1.49–6.35) | 4.36 (2.70–5.99) | 0.537 |
| Deceased patient (n)          | 5       | 3      | 0.072 |
| Hemodynamic characteristics by RHC |       |        |       |
| SvO₂ (%)                      | 71.60+/C6 9.67 | 73.63+/C6 5.88 | 0.503 |
| mRAP (mmHg)                   | 9.00+/C6 5.50 | 6.72+/C6 3.71 | 0.421 |
| RVSP (mmHg)                   | 91.44+/C6 29.73 | 96.56+/C6 28.81 | 0.671 |
| RVEDP (mmHg)                  | 14.00+/C6 6.69 | 11.67+/C6 6.67 | 0.400 |
| PASP (mmHg)                   | 90.56+/C6 30.30 | 95.72+/C6 27.04 | 0.657 |
| PADP (mmHg)                   | 43.33+/C6 14.37 | 41.00+/C6 16.02 | 0.716 |
| mPAP (mmHg)                   | 61.22+/C6 19.73 | 61.06+/C6 18.44 | 0.983 |
| Cardiac index (L/min/m²)      | 3.09+/C6 0.55 | 3.08+/C6 0.54 | 0.939 |
| PCWP (mmHg)                   | 8.89+/C6 3.26 | 7.78+/C6 3.00 | 0.386 |
| PVR (dyn·s·cm⁻⁵)              | 848.17+/C6 378.34 | 966.08+/C6 398.35 | 0.468 |
| DPG (mmHg)                    | 34.44+/C6 14.29 | 33.22+/C6 15.82 | 0.847 |
| Pulmonary vasoreactivity test, positive (n) | 1 | 5 | 0.628 |
| Negative (n)                  | 8       | 13     |       |
| Hemodynamic characteristics by echocardiography |       |        |       |
| RVAPD (mm)                    | 34.67+/C6 6.67 | 28.56+/C6 6.35 | 0.029* |
| LAAPD (mm)                    | 30.00+/C6 5.93 | 27.00+/C6 2.54 | 0.205 |
| LVEDD (mm)                    | 38.67+/C6 6.89 | 37.06+/C6 5.02 | 0.494 |
| RV/LV (%)                     | 94.66+/C6 29.38 | 79.45+/C6 24.12 | 0.191 |
| LVEF (%)                      | 69.18+/C6 6.09 | 66.82+/C6 5.63 | 0.328 |
| Pericardial effusion, yes (n) | 3       | 3      | 0.367 |
| No (n)                        | 6       | 15     |       |
| Blood gas analysis            |         |        |       |
| PH                            | 7.42+/C6 0.03 | 7.42+/C6 0.03 | 0.746 |
| pCO₂ (mmHg)                   | 32.12+/C6 4.38 | 35.11+/C6 3.85 | 0.081 |
| pO₂ (mmHg)                    | 80.57+/C6 8.89 | 85.21+/C6 17.76 | 0.470 |
| SaO₂ (%)                      | 95.97+/C6 1.11 | 95.91+/C6 1.74 | 0.925 |
| Hematology                    |         |        |       |
| RBC (10¹²/L)                  | 4.84+/C6 0.90 | 5.06+/C6 0.55 | 0.513 |
| HGB (g/L)                     | 136.11+/C6 27.75 | 152.06+/C6 14.76 | 0.137 |
| HCT (%)                       | 42.86+/C6 7.71 | 45.11+/C6 4.34 | 0.433 |
echocardiographic parameters, two patients had improved RV/LV, while two showed decreased RV/LV.

**Discussion**

Novel findings from the present study are that: (1) we reported the one- and three-year survival rates of HHT-PAH for the first time; (2) HHT-PAH patients might have a worse prognosis than matched IPAH patients; and (3) TBil might be a promising predictor for the long-term prognosis in HHT-PAH patients.

In the context of HHT, PH is categorized into two distinct types: pre- and post-capillary PH.\(^5,16\) Post-capillary PH is considered to be associated with liver vascular malformations and secondary to high CO, typically after the onset of left heart failure,\(^5\) while pre-capillary PH, which can also be called PAH in the context of HHT, is considered to be caused by pulmonary arteriopathy. HHT-PAH was thought...
to have largely increased PAP and PVR, increased transpulmonary gradient (TPG), decreased CO, and normal PCWP. However, HHT with post-capillary PH was considered to have largely increased CO, increased PAP and PCWP, and normal TPG and PVR. Recently, TPG has been replaced by DPG according to the new guideline. In this study, we initially enrolled 13 HHT patients who met the hemodynamic criteria of PAH, with high mPAP, high PVR, and normal PCWP. However, four patients of this cohort had increased cardiac index (≥4.0 L/min/m^2) and three of the four patients had definite hepatic AVMs detected by abdominal CT. In order to exclude the possibility of PH induced by high CO, we decided to remove the four HHT patients with high cardiac index to get a pure HHT-PAH cohort.

PAH was considered as a rare complication of HHT and its exact prevalence in the HHT population has not been elucidated. Sopéna et al. found that combining with PH could significantly reduce survival rates of HHT patients. There are previous studies which reported the long-term survival of individual HHT patients with PH and showed the survival of patients who had coexisting HHT and PH from any causes. However, these studies did not report the survival rates of HHT-PAH patients. In this study, we found that the one- and three-year survival rates of HHT-PAH patients were 77.8% and 53.3%, respectively, which were much lower than the reported idiopathic/familial PAH survival rates by the REVEAL Registry study (the one- and three-year survival rates were 91%±2% and 74%±2%, respectively). We then introduced a cohort of IPAH patients who matched with HHT-PAH patients on cardiac index, mPAP, PVR, PCWP, and WHO FC. Kaplan–Meier survival analyses between these two cohorts showed that HHT-PAH patients have a worse prognosis regardless of the same cardiopulmonary hemodynamic characteristics. By comparing the baseline characteristics of HHT-PAH and matched IPAH patients, we found that HHT-PAH patients had higher RRS, worse 6MWD, and larger RVAPD and RDW than matched IPAH patients. This explained why HHT-PAH patients had a worse prognosis on the one hand and also indicated that HHT-PAH patients might have worse exercise tolerance, severe symptoms, and worse clinical condition even with the same cardiopulmonary hemodynamic characteristics as IPAH patients.

Another point we want to highlight here is that HHT-PAH patients had wider RDW and lower MCHC than matched IPAH patients and deceased HHT-PAH had lower D/TBil than survivors. These all suggested the possible existence of subclinical hemolysis in HHT-PAH, though the comparisons of hemoglobin, hematocrit, bilirubin, and lactate dehydrogenase (LDH) did not show statistical significances between these two groups. Over the last decade, there has been increasing interest in hemolysis as a potential cause of PH. Free hemoglobin, when released from the erythrocyte, reduces the bioavailability of nitric oxide (NO), and promotes endothelial dysfunction with thrombosis, inflammation, vasoconstriction, and smooth muscle proliferation in the capillaries. Some studies have found that subclinical hemolysis plays important roles in the pathogenesis or pathophysiology of PAH and may be associated with the severity of pulmonary vascular disease and clinical outcomes. Though it is not possible to determine from the current study whether the subclinical hemolysis present in HHT-PAH patients represents a cause, effect, or epi-phenomenon of the illness, we suggested that subclinical hemolysis might be a feature of the HHT-PAH phenotype. Additional tests of hemolysis, including RBC lifespan or half-life (the golden standard), plasma-free hemoglobin, reticulocyte counts, erythrocyte creatine, and haptoglobin, are still needed to further confirm the values of subclinical hemolysis in HHT-PAH. Besides that, wider RDW and lower MCHC in HHT-PAH patients also suggested iron deficiency, which is highly prevalent in PAH and HHT and is associated with worse disease severity and clinical outcomes. However, we did not measure markers of iron metabolism in this study.

Comparisons of baseline characters between survival and deceased HHT-PAH showed that non-survivors had lower D/TBil than survivors. Univariate and multivariate Cox proportional hazards regression analyses found that baseline TBil could predict the mortality of HHT-PAH patients independently, even after adjusting by age or SvO2 or cardiac index or serum uric acid. So HHT-PAH patients with higher TBil indicated worse prognosis. We thought this was partially due to hemolysis and previous studies have also identified TBil as a predictive risk factor for both systolic and diastolic heart failure and PAH because of hemodynamic alterations, including elevated central venous pressure and decreased cardiac index; therefore, the recognition of liver dysfunction as a reflection of end-organ dysfunction would be important.
Table 3. Baseline demographics, and clinical and hemodynamic characteristics of survival and deceased HHT-PAH patients.

|                      | HHT-PAH |            |       |
|----------------------|---------|-----------|-------|
|                      | Survivor| Non-survivor|      |
| Patients (n)         | 4       | 5         | N/A   |
| Age (years)          | 32.55±11.58 | 34.97±9.86   | 0.744 |
| Body mass index (kg/m²) | 22.18±4.63   | 21.17±2.83   | 0.698 |
| WHO FC I/II (n)      | 2       | 2         | N/A   |
| WHO FC III/IV (n)    | 2       | 3         |       |
| 6MWD (m)             | 424.33±47.59 | 345.67±44.12 | 0.104 |
| REVEAL risk score    | 8.00±2.83 | 9.20±1.92   | 0.472 |
| Low risk (n)         | 2       | 1         | 0.714 |
| Average risk (n)     | 1       | 1         |       |
| High risk (n)        | 1       | 3         | 0.165 |
| ERS risk group, low risk (n) | 2   | 0         |       |
| Intermediate risk (n)| 2       | 4         |       |
| High risk (n)        | 0       | 1         |       |
| PAH-specific drug, yes (n) | 2   | 4         | 0.524 |
| No (n)               | 2       | 1         |       |
| Follow-up period (years) (Q1–Q3) | 6.26 (3.41–7.44) | 2.18 (0.78–4.37) | 0.086 |

Hemodynamic characteristics by RHC

|                      |       |       |     |
|----------------------|-------|-------|-----|
| SvO₂ (%)             | 69.95±10.67 | 72.92±9.83   | 0.670 |
| mRAP (mmHg)          | 7.25±2.99  | 10.40±6.95   | 0.430 |
| RVSP (mmHg)          | 85.25±33.41 | 96.40±29.36   | 0.610 |
| RVEDP (mmHg)         | 10.25±1.50 | 17.00±7.91   | 0.141 |
| PASP (mmHg)          | 84.25±31.26 | 95.60±32.11   | 0.611 |
| PAPD (mmHg)          | 40.5±10.54 | 45.60±17.76   | 0.630 |
| mPAP (mmHg)          | 58.00±16.15 | 63.80±23.75   | 0.691 |
| Cardiac index (L/min/m²) | 2.95±0.55  | 3.21±0.59    | 0.514 |
| PCWP (mmHg)          | 9.75±3.78  | 8.20±3.03    | 0.515 |
| PVR (dyn·s·cm⁻⁵⁻)    | 879.61±51.24 | 823.02±295.95 | 0.840 |
| DPG (mmHg)           | 30.75±13.25 | 37.40±15.88   | 0.525 |
| Pulmonary vasoreactivity test, positive (n) | 1   | 0     | 0.444 |

Hemodynamic characteristics by echocardiography

|                      |       |       |     |
|----------------------|-------|-------|-----|
| RVAPD (mm)           | 33.00±4.97 | 36.00±8.09    | 0.539 |
| LAAPD (mm)           | 29.25±7.14 | 30.75±5.44    | 0.749 |
| LVEDD (mm)           | 39.5±7.23  | 38.00±7.38    | 0.769 |
| RV/LV (%)            | 87.45±29.40 | 98.62±31.76   | 0.605 |
| LVEF (%)             | 67.65±5.11 | 70.40±7.09    | 0.537 |
| Pericardial effusion, yes (n) | 1   | 2     | 0.595 |

Blood gas analysis

|                      |       |       |     |
|----------------------|-------|-------|-----|
| PH                   | 7.41±0.02 | 7.40±0.04    | 0.170 |
| pCO₂ (mmHg)          | 34.78±2.51 | 30.00±4.58   | 0.106 |
| pO₂ (mmHg)           | 76.18±5.32 | 84.08±10.11  | 0.203 |
| SaO₂ (%)             | 95.30±0.71 | 96.50±1.14   | 0.111 |

Hematology

|                      |       |       |     |
|----------------------|-------|-------|-----|
| RBC (10¹²/L)         | 5.28±0.75 | 4.48±0.92    | 0.203 |
| HGB (g/L)            | 148.50±35.35 | 126.20±18.08 | 0.256 |
| HCT (%)              | 46.53±8.86 | 39.92±5.97   | 0.222 |
| MCV (fl)             | 87.58±4.85 | 91.15±7.38   | 0.449 |

(continued)
damage in right heart failure should also be paid much attention in HHT-PAH patients.

Even though there is no systematic evidence for the treatment of HHT-PAH at present, it seems rational to treat these patients with PAH-specific medication. Cases have reported the short-term or long-term effects of PAH-specific drugs (including bosentan, sildenafil, and epoprostenol) on HHT-PAH patients. It seemed that PAH-specific medication could improve the symptoms, exercise capacity, and cardiopulmonary hemodynamics of HHT-PAH patients. However, in this study, reassessments of four HHT-PAH patients after receiving long-term PAH-specific drugs did not show significant clinical improvement in every patient. Besides that, these

Table 3. Continued

|                | HHT-PAH       | Non-survivor | P       |
|----------------|---------------|--------------|---------|
| MCH (pg)       | 27.83 ± 3.35  | 29.10 ± 3.40 | 0.613   |
| MCHC (g/L)     | 316.25 ± 23.61| 318.50 ± 13.08| 0.873   |
| RDW (%)        | 15.43 ± 3.88  | 14.33 ± 2.05 | 0.634   |
| PLT (10³/L)    | 182.75 ± 54.91| 165.80 ± 24.25| 0.551   |
| PDW (%)        | 15.00 ± 2.17  | 12.75 ± 2.41 | 0.260   |

| Biochemistry   |               |              |         |
|----------------|---------------|--------------|---------|
| ALT (IU/L)     | 26.75 ± 17.63 | 23.00 ± 9.22 | 0.691   |
| AST (IU/L)     | 22.25 ± 4.79  | 29.20 ± 4.44 | 0.059   |
| GGT (IU/L)     | 41.25 ± 28.74 | 20.75 ± 8.38 | 0.220   |
| ALP (IU/L)     | 77.00 ± 29.44 | 55.50 ± 11.21| 0.221   |
| TBil (umol/L)  | 16.20 ± 4.48  | 33.35 ± 24.50| 0.195   |
| DBil (umol/L)  | 3.51 ± 2.25   | 3.28 ± 0.57  | 0.850   |
| D/TBil (%)     | 21.11 ± 4.72  | 14.54 ± 2.26 | 0.046*  |
| CREA (umol/L)  | 65.76 ± 5.79  | 61.98 ± 16.20| 0.674   |
| BUN (mmol/L)   | 6.24 ± 1.74   | 5.64 ± 1.15  | 0.555   |
| UA (umol/L)    | 371.49 ± 166.01| 4.78 ± 6.62  | 0.285   |
| HSCRP (mg/L)   | 26.90 ± 42.79 | 2.54 ± 1.45  | 0.428   |
| CRP (mg/L)     | 4.78 ± 6.62   | 1.20 ± 1.24  | 0.361   |
| ESR (mm/h)     | 6.00 ± 5.60   | 4.40 ± 2.30  | 0.621   |
| LDH (IU/L)     | 209.25 ± 26.99| 277.50 ± 108.60| 0.301   |
| PT (s)         | 13.73 ± 1.30  | 11.35 ± 7.08 | 0.534   |
| PTA (%)        | 93.75 ± 18.03 | 66.25 ± 38.50| 0.243   |
| INR            | 1.06 ± 0.14   | 1.16 ± 0.17  | 0.374   |
| APTT (s)       | 39.65 ± 3.67  | 51.35 ± 21.43| 0.323   |
| NT-proBNP (fmol/mL) | 1387.95 ± 1425.41 | 1695.50 ± 1038.84 | 0.718 |
| Big ET (fmol/mL)| 0.64 ± 0.35   | 0.54 ± 0.24  | 0.683   |

*P < 0.05.

NA, not applicable; PAH, pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; WHO FC, World Health Organization functional class; 6MWD, 6-min walk distance; ERS, European Respiratory Society; RHC, right heart catheterization; SvO₂, mixed venous oxygen saturation; mRAP, mean right atrial pressure; RVSP, right ventricle systolic pressure; RVEDP, right ventricle end diastolic pressure; PASP, pulmonary arterial systolic pressure; mPAP, mean pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; DPG, diastolic pressure gradient; RVAPD, right ventricular anteroposterior diameter; LAAPD, left atrial anteroposterior diameter; LVEDD, left ventricular end diastolic diameter; RV/LV, right ventricular ejection fraction; pCO₂, partial pressure of carbon dioxide; pO₂, partial pressure of oxygen; SaO₂, arterial oxygen saturation; RBC, red blood cell count; HGB, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; RDW, red cell distribution width; PLT, platelets count; PDW, platelet distribution width; ALT, alanine transaminase; GGT, gamma-glutamyl transpeptidase; ALP, alkaline phosphatase; Tbil, total bilirubin; Dbil, direct bilirubin; D/Tbil, total bilirubin/direct bilirubin; CREA, creatinine; BUN, blood urea nitrogen; UA, uric acid; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; NT-proBNP, N terminal pro-brain natriuretic peptide; big ET, big endothelin.
patients did not undergo a second RHC after receiving long-term PAH-specific drugs, so post-treatment cardiac index and PVR were unavailable. Therefore, strictly designed randomized controlled trials and pre- and post-treatment RHCs are still needed.

Our study had several limitations. First, this study consisted of patients referred to a single tertiary center, which may constitute a referral bias. Second, our center is a specialized hospital for cardiovascular diseases and all the recruited patients were suspected with PH, unknowing the diagnosis of HHT when they first came to us. Therefore, we cannot ascertain the exact prevalence of PAH in HHT. Third, gene mutation screening was not

Table 4. Univariate Cox proportional hazards regression analyses for primary endpoint of HHT-PAH patients.

| Variables          | Hazard ratio (95% CI) | P     |
|--------------------|-----------------------|-------|
| Age                | 0.982 (0.888–1.085)   | 0.716 |
| WHO FC III         | 1.708 (0.277–10.546)  | 0.564 |
| REVEAL risk score  | 1.548 (0.940–2.650)   | 0.112 |
| ERS risk group     | 93.99 (0.081–108827.28) | 0.207 |
| 6MWD               | 0.950 (0.888–1.018)   | 0.145 |
| PAH-specific drug  | 3.370 (0.357–31.853)  | 0.289 |
| SvO₂               | 1.006 (0.912–1.109)   | 0.907 |
| mRAP               | 1.186 (0.933–1.508)   | 0.163 |
| RVSP               | 1.007 (0.974–1.042)   | 0.664 |
| RVEDP              | 1.204 (0.983–1.475)   | 0.073 |
| PASP               | 1.010 (0.977–1.044)   | 0.572 |
| PADP               | 1.042 (0.971–1.118)   | 0.259 |
| mPAP               | 1.020 (0.968–1.075)   | 0.463 |
| PCWP               | 0.792 (0.562–1.115)   | 0.181 |
| PVR                | 1.000 (0.998–1.003)   | 0.718 |
| Cardiac index      | 1.074 (0.175–6.594)   | 0.938 |
| DPG                | 1.054 (0.978–1.136)   | 0.166 |
| RVAPD              | 1.182 (0.960–1.455)   | 0.115 |
| LAAPD              | 0.984 (0.817–1.185)   | 0.865 |
| LVEDD              | 0.945 (0.821–1.087)   | 0.427 |
| RV/LV              | 1.026 (0.986–1.067)   | 0.203 |
| LVEF               | 1.164 (0.899–1.507)   | 0.249 |
| Pericardial effusion | 0.147 (0.013–1.710) | 0.126 |
| pCO₂               | 0.796 (0.601–1.055)   | 0.113 |
| pO₂                | 1.049 (0.956–1.150)   | 0.313 |
| SaO₂               | 1.756 (0.750–4.113)   | 0.195 |
| RBC                | 0.546 (0.152–1.964)   | 0.354 |
| HGB                | 0.985 (0.952–1.018)   | 0.365 |
| HCT                | 0.830 (0.609–1.131)   | 0.239 |
| MCV                | 1.033 (0.862–1.238)   | 0.725 |
| MCH                | 1.057 (0.755–1.478)   | 0.748 |
| MCHC               | 1.010 (0.950–1.073)   | 0.756 |
| RDW                | 0.910 (0.629–1.316)   | 0.616 |
| PLT                | 0.995 (0.971–1.020)   | 0.708 |
| PDW                | 0.820 (0.524–1.284)   | 0.386 |
| ALT                | 0.999 (0.930–1.074)   | 0.989 |
| AST                | 1.355 (0.987–1.861)   | 0.060 |
| GGT                | 0.936 (0.788–1.112)   | 0.452 |
| ALP                | 0.921 (0.821–1.033)   | 0.162 |
| Tbil               | 1.067 (1.003–1.135)   | 0.041*|
| DBil               | 1.178 (0.628–2.209)   | 0.609 |
| D/Tbil             | 0.666 (0.381–1.162)   | 0.152 |
| CREA               | 0.989 (0.884–1.106)   | 0.843 |
| BUN                | 0.643 (0.269–1.540)   | 0.322 |
| CRP                | 0.950 (0.819–1.103)   | 0.501 |
| HSCRP              | 0.816 (0.503–1.323)   | 0.410 |
| UA                 | 0.998 (0.990–1.007)   | 0.700 |

Table 5. Multivariate Cox proportional hazards regression analyses for baseline characteristics to predict primary endpoints.

| Variable          | Hazard ratio (95% CI) | P     |
|-------------------|-----------------------|-------|
| Tbil              | 1.068 (1.002–1.137)   | 0.042*|
| Age               | 1.009 (0.879–1.158)   | 0.900 |
| Tbil              | 1.076 (1.002–1.155)   | 0.044*|
| SvO₂              | 1.045 (0.896–1.219)   | 0.573 |
| Tbil              | 1.068 (1.004–1.136)   | 0.038*|
| CI                | 1.300 (0.157–10.759)  | 0.807 |
| Tbil              | 1.066 (1.001–1.136)   | 0.048*|
| UA                | 1.000 (0.991–1.008)   | 0.947 |
| Tbil              | 1.074 (0.995–1.160)   | 0.068 |
| WHO functional class ≥ III | 0.655 (0.054–7.912) | 0.740 |
| Tbil              | 1.055 (0.987–1.127)   | 0.118 |
| REVEAL risk score | 1.382 (0.732–2.610)   | 0.319 |
| Tbil              | 1.214 (0.710–2.075)   | 0.479 |
| 6MWD              | 0.885 (0.643–1.218)   | 0.454 |
| Tbil              | 1.070 (0.997–1.149)   | 0.062 |
| NT-proBNP         | 1.000 (0.999–1.001)   | 0.847 |
| Tbil              | 1.070 (0.991–1.156)   | 0.084 |
| Pericardial effusion | 0.147 (0.009–2.505) | 0.185 |
| Tbil              | 1.082 (0.971–1.206)   | 0.152 |
| mRAP              | 0.933 (0.621–1.402)   | 0.739 |

*P < 0.05.
performed because of the expensive cost which was beyond most of the patients’ affordability. Forth, detailed information of post PAH-specific drug therapy were only available in four patients, but no second RHC record. Consequently, we could not confirm the therapeutic effect of PAH specific drug on HHT-PAH patients. Fifth, the study population of HHT-PAH was limited and may reflect a relatively small sample of the entire HHT-PAH population. Given that PAH is a rare manifestation of HHT, with prevalence of < 1% of HHT cases, it may be challenging to conduct large-scale studies. Finally, important parameters of hemolysis, including red blood cell lifespan or half-life (the golden standard test), plasma-free hemoglobin, reticulocyte counts, erythrocyte creatine, haptoglobin, and parameters reflecting iron metabolism, were also needed to confirm the values of iron deficiency and subclinical hemolysis in HHT-PAH patients.

In conclusion, the one- and three-year survival rates of HHT-PAH patients were 77.8% and 53.3%, respectively, which were worse than matched IPAH patients. Total bilirubin might be a promising predictor for the long-term prognosis in HHT-PAH patients.

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

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