Five year risk assessment and treatment patterns in patients with chronic thromboembolic pulmonary hypertension

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Abstract

Aims Repeated risk assessments and treatment patterns over long time are sparsely studied in chronic thromboembolic pulmonary hypertension (CTEPH); thus, we aimed to investigate changes in risk status and treatment patterns in incident patients with CTEPH over a 5 year period.

Methods and results Descriptive and explorative study including 311 patients diagnosed with CTEPH 2008–2019 from the Swedish pulmonary hypertension registry, stratified by pulmonary endarterectomy surgery (PEA). Risk and PH-specific treatment were assessed in surgically treated (PEA) and medically treated (non-PEA) patients at diagnosis and up to 5 years follow-up. Data are presented as median (Q1–Q3), count or per cent. Prior to surgery, 63% in the PEA-group [n = 98, age 64 (51–71) years, 37% female] used PH-specific treatment and 20, 69, and 10% were assessed as low, intermediate or high risk, respectively. After 1 year post-surgery, 34% had no PH-specific treatment or follow-up visit registered despite being alive at 5 years. Of patients with a 5 year visit (n = 23), 46% were at low and 54% at intermediate risk, while 91% used PH-specific treatment.

In the non-PEA group (n = 213, age 72 (65–77) years, 56% female), 28% were assessed as low, 61% as intermediate and 11% as high risk. All patients at high risk versus 50% at low risk used PH-specific treatment. The 1 year mortality was 6%, while the risk was unchanged in 57% of the patients; 14% improved from intermediate to low risk, and 1% from high to low risk. At 5 years, 27% had a registered visit and 28% had died. Of patients with a 5 year visit (n = 58), 38% were at low and 59% at intermediate risk, while 91% used PH-specific treatment.

Conclusions Risk status assessed pre-surgery did not foresee long-term post-PEA risk and pre-surgery PH-specific treatment did not foresee long-term post-PEA treatment. Medically treated CTEPH patients tend to remain at the same risk over time, suggesting a need for improved treatment strategies in this group.

Keywords Pulmonary hypertension; Pulmonary endarterectomy; Risk assessment

Received: 26 January 2022; Revised: 20 April 2022; Accepted: 3 June 2022

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare and progressive form of pulmonary hypertension (PH). It is a complication of pulmonary embolism, where residual pulmonary thromboembolic material leads to vascular remodelling and small-vessel arteriopathy with consequent chronic obstruction.1–4 Pulmonary endarterectomy (PEA) has been shown to significantly improve haemodynamic parameters, long-term functional status and exercise capacity.2–4 However, 30–40% of patients with CTEPH are considered inoperable.5–6 Furthermore, after PEA, up to a third of the patients have persistent or recurrent PH and may benefit from disease-targeted drug therapy.1,4–6 Currently, only one drug specifically targeting CTEPH is approved and available in Sweden,7,8 but based on clinical experience and in symptomatic patients, off-label use of pulmonary arterial hypertension specific therapies is common.9–11 CTEPH, with or without PEA, requires lifelong treatment with anticoagulants and, in cases of heart failure or hypoxaemia, diuretics, and oxygen therapy can be indicated.1

Risk assessment, adapted from the risk stratification suggested by the 2015 ESC/ERS guidelines for the diagnosis and treatment of PH,1 has been validated in CTEPH.12–14 However, repeated risk assessments over a longer time period are only sparsely studied,13 and the long-term treatment patterns in patients with CTEPH is yet to be described.

This retrospective cohort study of patients with CTEPH, based on data from the Swedish pulmonary arterial hypertension registry (SPAHR15), aimed to investigate the changes in risk status and treatment patterns over a 5 year period. Data were stratified by PEA surgery.

Methods

Study population

The SPAHR is a national quality registry that was started in 2008. All PAH/CTEPH-expert centres in Sweden participate and >90% of all incident patients diagnosed with CTEPH in Sweden are registered in SPAHR.15 Mortality data in SPAHR is updated daily by a link to the Swedish population registry. All patients were informed locally about their participation in SPAHR and had the right to decline. The present study complies with the Declaration of Helsinki and was approved by the Swedish ethical review authority (Dnr 2019-05171).

Adult patients diagnosed with CTEPH between 2008 and 2019 and registered in SPAHR were considered for inclusion in the study. Patients with no calculable risk score at time of diagnosis, or on treatment with an investigational drug at any point during the study duration, were excluded from this analysis. Patients registered at diagnosis but with no clinical follow-up visits registered at any time during the study period was considered lost to follow-up and excluded if they were alive at one year, but left included if they had died within the first year.

The study population were stratified by PEA surgery, that is, patients that had undergone the surgical treatment (PEA) and patients that had not been operated (non-PEA).

Variables and definitions

SPAHR includes information relevant for diagnosis, including measures from the diagnostic right heart catheterization as well as clinical investigations including demographics, comorbidities, World Health Organization Functional Class (WHO-FC), diffusing capacity of lung for carbon monoxide (DLCO), 6 min walk distance (6MWD), echocardiography, and blood tests. At follow-up visits, clinical investigations such as WHO-FC, echocardiography, 6MWD, and blood tests are recorded. Medical treatments are registered at time of diagnosis as well as at subsequent visits.

Plasma creatinine levels were used to estimate glomerular filtration rate (eGFR) according to the revised Lund–Malmö GFR estimating equation.16 Impaired kidney function was defined as an eGFR <30 mL/min/1.73 m². Obesity was defined as a BMI ≥ 30 kg/m².

The date of diagnosis was the day of the diagnostic right heart catheterization. In the PEA group, all subsequent visits refer too to the date of PEA surgery (Table 1, Figures 1 and 2). In the non-PEA group, all visits reference to the date of diagnosis (Table 2, Figures 1 and 3).

The visit time windows were 1 year (visit closest to 12 months in a window of 1–17 months); 2 years (visit closest to 24 months in a window of 18–29 months); 3.5 years (visit closest to 39 months in a window of 30–47 months); and 5 years (visit closest to 57 months in a window of 48–65 months). In the PEA group, 23% underwent PEA surgery 12 months after diagnosis. Thus, to reflect patient status closer to PEA, data from the pre-surgery visit is shown in Table 1. The pre-surgery visit was the visit registered most recently before the PEA; it might coincide with the visit where diagnosis was established or be a clinical visit after diagnosis was established.

After PEA surgery, patients in Sweden may be referred to their local hospital for continued care, if they are in stable condition and with no need for PH-specific treatment. Local hospitals do not report data to SPAHR, thus, patients with no registered visits or no PH-specific treatment after the early (1 year) post-PEA visit are presented separately in Figure 2.

Risk assessment

Risk assessment was based on specific variables, according to the SPAHR risk assessment tool17: WHO-FC, 6MWD, N-terminal pro brain natriuretic peptide (NT-proBNP), right
Table 1  Characteristics for patients in the PEA group at the visit closest, but prior, to the PEA

| Characteristic                  | Low risk (N = 20) | Intermediate risk (N = 68) | High risk (N = 10) | Total (N = 98) |
|---------------------------------|-------------------|----------------------------|-------------------|---------------|
| **Time to PEA from**            |                   |                            |                   |               |
| Diagnosis (months)              | 6 (4–13)          | 6 (3–9)                    | 4 (0.5–7)         | 6 (4–11)      |
| Pre-PEA visit (months)          | 4 (3–5)           | 4 (3–6)                    | 1 (0.3–3)         | 4 (2–6)       |
| Age (years)                     | 62 (54–72)        | 66 (54–72)                 | 68 (55–70)        | 65 (52–72)    |
| Sex (female, %)                 | 20                | 20                         | 68                | 10            |
| BMI (kg/m²)                     | 26 (22–28)        | 26 (24–28)                 | 60                | 26 (23–28)    |
| WHO-FC II/III/IV (%)            | 65/35/0           | 16/81/3                    | 67                | 37            |
| 6MWD (m)                        | 492 (450–537)     | 365 (289–434)              | 51                | 372 (302–466) |
| eGFR (mL/min/1.73 m²)           | 70 (62–76)        | 72 (61–79)                 | 67                | 72 (61–79)    |
| Haemodynamics                   |                   |                            |                   |               |
| mPAP (mmHg)                     | 38 (31–48)        | 46 (41–52)                 | 64                | 46 (39–52)    |
| mRAP (mmHg)                     | 5 (4–7)           | 7 (5–10)                   | 64                | 7 (5–10)      |
| PAWP (mmHg)                     | 10 (8–12)         | 9 (5–12)                   | 63                | 9 (6–12)      |
| CI (L/min/m²)                   | 2.5 (2.2–2.9)     | 2.2 (1.9–2.6)              | 63                | 1.8 (1.7–2.1) |
| PVR (Wood units)               | 5.7 (4.2–8.6)     | 8.8 (6.9–10.5)             | 64                | 9.9 (9.2–10.7) |
| SvO₂ (%)                        | 66 (63–68)        | 59 (55–63)                 | 61                | 60 (53–65)    |
| SaO₂ (%)                        | 93 (90–96)        | 89 (87–94)                 | 55                | 90 (86–94)    |
| Echocardiography                |                   |                            |                   |               |
| RA area (cm²)                   | 19 (16–21)        | 27 (22–32)                 | 27                | 30 (30–30)    |
| Pericardial fluid (%)           | 0                 | 13                         | 41                | 100           |
| Co-morbidities*                 |                   |                            |                   |               |
| Systemic hypertension (%)       | 30                | 36                         | 59                | 12            |
| Diabetes mellitus (%)           | 0                 | 20                         | 59                | 12            |
| Atrial fibrillation (%)         | 10                | 20                         | 59                | 12            |
| Ischaemic stroke (%)            | 0                 | 20                         | 59                | 12            |
| Ischaemic heart disease (%)     | 0                 | 20                         | 59                | 12            |
| Obesity (%)                     | 20                | 20                         | 66                | 20            |
| Renal dysfunction (%)           | 0                 | 19                         | 66                | 10            |
| PH-specific treatment           |                   |                            |                   |               |
| Monotherapy (%)                 | 50                | 20                         | 68                | 70            |
| Dual therapy (%)                | 10                | 20                         | 68                | 30            |
| No treatment (%)                | 40                | 20                         | 68                | 0             |
| Supplemental treatment          |                   |                            |                   |               |
| Anticoagulants (%)              | 95                | 20                         | 68                | 100           |
| Supplemental oxygen (%)         | 5                 | 20                         | 67                | 30            |
| Diuretics (%)                   | 15                | 20                         | 68                | 80            |

6MWD, 6 min walking distance; BMI, body mass index; CI, cardiac index; DLCO, diffusing capacity of lung for carbon monoxide; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro brain natriuretic peptide; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; SaO₂, arterial oxygen saturation; SvO₂, mixed venous oxygen saturation; WHO-FC, World health organization functional class.

*Data shown by low, intermediate and high risk as median (Q1–Q3) or per cent. Sample sizes (n) are shown after the result.

*aAt the time of diagnosis.
atrial area, mean right atrial pressure, pericardial effusion, cardiac index (CI), and mixed venous oxygen saturation (SvO₂). Each variable was graded from 1 to 3 where 1 = ‘Low risk’, 2 = ‘Intermediate risk’, and 3 = ‘High risk’ and the sum of all grades was divided by the number of available variables for each patient rendering a mean grade. The mean grade was rounded off to the nearest integer, which was then used to define the patient’s risk group. A risk score was considered incalculable when there were less than two variables available for an individual patient. Details regarding the SPAHR risk assessment method have been published previously.17 An incalculable risk score at a follow-up visit was regarded as a missing value.

Statistics

R 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria) was used for statistical and graphical computing. Results are expressed as medians with first and third quartiles (Q1–Q3) or absolute numbers and percentages of patients. Survival was analysed using the Kaplan–Meier method. Patients were censored at the date of lung transplantation, the last observational time point (31 December 2019) or the end of the 5 year study interval. In the present study, a descriptive analysis approach was pursued; thus, no formal hypothesis nor statistical testing was performed.

Results

Study population

There were 342 incident patients diagnosed with CTEPH registered in SPAHR. Patients with incalculable risk score at time of diagnosis (n = 2), treatment with an investigational drug at any point during the study duration (n = 1), or alive one year after diagnosis but with no registered visit after diagnosis (n = 28) were excluded, leaving a study population of 311 patients. Of these, 98 (32%) patients had undergone PEA, while 213 (68%) were treated conservatively (non-PEA), as shown in Figure 1.

At time of diagnosis, the median (Q1–Q3) age of the study population was 70 (62–76) years and 50% were female. There was no difference in age between the sexes, but women were more often obese, in WHO FC III-IV, had a shorter 6MWD, and a higher pulmonary vascular resistance than men (Supporting Information, Table S1). Upfront PH-specific medical treatment was administered more often to women (76%) compared with men (66%), whereas men were more often treated by PEA (Supporting Information, Table S1).

Pulmonary endarterectomy surgery group: at time of diagnosis

The median age at diagnosis for patients who underwent PEA surgery (n = 98) was 64 (51–71) years and 37% were female. A third of the patients (32%) had hypertension and a fifth (19%) were obese. Mono and dual PH-specific therapies were administered to 49% and 11% respectively while 40% remained untreated within 3 months from diagnosis. A majority of patients received anticoagulant treatment (94%) and 43% were treated with diuretics. Median time from diagnosis to PEA surgery was 6 (4–11) months. Seventy-five patients (77%) underwent surgery within 12 months of diagnosis; of those assessment of risk yielded, 17% in low risk, 77% in intermediate risk, and 5% in high risk at time of diagnosis.
The 1, 3, and 5 year survival after diagnosis for the PEA group, calculated by Kaplan-Meier analyses, was 95%, 91%, and 87%, respectively.

**Pulmonary endarterectomy surgery group: pre-surgery visit**

The pre-surgery visit ($n = 98$), i.e. the most recent visit before the PEA, occurred 4 (2–6) months prior to the surgery ($Table 1$, $Figure 2$). At the pre-surgery visit, risk assessment yielded 20% in low risk, 69% in intermediate risk, and 10% in high risk ($Figure 2$). For patients at low risk, time from diagnosis to PEA was 6 (4–13) months, for patients at intermediate risk it was 6 (3–9) months and for those at high risk 4 (0.5–7) months. Mono and dual PH-specific therapy were administered to 46% and 17% of patients, respectively, while 37% were not on any PH-specific treatment ($Table 1$, $Figure 2$, and Supporting Information, $Table S2$). No patients at high risk...
Table 2  Characteristics at time of diagnosis for patients in non-PEA group by low, intermediate, and high risk

| Characteristic                  | Low risk (N = 60) | n | Intermediate risk (N = 129) | n | High risk (N = 24) | n | Total (N = 213) | n |
|---------------------------------|-------------------|---|----------------------------|---|-------------------|---|----------------|---|
| Age (years)                     |                   |   |                            |   |                   |   |                |   |
|                                 | 67 (58–74)        | 60| 73 (67–78)                 | 129| 72 (67–80)        | 24| 72 (65–77)     | 213|
| Sex (female, %)                 | 52                |   | 60                         |   | 57                |   | 62             |   |
|                                 |                   |   |                            |   |                   |   | 24             |   |
| BMI (kg/m²)                     | 27 (25–30)        | 58| 25 (23–29)                 | 124| 24 (22–27)        | 23| 26 (24–30)     | 205|
| WHO-FC III/IV (%)               | 53/47/0           | 59| 1284/4                     | 128| 4/74/22           | 23| 22/73/5        | 210|
| 6MWD (m)                        | 450 (339–526)     | 39| 305 (220–390)              | 102| 120 (90–186)      | 14| 325 (221–424)  | 155|
| eGFR (mL/min/1.73 m²)           | 70 (61–83)        | 58| 57 (47–68)                 | 127| 49 (39–58)        | 24| 60 (49–71)     | 209|
| DLCO (% pred)                   | 71 (61–80)        | 32| 60 (46–74)                 | 69  | 59 (34–81)        | 6  | 65 (51–78)     | 107|
| Hb (g/L)                        | 148 (138–152)     | 59| 146 (136–155)              | 127| 139 (128–150)     | 23| 146 (136–153)  | 209|
| NT-proBNP (ng/L)                | 127 (76–249)      | 51| 1520 (507–3365)            | 111| 5258 (3294–9874)  | 24| 1022 (226–3306)| 186|
| Haemodynamics                   |                   |   |                            |   |                   |   |                |   |
| mPAP (mmHg)                     | 35 (26–40)        | 60| 43 (34–50)                 | 123| 48 (45–55)        | 22| 41 (33–49)     | 205|
| mRAP (mmHg)                     | 5 (3–6)           | 59| 7 (4–10)                   | 118| 15 (10–19)        | 22| 6 (4–10)       | 199|
| PAWP (mmHg)                     | 10 (6–12)         | 60| 9 (6–11)                   | 122| 10 (7–13)         | 21| 9 (6–12)       | 203|
| CI (L/min/m²)                   | 2.8 (2.5–3.0)     | 60| 2.0 (1.9–2.5)              | 120| 1.5 (1.4–1.7)     | 21| 2.2 (1.9–2.7)  | 201|
| PVR (Wood units)                | 4.8 (3.3–6.0)     | 59| 7.7 (6.0–10.8)             | 122| 14.4 (11.4–16.7)  | 21| 7.0 (5.2–10.7) | 202|
| SvO₂ (%)                        | 68 (66–72)        | 57| 59 (55–65)                 | 113| 47 (39–52)        | 22| 62 (55–68)     | 192|
| SaO₂ (%)                        | 93 (91–95)        | 50| 91 (85–94)                 | 102| 90 (86–92)        | 19| 92 (88–94)     | 171|
| Echocardiography                |                   |   |                            |   |                   |   |                |   |
| RA area (cm²)                   | 18 (13–22)        | 22| 24 (19–29)                 | 56  | 29 (28–32)        | 5  | 23 (18–28)     | 83 |
| Pericardial fluid (%)           | 2                 | 48| 7                          | 96  | 45                | 11| 8              | 155|
| Co-morbidities                  |                   |   |                            |   |                   |   |                |   |
| Systemic hypertension (%)       | 45                |   | 55                         | 48  | 115               | 30| 20             | 45 |
| Diabetes mellitus (%)           | 7                 |   | 55                         | 11  | 114               | 15| 20             | 10 |
| Atrial fibrillation (%)         | 4                 |   | 54                         | 13  | 114               | 35| 20             | 13 |
| Ischaemic stroke (%)            | 4                 |   | 55                         | 4   | 114               | 5 | 20             | 4  |
| Ischaemic heart disease (%)     | 2                 |   | 55                         | 16  | 114               | 25| 20             | 13 |
| Obesity (%)                     | 29                |   | 58                         | 24  | 124               | 9 | 23             | 24 |
| Renal dysfunction (%)           | 3                 |   | 58                         | 6   | 127               | 12| 24             | 6  |
| PH-specific treatment           |                   |   |                            |   |                   |   |                |   |
| Monotherapy (%)                 | 48                |   | 60                         | 80  | 129               | 83| 24             | 71 |
| Dual therapy (%)                | 2                 |   | 60                         | 5   | 129               | 17| 24             | 5  |
| No treatment (%)                | 50                |   | 60                         | 16  | 129               | 0 | 24             | 23 |
| Supplemental treatment          |                   |   |                            |   |                   |   |                |   |
| Anticoagulants (%)              | 95                |   | 59                         | 95  | 129               | 96| 24             | 95 |
| Supplemental oxygen (%)         | 3                 |   | 59                         | 21  | 129               | 50| 24             | 19 |
| Diuretics (%)                   | 36                |   | 59                         | 68  | 129               | 96| 24             | 62 |

6MWD, 6 min walking distance; BMI, body mass index; CI, cardiac index; DLCO, diffusing capacity of lung for carbon monoxide; eGFR, estimated glomerular filtration rate; Hb, haemoglobin; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro brain natriuretic peptide; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RA, right atrial; SaO₂, arterial oxygen saturation; SvO₂, mixed venous oxygen saturation; RA, right atrial; WHO-FC, World health organization functional class.

Data are shown as median (Q1–Q3) or per cent. Sample sizes (n) are shown after the result.
were untreated. For patients at low and intermediate risk pre-surgery, the distribution of PH-specific therapy was unchanged from diagnosis while among patients at high risk the proportion on dual therapy had increased since diagnosis.

**Pulmonary endarterectomy surgery group: post-surgery visits**

Five years after PEA, 62 patients (63%) were alive, 13 (13%) had died, and 23 (23%) were censored at study-end, which was encountered earlier than 5 years after PEA (Figure 2). Of the 62 patients that were alive, 34 patients had no PH-specific treatment or visit registered behind the 2 year post-PEA visit.

Among the 37 patients treated with PH-specific drugs at a long-term visit (Figure 1), 13 were assessed as low risk (monotherapy = 11, combination therapy = 2), 23 as intermediate risk (monotherapy = 16, combination therapy = 7) and one as being at high risk (on combination therapy).

**Non-pulmonary endarterectomy surgery group**

In the non-PEA group (n = 213), the median age at diagnosis was 72 (65–77) years and 56% were female (Table 2). Almost
half of the patients (45%) had hypertension and a quarter (24%) were obese. Mono and dual PH-specific treatment was administered to 71% and 5% respectively, while 23% did not receive a PH-specific drug within 3 months of diagnosis (Table 2, Figure 3, and Table S3). A majority (95%) of patients were treated with an anticoagulant and 62% with diuretics. Four patients underwent BPA, two at time of diagnosis and two at 1.5 and 2.8 years after diagnosis. One patient with BPA at time of diagnosis remained untreated for the duration of the study while three patients were on and remained on PH-specific therapy from diagnosis.

Fifty-eight patients had a registered 5 year visit, whereas 59 patients had died and three had undergone lung transplant during the study period; 10%, 19%, and 32% had not reached the 2, 3.5, and 5 year visit windows, respectively (Figure 3).

At time of diagnosis, 28% of non-PEA patients were in low risk, 61% in intermediate risk, and 11% in high risk (Table 2). All patients assessed as high risk and 50% of patients assessed as low risk received PH-specific medical treatment. Among patients at high risk, 50% used supplemental oxygen and 96% diuretics.

At 1 year, 57% remained in the same risk class as at diagnosis while 14% had improved from intermediate to low risk and 0.5% from high to low risk and 6% had died (Figure 3).

The 1, 3 and 5 year survival after diagnosis for the non-PEA group, calculated by Kaplan–Meier analyses, was 92%, 77%, and 61%, respectively.

**Non-pulmonary endarterectomy surgery group without pulmonary hypertension-specific treatment upfront**

Of 50 patients (23%) with no PH-specific treatment at diagnosis (low risk n = 30, intermediate risk n = 20), 19 remained untreated at 1 year, whereas 17 remained in the same risk group (low risk n = 14 and intermediate n = 3). Of the 24 patients that had started PH-specific treatment at 1 year, 20 remained at the same risk as at diagnosis (low risk n = 8, intermediate risk n = 12). No patient untreated at diagnosis escalated to high risk during the study period but ten patients died.

**Non-pulmonary endarterectomy surgery group with pulmonary hypertension-specific treatment upfront**

Among 152 patients (71%) with upfront PH-specific monotherapy (low risk n = 29, intermediate risk n = 103, and high risk n = 20), 100 patients remained on monotherapy at 1 year, whereof 58 remained in the same risk group (low n = 12, intermediate n = 41, and high n = 5) as at diagnosis and no patients had died. At 1 year, 31 patients (20%) on upfront monotherapy had escalated to combination therapy and, of those, 18 remained at the same risk status as at diagnosis, 9 had lower, and 4 had higher risk status than at baseline.

**Risk assessment**

At diagnosis, a median of 7 [Q1–Q3; 6–7] variables for risk assessment were available per patient and at the pre-surgery visit for the PEA group, 5 [Q1–Q3; 4–7] variables. At follow-up visits 5 [Q1–Q3; 3–5] variables for risk assessment were available per patient. WHO-FC, 6MWD, and at least one measure of right ventricular function (NT-proBNP, echocardiography and/or right heart catheterization) were available for 72% of patients at baseline and in 75% of the follow-up visits.

**Discussion**

In the present observational, registry study including a national cohort of patients with CTEPH, two thirds of the patients were at an intermediate risk level at diagnosis while only a tenth were assessed as being at an high risk level. The proportion of patients treated upfront with PH-targeted medical treatment increased with risk severity; half of the patients at low risk and all patients at high risk received a PH-targeted treatment upfront. In patients who underwent PEA, the pre-PEA risk did not foresee long-term risk after surgical intervention, and pre-surgery treatment with PH-specific drugs did not foresee the treatment patterns after intervention. Patients without PEA tend to remain at the same risk status over time, suggesting room for improved treatment strategies in this group.

PEA surgery was performed in a third of the patients. This is in line with reports from other registries during the same time period. However, some registries report distinctly higher proportions, 50–75%, of patients undergoing PEA. The prospective study design of these registries might have affected the rate of PEA, but despite this, the results point toward an underuse of PEA and a higher proportion of patients than previously thought might be operable. The low perioperative mortality also supports this approach. Long-term outcome reported by these studies adds potentially important knowledge for adequate selection of patients suitable for PEA. The reason for not choosing PEA, including assessed operability, was not available in the present study. Thus, it was not possible to determine if PEA was underused in Sweden during the time of this study.

The risk distribution assessed pre-surgery in the PEA group and at diagnosis in the non-PEA group was similar. This suggests that operability, based on age, co-morbidity and the characteristics of the thromboembolic lesions (location, extension, etc.) was the primary determining factor for choosing/not choosing PEA. The patients in the PEA group were
younger, had higher mean pulmonary artery pressure and pulmonary vascular resistance, as well as less co-morbidities than the non-PEA group. Including these factors in the risk assessment tool might yield information important for outcome after surgery.

The proportion of patients on PH-specific treatment prior to PEA was higher in the present study compared with the recently presented worldwide CTEPH registry.\textsuperscript{21} The role of pre-surgery treatment with a PH-specific drug and its relation to operability or surgical success is not clear.\textsuperscript{5,22} In the present study, patients on combination therapy before the PEA tended to continue on PH-specific treatment after surgery, while receiving monotherapy or no PH-specific treatment prior to PEA did not predict the post-PEA treatment. In addition, while all patients at high risk received PH-targeted treatment before PEA, being at high-risk pre-PEA did not foresee treatment with a PH-specific drug after surgery.

The ratio of men vs. women that underwent PEA was 3:2 in the present study. The proportion of women was lowest in the low-risk group, while in the high-risk group, though small numbers, the sex distribution was evenly divided. There were no obvious reasons for this. The study population was equally divided between sexes, and age, haemodynamic status, and number of co-morbidities were similar between men and women. One might speculate that a perceived lower functional status, i.e. worse symptom burden and lower exercise tolerance among women, led to the higher proportion of medical treatment and lower proportion of surgery than among men. The proportion of men undergoing PEA varies from 35% to 65% in the literature and the rate seems to independent of country and time period.\textsuperscript{2,23,24} One reason for this large variation might be the lack of knowledge as to which patients who will benefit from PEA.\textsuperscript{1} The main operability criteria suggested in the 2015 ESC/EURS PH guidelines are: accessible thrombi and a patient expected to tolerate the surgical procedure.\textsuperscript{1} There is yet no consensus on how to use pre-PEA haemodynamic measurements or functional status to predict long-term outcome after PEA surgery,\textsuperscript{1} and more studies in this area are warranted.

At the 1 year post-PEA visit, the proportion of patients in low risk had increased and subsequently, patients at intermediate or high risk decreased. Half of the patients that were alive 5 years after the PEA surgery had none or only an early visit registered after the PEA or no PH-specific treatment registered after surgery. No registered visits long term after PEA were, in this study population, considered indicative of not being followed at a PAH/CTEPH-specialist centre and suggesting a successful PEA and no need for a disease specific medical treatment. However, this suggestion should be considered speculative and recurring PH could be missed due to the lack of follow-up visits at the specialist centre.\textsuperscript{22} A general definition of residual PH after PEA is missing,\textsuperscript{1,22} and while results from the present study are in line with previously suggested levels of residual PH, a recent consensus statement suggest it might be distinctly higher.\textsuperscript{22}

In the non-PEA group, a majority was treated with a PH-specific treatment upfront and, at 1 year, this had increased even further. The highest proportion of untreated patients was assessed as low risk, while most patients at intermediate, and all patients at high risk, were on an upfront PH-specific treatment. Of patients who were untreated at diagnosis, no one escalated to high risk during the study period but ten of the patients died. The registry did not contain information as to why some patients did not start PH-specific treatment. One might speculate that riociguat as a treatment for CTEPH not being available in Sweden until 2015, there might have been hesitation to start a non-approved treatment. As previously shown, patients presenting with a high risk at diagnosis had worse outcome than patients with intermediate or low risk status.\textsuperscript{12-14} Patients in the non-PEA group tend to remain at the same risk over time, suggesting room for improved treatment strategies and possibly, higher rates of PEA.

Strengths and limitations

The analyses include incident patients diagnosed with CTEPH since 2008. As all PAH/CTEPH specialist centres in Sweden participate in SPAHR, the national coverage of patients diagnosed with CTEPH in Sweden is > 90% and thus, data reflect a national real-life patient population as seen in clinical practice.

Limitations typically associated with retrospective, observational registry studies, such as lack of standardization of registered variables and missing data, exist in the presented study and should be taken into account when interpreting the results. Patients included in the registry during the last four years of the study period will not have had clinical visits during the full study period, limiting the weight of the results at the last follow-up visits. The reason for not undergoing PEA is not registered in SPAHR and this limits the analyses of PEA group. Patients with no PH-specific treatment and considered in a stable condition have the option to be followed at their local hospital. Local hospitals do not report to SPAHR, thus data from these visits are not included in the study.

Conclusions

A majority of patients with CTEPH were assessed as being at intermediate risk at diagnosis. The proportion of patients with a PH-targeted medical treatment upfront or pre-PEA increased with risk severity. In patients who underwent PEA, the pre-PEA risk did not foresee long-term risk after surgical intervention, and pre-surgery treatment with PH-specific drugs did not foresee the treatment patterns after intervention. Patients
without PEA tend to remain at the same risk status over time, suggesting room for improved treatment strategies in this group.

Acknowledgements

We acknowledge the work of the SPAHR registrars at the PAH/CTEPH-specialist clinics, the members of the SPAHR steering committee, and Uppsala Clinical Research Centre for administering SPAHR.

Conflict of interest

Barbro Kjellström, Habib Bouzina, Erik Björklund, Kjell Jansson, Magnus Nisell, Göran Rådegran, Håkan Wåhlander, Clara Hjalmarsson, and Stefan Söderberg have no conflicts of interests related to the content of this manuscript. Roger Hesselstrand was employed at the University hospital in Lund at the time when data was collected, analysed and the manuscript was prepared. RH is today associated professor at Lund University and an employee of Boehringer-Ingelheim AB, Sweden. Amélie Beaudet and Susan C. Edwards are employees of Actelion Pharmaceuticals, a Janssen Pharmaceutical Company of Johnson & Johnson, Allschwil, Switzerland. Representatives of Actelion Pharmaceuticals, a Janssen Pharmaceutical Company of Johnson & Johnson, Allschwil, Switzerland and Janssen Cilag AB, Solna, Sweden listed as authors of this paper, participated in study design, interpretation of data and drafting the manuscript, but did not participate in data analyses.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Patient characteristics at time of diagnosis stratified by sex. Data is shown as median (Q1-Q3) or percent. Sample sizes (n) are shown after the result.

Table S2. Detailed treatment and event data in the PEA group. All values are presented as counts. Data in supplemental Table S2 was stratified by risk group at pre-PEA visit and the patients in low, intermediate, high risk groups (number given in parenthesis) remains the same over time.

Table S3. Detailed treatment and event data in the non-PEA group. All values are presented as counts. Data in supplemental Table S3 was stratified by risk group at diagnosis and the patients in low, intermediate, high risk groups (number given in parenthesis) remains the same over time.

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**Funding**

As a national quality register, SPAHR receive financial support from the Swedish Association of Local Authorities and Regions. This study was funded by Actelion Pharmaceuticals, a Janssen Pharmaceutical Company of Johnson & Johnson, Allschwil, Switzerland. Representatives of Actelion Pharmaceuticals, a Janssen Pharmaceutical Company of Johnson & Johnson, Allschwil, Switzerland and Janssen Cilag AB, Solna, Sweden listed as authors of this paper, participated in study design, interpretation of data and drafting the manuscript, but did not participate in data analyses.
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DOI: 10.1002/ehf2.14033