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Chronic thromboembolic pulmonary hypertension in Saudi Arabia: preliminary results from the SAUDIPH registry

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ABSTRACT

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare, progressive vascular disease with poor prognosis if left untreated. This study aims to assess the patient characteristics, treatment approach and clinical and survival outcomes for CTEPH patients enrolled in the Systematic Prospective Follow Up for Better Understanding of Clinical Characteristics of Patients with Pulmonary Hypertension Disease (SAUDIPH) registry.

Methods: This study presents a subanalysis of CTEPH patients enrolled in the SAUDIPH registry. This registry enrolled patients with pulmonary hypertension, established through right heart catheterisation, under clinical management at a specialised tertiary care centre. Patients received standard care during the period of the registry.

Results: At the time of this analysis, 64 CTEPH patients were enrolled in the registry. Mean age at diagnosis was 39.7 years and there was a female predominance (67.6%). At baseline, most patients were in World Health Organization functional classes III or IV (70.1%). At the last follow-up visit, most patients (63.2%) had undergone endarterectomy, showing significant improvement in disease severity from baseline. Patients who underwent endarterectomy showed numerically higher (p=0.126) probability of survival at 1 year (97.5%) *versus* those who did not undergo endarterectomy (94.4%).

Conclusion: Patients were diagnosed at relatively young age, but still showed high disease severity, suggesting delay in diagnosis. Patients who underwent surgical treatment showed substantial improvements in clinical and haemodynamic parameters, while the remaining patients tended to show disease progression. The 96.6% 1-year cumulative probability of survival was high compared to previous studies.

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The SAUDIPH registry was designed to follow pulmonary hypertension patients in Saudi Arabia. This study assesses patient characteristics and treatment approaches of chronic thromboembolic pulmonary hypertension patients enrolled in the SAUDIPH registry. http://bit.ly/2uCWpBe

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Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare, progressive vascular disease that is usually a result of pulmonary embolism [1, 2]. It is characterised by thromboembolic lesions in the pulmonary arteries that lead to increased pulmonary artery pressure and increased pulmonary vascular resistance (PVR), ultimately leading to right heart failure [1–3]. The prognosis is poor if left untreated, with a low probability of medium- to long-term survival [1–3].

Contrary to other aetiologies of pulmonary hypertension, the pathophysiology of CTEPH has a crucial mechanical component, which makes it suitable for potentially curative surgical intervention [4]. Pulmonary endarterectomy for removal of accessible thromboembolic material is the recommended gold-standard treatment according to European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines [3], since this procedure is associated with improved survival [5, 6]. Nevertheless, not all patients are eligible for pulmonary endarterectomy, since the location of the thromboembolic material might be inaccessible, or the patients might be too frail to undergo the procedure [5]. For such cases, pharmacological treatment has improved and therefore, patients can expect some clinical and surgical gains even when surgical treatment is not an option [5]. Additional surgical procedures have been proposed, such as balloon pulmonary angioplasty [7], which could become a valuable option for patients who present thromboembolic material that is difficult to access using the standard procedures [8].

However, CTEPH remains underdiagnosed according to recent studies [9]. Given that it is a potentially treatable condition, there is a clear need to further improve awareness among clinicians to avoid misdiagnosis, as well as to improve referral networks to ensure that patients receive adequate treatment as soon as possible. Since this is a rare condition, for which the treatment approaches are rapidly evolving [8], there is an increasing need for real-world data on the characteristics of CTEPH patients, including their clinical and survival outcomes, to validate the value of the different contemporary treatment approaches.

The Systematic Prospective Follow Up for Better Understanding of Clinical Characteristics of Patients with Pulmonary Hypertension Disease (SAUDIPH) registry was designed to access the characteristics and outcomes of pulmonary hypertension patients in a specialised referral centre in Saudi Arabia. This study aims to assess the patient characteristics, treatment approach and clinical and survival outcomes for patients with CTEPH enrolled in the SAUDIPH registry.

Material and methods

Study design

This study presents a subanalysis of patients enrolled in the SAUDIPH registry, focusing on the CTEPH population. Other publications will assess the overall population in the registry, as well as specific aetiologies such as pulmonary arterial hypertension (PAH).

The SAUDIPH registry is aimed at characterising the pulmonary hypertension population under clinical management in the King Faisal Specialist Hospital (Riyadh, Saudi Arabia), which is a tertiary-care government academic hospital where patients are accepted from all over the Kingdom following electronic referral through a centralised referral system.

Patients with a diagnosis of pulmonary hypertension, established through gold-standard assessment (right heart catheterisation) were invited to participate in this registry. Patients with previously diagnosed pulmonary hypertension (*i.e.* prevalent cases) were allowed to participate in the registry; such patients were invited to participated when the registry began or when they were referred to the study centre. Reasonable efforts were made to obtain detailed clinical data for prevalent cases, namely diagnosis date and treatment history.

The first patient was enrolled on October 7, 2007 and the last patient considered for this analysis was enrolled on March 20, 2018. Since this is an ongoing registry, the last follow-up visit considered for the study took place on April 19, 2018, with a data-cut on the same date. For this analysis, only patients with diagnosis of CTEPH (pulmonary hypertension group 4.1) were considered.

The SAUDIPH registry received favourable opinion from the research ethics committee and the institutional review board of the King Faisal Specialist Hospital. All patients provided their written informed consent prior to enrolment in the registry.

Clinical care

Patients received standard care during the period of the registry, according to the routine clinical practice of the study centre. Once patients were referred to the study centre, they were assessed in the clinic or admitted to the unit depending on the clinical condition. A standard assessment was completed as recommended in the applicable ESC/ERS guidelines, including right heart catheterisation to establish the

diagnosis of pulmonary hypertension. The criteria for diagnosis of CTEPH included mean pulmonary arterial pressure (mPAP) ⩾25 mmHg and pulmonary capillary wedge pressure ⩽15 mmHg in the presence of occlusive thrombi/emboli in the elastic pulmonary arteries, mismatched perfusion defects on lung scan and specific diagnostic signs for CTEPH seen by multidetector computed tomographic angiography, magnetic resonance imaging or conventional pulmonary cineangiography, such as ring-like stenoses, webs/slits and chronic total occlusions (pouch lesions or tapered lesions) after ⩾3 months of anticoagulation [3].

Patients were invited to participate in the registry and received standard care. Patients attended follow-up visits according to routine clinical practice, typically every 3 months, except when the clinical condition required more frequent visits.

Assessments

Patient data for the SAUDIPH registry are collected directly from the electronic medical records, which are maintained on a disease-specific tool (PAH Tool; Inovultus Lda, Santa Maria da Feira, Portugal). For this analysis, the following baseline variables were considered: demographic (age, sex), clinical characteristics (diagnosis age, World Health Organization functional class (WHO FC), 6-min walk distance (6MWD), symptoms, N-terminal pro-brain natriuretic peptide (NT-proBNP)) and haemodynamic parameters. The following variables were considered during follow-up: clinical variables (WHO FC, 6MWD, symptoms, NT-proBNP), haemodynamic parameters and most recent treatment strategy. Survival was established based on electronic medical records when the data-cut took place, on April 19, 2018.

Statistical analysis

Data were summarised using descriptive statistics: continuous variables are presented as mean±SD or median (interquartile range (IQR)), while categorical variables are presented as absolute or relative frequencies. Continuous variables were subjected to normality testing (Kolmogorov–Smirnov test or Shapiro–Wilk tests), and when the normality assumption was validated parametric tests were used.

One-way ANOVA (or Kruskal–Wallis rank sum test) was used to compare baseline characteristics according to disease severity subgroups for continuous variables, while for categorical variables, Chi-squared tests *via* logistic regression were used. Multiple comparisons were performed *via* the Bonferroni *post hoc* method.

Changes from baseline to last follow-up visit were assessed using paired t-tests (or Wilcoxon signed-rank test) for continuous variables and the McNemar test for categorical variables.

The Kaplan–Meier method was used to estimate cumulative survival and differences between the survival curves were assessed using the log-rank test. The use of Cox proportional hazard models was planned to test the effects of different factors on the instantaneous risk of death. However, due to the limitations associated with the underlying data (few events, small sample) such analyses could not be conducted.

Statistical analyses were performed using R (version 3.1.1; R Foundation for Statistical Computing, Vienna, Austria), using a 5% significance level.

Results

Study population and baseline characteristics

In the SAUDIPH registry, from October 7, 2007 to March 20, 2018, 64 patients with CTEPH were enrolled and had at least one follow-up visit at the time of this study. Median (IQR) follow-up time was 16.6 (4.5–33.2) months. Table 1 presents the baseline characteristics of the study population. Mean age at diagnosis was 39.7 years and there was a female predominance (67.6%). At baseline, most patients were in WHO FC III or IV (70.1%); patients in WHO FC I tended to be younger and predominantly male, but these trends did not reach statistical significance. The most common risk factors identified among the study population at baseline were pulmonary embolism (100%), antiphospholipid syndrome (43%), deep venous thrombosis (22%) and systemic lupus erythematosus (13%).

At baseline, patients showed low median 6MWD (214.0 m) and relatively high Borg dyspnoea (3.5 Borg units) and fatigue scores (3.4 Borg units), as well as high NT-proBNP levels (702.5 $pg{\cdot}mL^{-1}$). Clinical parameters tended to worsen with increasing disease severity measured through WHO FC, with statistically significant differences for 6MWD (p=0.009) and NT-proBNP (p=0.031). In terms of haemodynamic parameters, patients with increasing disease severity also tended to show worse haemodynamic data, but only reaching statistical significance for oxygen base saturation (table 1).

Most patients (85.3%) in the study population constituted incident cases of CTEPH. Prevalent cases showed no significant differences in baseline characteristics, except for higher minimum oxygen saturation (p=0.038) compared to incident cases.

TABLE 1 Baseline demographic, clinical and haemodynamic characteristics of the chronic thromboembolic pulmonary hypertension (CTEPH) population according to World Health Organization functional class (WHO FC)

	Total	WHO FC				p-value
		I	II	III	IV	
Subjects	68	3	18	34	13	
Demographic						
Age at diagnosis years	39.7±11.8	28.3±7.5	42.0±11.2	39.8±12.8	39.1±10.2	0.328
Sex						
Female	46 (67.6)	0 (0.0)	13 (72.2)	23 (67.6)	10 (76.9)	0.113
Male	22 (32.4)	3 (100.0)	5 (27.8)	11 (32.4)	3 (23.1)	
Clinical						
6MWD m	214.0 (145.0–424.5)	451.5 (401.2–501.8)	395.5 (299.0–448.5)	189.0 (92.0–275.0)	149.5 (103.5–179.0)	0.009
Borg dyspnoea Borg units	3.5±2.1	2.0±2.8	2.6±1.5	4.4±2.2	3.8±2.6	0.131
Borg fatigue Borg units	3.4±2.1	2.0±2.8	2.3±1.1	4.4±2.2	3.8±2.6	0.062
Syncope	5 (7.4)	0 (0.0)	0 (0.0)	3 (8.8)	2 (15.4)	0.457
NT-proBNP pg·mL^{-1}	702.5 (119.2–1645.2)	129.0 (89.0–724.5)	212.0 (67.0–981.0)	702.0 (130.0–1215.0)	1778.0 (1051.0–2610.0)	0.031
Heart failure	1 (1.5)	0 (0.0)	0 (0.0)	1 (2.9)	0 (0.0)	1.000
Haemodynamics						
Cardiac index L·min^{-1}·m^{-2}	2.0 (1.7–2.3)	2.0 (1.8–2.0)	1.9 (1.7–2.1)	2.0 (1.8–2.3)	1.8 (1.7–2.4)	0.704
Cardiac output L·min^{-1}	3.7 (3.1–4.3)	4.3 (3.4–4.3)	3.7 (3.0–4.2)	4.0 (3.4–4.3)	3.2 (2.8–4.0)	0.542
mPAP, mmHg	49.6±14.3	55.0±19.7	47.1±13.4	49.9±15.3)	51.0±12.9	0.791
Oxygen saturation baseline %	96.2±2.3	96.5±2.1	96.0±2.0	97.2±2.2	94.0±2.0	0.047
Oxygen saturation minimum %	89.6±5.6	94.5±0.7	89.9±5.2	89.7±5.8	86.6±6.7	0.410
PADP mmHg	28.0 (23.0–38.0)	32.0 (25.5–38.0)	27.0 (22.0–36.0)	30.5 (23.5–38.0)	29.0 (23.0–35.0)	0.944
PASP mmHg	78.9±26.1	92.7±32.0	74.9±24.0	77.6±28.8	84.0±21.2	0.622
PCWP mmHg	15.0 (11.0–18.0)	10.0 (9.5–15.0)	15.0 (11.0–19.0)	14.0 (11.8–18.0)	15.0 (11.0–18.8)	0.836
PVR Woods units	9.7 (4.9–13.1)	11.6 (8.5–15.6)	9.6 (4.6–11.8)	9.6 (5.2–13.2)	9.4 (5.1–13.4)	0.880
RAP mmHg	13.0±6.1	10.7±12.5	12.0±4.8	12.2±4.6	17.2±8.2	0.082
Stroke volume mL·beat^{-1}	50.9±18.0	51.9±15.1	51.7±14.3	52.3±19.7	46.3±20.0	0.810
SVR WU	18.2 (15.9–22.3)	16.8 (16.0–22.2)	18.3 (15.5–22.8)	17.7 (15.8–20.5)	18.6 (16.2–25.7)	0.846
TPR WU	14.0 (8.0–17.4)	16.1 (11.9–19.6)	14.1 (8.2–16.4)	13.4 (7.9–16.4)	14.5 (13.0–19.1)	0.701

Data are presented as n, mean±SD, n (%) or median (interquartile range), unless otherwise stated. 6MWD: 6-min walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; mPAP: mean pulmonary arterial pressure; PADP: pulmonary artery diastolic pressure; PASP: pulmonary artery systolic pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; SVR: systemic vascular resistance; TPR: total pulmonary resistance.

Treatment and follow-up

Most patients (63.2%) had already undergone endarterectomy at the last follow-up visit (table 2) and, at the time of this analysis, nine patients were scheduled for endarterectomy. The main reasons for not performing endarterectomy procedures in the remaining patients included distal CTEPH and multiple comorbidities.

In terms of pharmacological treatment, at the last follow-up visit, 7.9% of patients were on single pulmonary hypertension-specific treatment (mostly macitentan or sildenafil) and 20.6% were on combination pulmonary hypertension-specific treatment (mostly macitentan plus sildenafil) (table 3). Among patients who underwent endarterectomy, 18.6% were treated with pulmonary hypertension-specific monotherapy and 14.0% with combination therapy at the last follow-up visit: 12 out of 14 patients were kept on pulmonary hypertension medical therapy based on right heart catheterisation results post-endarterectomy (residual pulmonary hypertension) and two out of 14 patients were kept on pulmonary hypertension therapy based on echocardiography results in addition to clinical assessment pre-right heart catheterisation.

TABLE 2 Change in clinical and haemodynamic parameters from baseline to last follow-up visit

	Overall CTEPH		No endarterectomy		Endarterectomy	
	Baseline	Last visit	Baseline	Last visit	Baseline	Last visit
Subjects	68		25		43	
Clinical						
WHO FC						
I/II	20 (29.9)	45 (67.2)	9 (36.0)	7 (29.2)	12 (27.9)	38 (88.4)*
III/IV	47 (70.1)	22 (32.8)	16 (64.0)	17 (70.8)	31 (72.1)	5 (11.6)
6MWD m	273.3±159.4	345.1±148.6*	255.4±167.8	179.4±112.1	282.7±157.8	428.0±78.2
Borg dyspnoea Borg units	3.5±2.1	2.6±2.4)	4.1±1.4	4.7±1.9	3.1±2.4	1.6±2.0
Borg fatigue Borg units	3.4±2.1	2.6±2.4	3.9±1.4	4.7±1.9	3.1±2.4	1.6±2.0
Syncope	5 (7.5)	2 (3.0)	3 (12.0)	1 (4.2)	2 (4.7)	1 (2.3)
NT-proBNP pg·mL^{-1}	702.5 (119.2–1645.2)	221.0 (102.0–1112.5)	702.5 (209.8–1806.8)	500.0 (177.0–1674.5)	696.0 (94.8–1275.5)	147.5 (70.8–321.2)
Heart failure	1 (1.5)	1 (1.5)	0 (0.0)	1 (4.2)	1 (2.3)	0 (0.0)
Haemodynamics						
Cardiac index L·min^{-1}·m^{-2}	2.0 (1.7–2.3)	2.0 (1.8–2.7)	2.0 (1.8–2.2)	2.5 (1.9–3.0)	2.0 (1.7–2.3)	2.0 (1.8–2.6)
Cardiac output L·min^{-1}	3.9±1.2	4.4±1.7	3.9±0.9	4.9±3.9	3.9±1.3	4.3±1.6
mPAP mmHg	49.6±14.3	41.8±15.9	49.9±14.2	53.5±17.7	49.5±14.5	40.4±15.7
Oxygen saturation baseline %	96.2±2.3	96.7±2.2	96.4±1.8	96.0±3.0	96.2±2.5	97.0±1.6
Oxygen saturation minimum %	89.6±5.6	92.0±4.8	90.9±5.4	89.8±5.9	89.0±5.7	93.0±3.9*
PADP mmHg	28.0 (23.0–38.0)	23.5 (16.8–36.8)	29.0 (23.2–33.5)	34.5 (27.8–41.2)	28.0 (22.5–38.5)	23.5 (16.2–35.2)
PASP mmHg	78.9±26.1	61.6±26.9	79.9±23.4	76.5±16.3	78.3±27.6	59.9±27.6
PCWP mmHg	15.0 (11.0–18.0)	15.0 (11.8–17.5)	15.0 (11.2–21.0)	23.5 (20.2–26.8)	14.5 (10.0–18.0)	14.5 (11.2–16.8)
PVR Woods units	9.7 (4.9–13.1)	4.1 (2.6–14.7)	8.1 (5.4–11.6)	12.2 (6.8–17.5)	9.8 (4.9–13.5)	4.1 (2.7–13.7)
RAP mmHg	13.0±6.1	11.5±4.9	13.1±6.0	18.0±1.4$^{\#}$	12.9±6.2	10.8±4.6$^{\#}$
Stroke volume mL·beat^{-1}	50.9±18.0	57.3±28.3	53.8±15.7	73.3±58.5	49.5±19.0	55.4±25.5
SVR WU	19.8±7.4	20.7±9.5	17.8±4.6	18.3±13.4$^{\#}$	20.7±8.3	21.0±9.5$^{\#}$
TPR WU	14.0 (8.0–17.4)	8.1 (5.8–18.8)	13.5 (8.0–16.4)	18.1 (11.7–24.5)	14.1 (8.1–17.9)	8.1 (5.9–17.7)

Data are presented as n, n (%), mean±SD or median (interquartile range), considering only patients who had last visit assessments. CTEPH: chronic thromboembolic pulmonary hypertension; WHO FC: World Health Organization functional class; 6MWD: 6-min walk distance; NT-proBNP: N-terminal pro-brain natriuretic peptide; mPAP: mean pulmonary arterial pressure; PADP: pulmonary artery diastolic pressure; PASP: pulmonary artery systolic pressure; PCWP: pulmonary capillary wedge pressure; PVR: pulmonary vascular resistance; RAP: right atrial pressure; SVR: systemic vascular resistance; TPR: total pulmonary resistance. $^{\#}$: it was not possible to perform a comparison due to data inconsistency. *: p<0.05 (change through last visit).

TABLE 3 Treatment approach at the last follow-up visit

Subjects	68
Single pulmonary hypertension-specific treatment	19 (29.7)
Macitentan	7 (36.8)
Riociguat	2 (10.5)
Sildenafil	10 (52.6)
Combination pulmonary hypertension-specific treatment	14 (20.6)
Iloprost + macitentan + riociguat	1 (7.1)
Bosentan + sildenafil	2 (14.3)
Iloprost + macitentan + riociguat	1 (7.1)
Macitentan + riociguat + selexipag	1 (7.1)
Macitentan + sildenafil	9 (64.3)
Surgical treatment	43 (63.2)
Lung transplantation	0 (0)
Endarterectomy	43 (63.2)

Data are presented as n or n (%).

Table 2 presents the changes in clinical and haemodynamic parameters from baseline to the last follow-up visit. Disease severity was reduced substantially over the study period: at baseline 29.9% of patients were in WHO FC I/II *versus* 67.2% at the last follow-up visit. However, the difference was only statistically significant among patients who underwent endarterectomy (88.4% in WHO FC I/II), and not in those who did not undergo endarterectomy (29.2% in WHO FC I/II). 6MWD improved significantly during the study for the overall population; those who underwent endarterectomy showed numerical improvements (from 282.7 m at baseline to 428.0 m at last follow-up visit), in contrast to those who did not undergo endarterectomy. Symptoms (dyspnoea, fatigue, syncope) and NT-proBNP levels tended to improve over the period of the study, but the differences did not reach statistical significance.

Survival

During the period of the study, three patients died. Only one of the deceased patients had undergone endarterectomy. The causes of death were right heart failure and sepsis.

Table 4 presents Kaplan–Meier survival estimates for the overall population and according to endarterectomy use. The cumulative probability of 1-year survival was 96.6% (95% CI 92–100%) for the overall study population. Patients who underwent endarterectomy showed numerically higher probability of survival at 1 year (97.5%) *versus* those who did not undergo endarterectomy (94.4%), but the differences were not statistically significant (p=0.126). Incident cases tended to show higher cumulative probability of survival at 1 year (100.0%) compared to prevalent cases (98.0%), but the trend was not statistically significant (p=0.538). Survival estimates for the overall population and prevalent or incident cases are available in the supplementary material. These were not considered in the main analysis, due to the reduced statistical power.

It was not feasible to assess the main factors associated with mortality, due to the reduced number of events and small sample size.

Discussion

This study characterised the CTEPH population included in the SAUDIPH registry and provided the first data on the clinical evolution and survival outcomes of this highly relevant population in the context of

TABLE 4 Survival analysis for the overall study population and according to the use of endarterectomy

	Overall CTEPH	Surgical treatment		p-value
		No endarterectomy	Endarterectomy	
Subjects n	68	25	43	
Cumulative probability of survival[#] 1 year from diagnosis % (95% CI)	96.6 (92.0–100)	94.4 (84.4–100)	97.5 (92.8–100)	0.126

CTEPH: chronic thromboembolic pulmonary hypertension. [#]: estimate based on Kaplan–Meier method.

pulmonary hypertension. This is one of the most relevant aetiologies of pulmonary hypertension to study since it is potentially curable (or at least to a large extent treatable), and this study demonstrated that surgical treatment has as crucial impact on patient prognosis.

The demographic trends of this study population are in line with what would be expected for a Saudi pulmonary hypertension population. We found a female predominance, which is widely described in the pulmonary hypertension literature [1]. Age at diagnosis in this CTEPH cohort was substantially lower (40 years) than generally reported in studies from other regions (usually late fifties to 70 years). This trend has been found previously in other Saudi pulmonary hypertension populations [10–12] and is thought to be associated with the fact that the overall Saudi population is younger than populations of Western developed countries: ~69% of the population is aged <40 years and 47% is aged 25–49 years [13]. It is clinically significant that even for pulmonary hypertension associated with thromboembolism, which is generally associated with increasing age, the Saudi population develops these conditions at a younger age.

The population showed baseline clinical and haemodynamic parameters indicative of advanced CTEPH, including low 6MWD, cardiac index and cardiac output, as well as high NT-proBNP, mPAP, PVR and right atrial pressure, which are associated with worse prognosis [3, 6]. This relatively severe presentation is probably linked to a delay in diagnosis, which could be explained by lack of awareness of this rare condition in the medical community or to initial misdiagnosis that is only put forward for pulmonary hypertension treatment at a later stage.

After a median follow-up time of 16.6 months, patients showed substantial improvements in clinical and haemodynamic parameters. These gains are largely due to the wide availability of surgical treatment, namely pulmonary endarterectomy [4, 14, 15]. Patients who underwent endarterectomy showed significant improvements in their WHO FC classification, reflecting a wide reduction in disease severity, while patients who did not undergo endarterectomy did not improve, despite the wide use of targeted treatment. In terms of specific improvements in clinical and haemodynamic parameters, we found numerical improvements for most parameters, but these were largely driven by the patients who underwent surgical treatment. Among such patients, we found statistically significant improvements in WHO FC and minimum oxygen saturation. The changes in the remaining parameters, for patients who underwent endarterectomy, did not reach statistical significance due to the limited statistical power of this small sample, but we found substantial numerical improvements for 6MWD, Borg dyspnoea and fatigue scores, NT-proBNP, cardiac output, mPAP, oxygen saturation, pulmonary artery diastolic pressure, pulmonary artery systolic pressure, PVR and systemic vascular resistance. These findings are in agreement with the literature on the surgical treatment of CTEPH [4, 14, 15] and highlight the importance of surgical intervention in achieving the best treatment outcomes in these populations.

The estimated 1-year survival in this cohort of CTEPH patients was 96.6%, which is high compared to other previous studies of the CTEPH population (including the recently published international registry of CTEPH) [6, 16–19], which did not appear to be driven by survivor bias in prevalent cases (in fact, prevalent cases had lower estimated survival). Nonetheless, there are other smaller studies that show comparable 1-year survival estimates and, importantly, show comparable disease characteristics such as disease severity measured by WHO FC [20]. Therefore, higher 1-year survival estimates appear to be associated with patient characteristics (disease severity) and the wide availability of pulmonary enterectomy.

Most patients in this cohort underwent pulmonary endarterectomy and these patients showed numerically higher 1-year estimated survival (97.5% *versus* 94.4%). The differences in survival estimates did not reach statistical significance, due to the limited number of patients (especially in the no-endarterectomy group), but these results still highlight the crucial role of surgical interventions in improving survival for CTEPH [4, 14, 15]. Other factors that could explain these results include better post-operative care, and implementation of a comprehensive CTEPH programme in the study centre.

Therefore, since this is a potentially treatable/curable condition, it is important to continue to ensure that all patients are referred in a timely manner, namely through the development of awareness programmes in the region to educate general physicians towards earlier referral of suspected CTEPH cases. Additionally, further efforts should be made in the development of innovative surgical interventions to address the needs of patients who are not eligible for conventional pulmonary endarterectomy. Balloon pulmonary angioplasty is planned to be available at our institution in near future.

This study has several limitations that are difficult to address in a rare condition such as CTEPH. The population is relatively small, which can impair the statistical analyses, particularly when comparing various small subgroups. Both prevalent and incident cases were included in this study, since the base registry includes both types of patients. We compared the characteristics of prevalent and incident cases

and did not find relevant differences, even in terms of survival estimates where the potential toward bias would be more significant. Additionally, the median follow-up time of the CTEPH cohort in the SAUDIPH registry is still relatively short (1.3 years), which impedes robust longer-term survival estimates, due to the low number of patients at risk and the low number of mortality events. The registry will continue to assess the clinical evolution of these patients to provide more robust data for the Saudi CTEPH population in the future.

In conclusion, this study presents the first analysis of CTEPH patients in the SAUDIPH registry. Patients were diagnosed at relatively young age, but still showed high disease severity, which suggests delayed diagnosis. Patients who underwent surgical treatment showed substantial improvements in clinical and haemodynamic parameters, while the remaining patients tended to show disease progression even with the wide use of targeted pharmacological treatment. The 96.6% 1-year cumulative probability of survival was high compared to previous studies, which appears to be associated with technical advances in surgical techniques, better post-operative care, and implementation of a comprehensive CTEPH programme.

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