RESEARCH ARTICLE

Disease characteristics and clinical outcome over two decades from the Swiss pulmonary hypertension registry

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Abstract

Pulmonary hypertension (PH), especially pulmonary arterial and chronic thromboembolic pulmonary hypertension (PAH/CTEPH), are rare and progressive conditions. Despite recent advances in treatment and prognosis, PH is still associated with impaired quality of life and survival. Long-term PH-registry data provide information on the changing PH-epidemiology and may help to direct resources to patient's needs. This retrospective analysis of the Swiss Pulmonary Hypertension Registry includes patients newly diagnosed with PH (mainly PAH/CTEPH) registered from January 2001 to June 2019 at 13 Swiss hospitals. Patient characteristics (age, body mass index, gender, diagnosis), hemodynamics at baseline, treatment, days of follow-up, and events (death, transplantation, pulmonary endarterectomy, or loss to follow-up) at last visit were analyzed. Patients were stratified into four time periods according to their date of diagnosis. Survival was analyzed overall and separately for PAH/CTEPH and time periods. 1427 PH patients were included (thereof 560 PAH, 383 CTEPH). Over the years, age at baseline (mean $\pm$ SD) significantly increased from 59 ± 14 years in 2001–2005 to 66 ± 14 years in 2016–2019 ($p < 0.001$) while the gender distribution tended toward equality. Mean pulmonary artery pressure and pulmonary vascular resistance significantly decreased over time (from 46 ± 15 to 41 ± 11 mmHg, respectively, 9 ± 5 to 7 ± 4 WU, $p < 0.001$). Three-year survival substantially increased over consecutive periods from 69% to 91% (for PAH 63%–95%, for CTEPH 86%–93%) and was poorer in PAH than CTEPH independently of time period ($p < 0.001$). Most patients were treated with mono- or combination therapy and an increasing number of CTEPH underwent pulmonary endarterectomy (40% 2016–2019 vs. 15%

Paula Appenzeller and Mona Lichtblau contributed equally to this study.

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2001–2005). This long-term PH registry reveals that over two decades of observation, newly diagnosed patients are older, less predominantly female, have less impaired hemodynamics and a better survival.

INTRODUCTION

Pulmonary hypertension (PH) is a rare and progressive condition and despite recent advances in treatment and prognosis, is still associated with impaired quality of life and survival.[1,2] PH is characterized by multifactorial pathobiology resulting in a remodeling of the pulmonary vasculature.[3,4] This leads to progressive increase in pulmonary vascular resistance (PVR), which in turn leads to an increase in pulmonary arterial pressure (PAP) and can finally cause right heart failure.[5] Patients suffer from a variety of symptoms, the most prominent being exertional dyspnea leading to reduced exercise capacity, quality of life, and premature death. Although the pathophysiology of PH is still not fully understood, many studies indicate involvement of excessive vasoconstriction, endothelial dysfunction including smooth muscle cell proliferation, inflammation, and thrombosis.[3,4,6] Vascular remodeling is further promoted by the dysregulation of vasodilators and vasoconstrictors, leading to an imbalance that leans toward chronic vasoconstriction. This increasing remodeling leads to progression of symptoms and disease severity. As of yet, most forms of PH cannot be cured, and targeted medication aims to improve symptoms and to slow disease progression, thus increasing quality of life.[7]

PH can either arise independently, as a consequence or in association with various diseases[8] and is, according to guidelines, defined as mean $PAP \geq 25 \, mmHg$[7] and further classified according to the pulmonary artery wedge pressure (PAWP) into precapillary ($PAWP \leq 15 \, mmHg$) and postcapillary PH ($PAWP > 15 \, mmHg$).[7] A new hemodynamic definition was recently proposed, defining precapillary PH as mean pulmonary artery pressure (mPAP) $> 20 \, mmHg$ and $PVR \geq 3 \, WU$.[8] The latest European guidelines from 2016[7] classify PH into five major clinical groups: pulmonary arterial hypertension (PAH, Group I), PH due to left heart disease (Group II), PH due to lung disease (Group III), chronic thromboembolic pulmonary hypertension (CTEPH, Group IV), and PH with unclear and/or multifactorial mechanisms (Group V) and this structure was largely kept according to latest proposals.[8] This study will focus on the two main pulmonary vascular diseases, PAH (Group I) and CTEPH (class IV).

In recent years, there have been advances in the medical therapy for PAH/CTEPH. Based on pathophysiology, the five major drug classes currently in use are prostanoids (oral, subcutaneous, or intravenous), endothelin receptor antagonists, phosphodiesterase-5-inhibitors, soluble guanylate cyclase stimulators, and prostacyclin-receptor-agonists, targeting the three specific pathways: the nitric-oxide pathway, the entothelin-1, and the prostacyclin-thromboxane pathway.[6,7] Several studies[9–14] have shown a benefit of combination therapy over monotherapy and thus the latest guidelines[7] recommend combination therapy either initially or sequentially in PAH patients who do not meet therapeutic goals. For CTEPH, potentially curable pulmonary endarterectomy (PEA) is recommended. For inoperable, recurrent, and persistent patients, riociguat or off label PH-medication, or recently balloon-angioplasty, is recommended according to guidelines.[7,15,16]

The Swiss Pulmonary Hypertension Registry is a collaboration between 13 Swiss hospitals and allows entering PH-patient data from all five diagnostic groups with focus on PAH/CTEPH. It has been established in 1998 and is designed to assess disease severity and characteristics regularly. The last analysis dates back to 2012[17] showing how PH has progressed over time since 1998.

This analysis of the Swiss PH Registry aims to provide long-term data on the development of the epidemiology and characteristics of incident PH in Switzerland from January 2001 to June 2019 with a focus on PAH and CTEPH providing outcome data over different periods of diagnosis.

METHODS

The design of the Swiss Pulmonary Hypertension Registry has been described previously.[17,18] All participants gave written informed consent upon registration in the registry, which allows the use of data for research. The clarification of responsibility conducted by the Cantonal Ethics Review Board concluded that no further ethical considerations must be made before analysis (BASEC-Nr. Req-2019-00662). Each center was responsible to classify patients into one of the five major PH groups, which remained generally stable over different PH-WHO

meetings[7,19,20]: PAH, PH due to left heart disease, PH due to lung disease, CTEPH, and PH with unclear or multifactorial etiology. Patients were at least followed on a yearly basis. Events such as death, lung transplantation, PEA, or loss-to-follow-up were registered.

Patients were excluded from analysis, if they had no informed consent, were <18 years old at diagnosis or if mandatory parameters for diagnosis and classification were missing (such as mPAP). Patients with a baseline entry before the year 2000 were excluded, as they were mostly prevalent patients, which are known to have a better prognosis than incident patients.[21]

The variables analyzed included baseline data such as hemodynamics by right heart catheterization (heart rate,

mPAP, PAWP, right atrial pressure [RAP], PVR, cardiac index [CI], arterial partial pressure of oxygen [pO_2], mixed venous oxygen saturation), patients characteristics (age, body mass index, gender, classification), New York Heart Association functional class (NYHA, entered as I–IV or "not classifiable") and 6-min walking distance (6MWD).

Treatment was summarized into three categories according to data retrieved from patients' last visit: monotherapy, double therapy, and triple therapy. These categories include PH-specific treatment with prostanoids (oral, subcutaneous, or intravenous), endothelin receptor antagonists, phosphodiesterase-5-inhibitors, soluble guanylate cyclase stimulators, and prostacyclin-receptor-agonists.

TABLE 1 Baseline characteristics of patients according to different time periods of diagnosis

Periods	2001–2005	2006–2010	2011–2015	2016–2019	*p*-value
Demographics					
Number of patients	269	499	439	220	
Female (%)	157 (58)	257 (52)	233 (53)	114 (52)	0.313
Age (years)	59 ± 14	62 ± 15	63 ± 15	66 ± 14	**<0.001**
BMI (kg/m^2)	26 ± 7	27 ± 6	27 ± 6	27 ± 6	0.447
Classification—diagnosis					**<0.001**
PAH	136 (51)	190 (38)	165 (38)	69 (31)	
Veno-occlusive disease	0 (0)	0 (0)	3 (1)	1 (1)	
PH due to left heart disease	40 (15)	75 (15)	58 (13)	23 (10)	
PH due to lung disease	23 (9)	83 (17)	89 (20)	33 (15)	
CTEPH	59 (22)	131 (26)	104 (24)	89 (41)	
Miscellaneous	11 (4)	20 (4)	20 (5)	5 (2)	
Characteristics					
mPAP (mmHg)	46 ± 15	43 ± 13	41 ± 13	41 ± 11	**<0.001**
CI (L/min/m^2)	2.5 ± 0.8	2.7 ± 2.4	2.7 ± 0.8	2.6 ± 0.7	0.239
PVR (WU)	9 ± 5	8 ± 6	7 ± 5	7 ± 4	**<0.001**
NYHA	2.8 ± 0.9	2.6 ± 1.0	2.8 ± 0.8	2.8 ± 0.6	**<0.001**
NYHA (%)					**<0.001**
I	6 (2)	17 (3)	15 (3)	6 (3)	
II	49 (18)	99 (20)	90 (21)	50 (23)	
III	124 (46)	198 (40)	210 (48)	81 (37)	
IV	44 (16)	51 (10)	47 (11)	16 (7)	
Not classified	46 (17)	134 (27)	77 (18)	67 (31)	
6MWD (m)	356 ± 141	354 ± 140	371 ± 139	383 ± 142	0.154

Note: Data are given as mean ± SD or numbers (%). In bold: significant *p*-values (*p* < 0.05) tested by χ^2 (categorical variables) or ANOVA (continuous variables).
Abbreviations: 6MWD, 6-min walking distance; ANOVA, analysis of variance; BMI, body mass index; CI, cardiac index; CTEPH, chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary arterial pressure; NYHA, New York Heart Association functional class; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance.
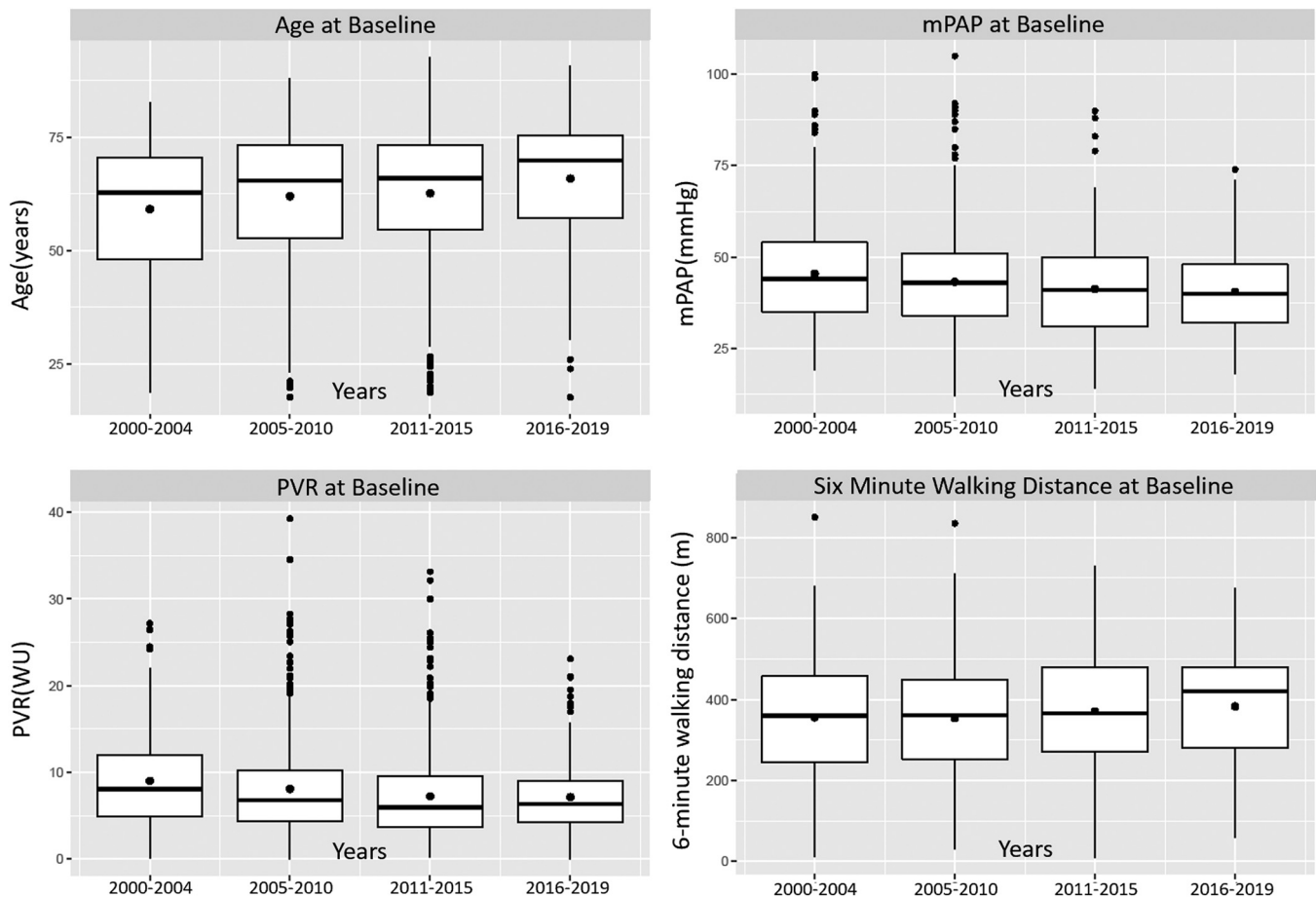
FIGURE 1 Age, mean pulmonary arterial pressure (mPAP), pulmonary vascular resistance (PVR), and 6-min walking distance at baseline by time period of diagnosis. The *x*-axis presents the time periods of diagnosis. The boxplots present median and IQR while the single point within the box presents the mean. The points along the whiskers represent outliers

Data analysis and statistics

Normality distribution was tested using histograms and QQ plots and as the majority were normally distributed and each group had a sample size with $n > 30$, data are presented as mean $\pm$ SD or numbers (%). Patients were split into four time-period groups according to the date of their baseline visit: 2001–2005, 2006–2010, 2011–2015, 2016–2019 (until June 30).

The comparison of groups by time period was done using analysis of variance (ANOVA) for continuous variables and χ^2 test for categorical variables. Baseline characteristics were analyzed overall including all pre-defined parameters, and more detailed separately for PAH and CTEPH. Statistically significant results ($p < 0.05$) were further classified by linear regression to assess for trends over the different time periods. Survival analysis was summarized using Kaplan–Meyer methods and life tables. Outcome-comparison between different groups was done based on the log-rank test. We additionally performed a Cox-regression analysis (outcome death or transplant) adjusting for baseline time period, which was the main object of interest, PH-group, age at baseline, gender, and NYHA functional class. Additionally, the number and type of events were analyzed overall and separately for PAH and CTEPH. According to recommendation for registry analysis, no corrective measures such as imputation or case wise deletion were used.[22] The analysis was done using R (Version 3.6.1, RStudio Version 1.2.5019).

RESULTS

Epidemiology of baseline demographics and characteristics

Of 1640 patients registered in the Swiss Registry, 72 were younger than 18 years at diagnosis, 48 had no diagnostic classification, 22 had no mPAP, and 71 were prevalent patients registered before the year 2000. This resulted in 1427 patients eligible for analysis (Figure S1).

TABLE 2 Baseline characteristics of patients with PAH by time periods of diagnosis

Periods	2001–2005	2006–2010	2011–2015	2016–2019	p-value
Demographics					
Number of patients	136	190	165	69	
Female (%)	88 (65)	109 (57)	101 (61)	39 (58)	0.554
Age (years)	56 ± 16	58 ± 16	58 ± 16	65 ± 14	**0.002**
BMI (kg/m^2)	26 ± 7	26 ± 6	26 ± 6	26 ± 5	0.983
Classification					**<0.001**
PAH	136 (100)	190 (100)	165 (100)	69 (100)	
Idiopathic	68 (50)	94 (50)	90 (55)	28 (41)	
Heritable	0 (0)	0 (0)	7 (4)	8 (12)	
Drugs and toxin induced	47 (32)	40 (21)	9 (5)	2 (3)	
Associated with	21 (16)	54 (28)	59 (36)	31 (45)	
Connecitive tissue disease	12 (9)	26 (14)	32 (19)	27 (39)	
HIV Infection	2 (2)	9 (5)	6 (4)	0 (0	
Portal hypertension	2 (2)	4 (2)	8 (5)	3 (4)	
Congenital heart disease	5 (4)	15 (8)	12 (7)	1 (1)	
Veno-occlusive disease	0 (0)	2 (1)	0 (0)	0 (0)	
Hemodynamics and vital signs					
Heart rate (bpm)	79 ± 12	81 ± 16	78 ± 14	76 ± 15	0.191
mPAP (mmHg)	46 ± 16	45 ± 14	43 ± 14	41 ± 12	0.074
PAWP (mmHg)	9 ± 3	10 ± 4	10 ± 3	9 ± 4	0.612
RAP (mmHg)	9 ± 8	7 ± 4	8 ± 4	8 ± 4	0.093
PVR (WU)	10 ± 6	9 ± 6	8 ± 5	8 ± 5	**0.007**
CI (L/min/m^2)	2.6 ± 0.9	2.8 ± 3.8	2.8 ± 0.9	2.6 ± 0.6	0.793
Arterial oxygen saturation (%)	92 ± 6	94 ± 4	92 ± 5	92 ± 5	0.108
Mixed venous oxygen saturation (%)	63 ± 11	64 ± 9	65 ± 10	63 ± 9	0.383
Vasoreactivity test positive (%)	27 (24)	20 (15)	16 (14)	11 (28)	0.062
Functional class and exercise capacity					
NYHA	2.7 ± 1.0	2.5 ± 1.0	2.7 ± 0.7	2.7 ± 0.7	0.148
NYHA (%)					0.070
I	2 (2)	6 (3)	7 (4)	3 (4)	
II	31 (23)	42 (22)	41 (25)	18 (26)	
III	61 (45)	74 (39)	73 (44)	32 (46)	
IV	19 (14)	19 (10)	16 (10)	6 (9)	
Not classified	23 (17)	49 (26)	28 (17)	10 (15)	
6MWD (m)	366 ± 144	365 ± 144	398 ± 136	382 ± 134	0.243

Note: Data are given as mean ± SD or numbers (%). In bold: significant p-values ($p < 0.05$) tested by χ^2 (categorical variables) or ANOVA (continuous variables).

Abbreviations: 6MWD, 6-min walking distance; ANOVA, analysis of variance; BMI, body mass index; CI, cardiac index; mPAP, mean pulmonary arterial pressure; NYHA, New York Heart Association functional class; PAH, pulmonary arterial hypertension; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

Baseline characteristics of all patients grouped by time period of diagnosis are shown in Table 1. The number of incident patients peaked 2006–2010 and decreased over the following consecutive periods. The female-to-male ratio tended to decrease over time from 1.4:1 (58% female) in 2001–2005 to an almost equal distribution in 2016–2019 (1.08:1, 52% female). Age (mean ± SD) at baseline significantly increased from 59 ± 14 years in 2001–2005 to 66 ± 14 years in 2016–2019 (ANOVA $p < 0.001$, linear regression coefficient 1.96 years [increase per time period], $p < 0.001$, Figure 1). Overall time periods, PAH and CTEPH were the most frequent diagnoses. The number of CTEPH patients registered increased over time up to 41% of patients registered from 2016 to 2019 resulting in more CTEPH than PAH (31%) for the first time. In terms of characteristics, mPAP and PVR (mean ± SD) significantly decreased over the consecutive periods from 46 ± 15 mmHg in 2001–2005 to 41 ± 11 mmHg in 2016–2019 and 9 ± 5 to 7 ± 4 WU, respectively (ANOVA $p < 0.001$, linear regression with coefficient −1.73 mmHg (decrease per time period) and $p < 0.001$ for mPAP and −0.67 WU (decrease per time period) and $p < 0.001$ for PVR. Most patients are diagnosed in NYHA functional class III over all time periods.

Detailed baseline characteristics for patients with PAH are shown in Table 2. Of 560 patients classified as PAH, the most prominent subgroups are idiopathic PAH and PAH associated with connective tissue disease (41% and 39%, respectively, for 2016–2019). Before 2011 there is a high proportion of drug and toxin-induced PAH, which is no longer present in the two subsequent periods and heritable PAH is only classified after 2010. PVR slightly but significantly decreased over time (linear regression showing a coefficient of −0.84 WU [decrease per time period] and $p = 0.001$), mPAP tended to decrease (46 ± 16 to 41 ± 12 mmHg, $p = 0.074$) and PAWP, RAP, and CI remained stable. Also, in PAH, age (mean ± SD) significantly increased over time periods from 56 ± 16 years in 2001–2005 to 65 ± 14 years in 2016–2019 (ANOVA $p = 0.001$, linear regression coefficient 2.25, $p = 0.001$).

Characteristics of 383 CTEPH-patients are displayed in Table 3. CTEPH did not show a significant change in age, demographics or hemodynamics over time periods, except for a decreasing PVR (ANOVA $p < 0.05$, linear regression coefficient −0.67 WU [increase per time period], $p < 0.05$).

Treatment

Table 4 shows that most patients were treated with mono- or double therapy (39% and 27%, respectively). This pattern is also found for PAH or CTEPH separately.

In CTEPH, the proportion of patients undergoing PEA increases from 15% in 2001–2005 to 40% in 2016–2019.

Events and survival

Table S1 shows the number and types of events overall and separately for PAH and CTEPH. The number of deaths overall, in PAH and CTEPH are 451 (32%), 210 (38%), and 76 (20%), respectively. A total of 90 (25%) out of all CTEPH patients underwent successful PEA-surgery. Only 27 (2%) patients had lung transplantation during the observational period.

Kaplan–Meyer survival curves according to the different diagnostic periods are shown in Figure 2, indicating the poorest survival for patients diagnosed 2001–2004 with a significantly better survival over successive time periods ($p = 0.001$). The increasing survival over time is also found for PAH and CTEPH separately, shown in Figures S2 and S3, with 63%–95% ($p = 0.025$) and 86%–93% ($p = 0.055$). PAH patients reveal a poorer survival than those with CTEPH independently of time period ($p < 0.001$) (Figure 3). Survival probability derived from Kaplan–Meyer methods are given in Table S2 and reveal that survival increased over time periods. We performed univariate Cox-regression analysis for time period, PH-group, age at baseline, gender, and NYHA functional class. The main target of interest was the influence of time period on survival, while the other factors were used for adjustment purposes only (see Table 5 and Figure 4). It revealed that more recent time periods, CTEPH, a lower age at diagnosis and female sex were associated with better, whereas PH in lung disease and NYHA class IV was associated with worse survival. In multivariable Cox-regression including all parameters, more recent time periods, CTEPH, a younger age at diagnosis and female sex remained significant predictors of transplant-free survival (Table 5, Figure 4).

DISCUSSION

This very long-term analysis of the Swiss Pulmonary Hypertension Registry provides unique data on the epidemiology of PH-patients in Switzerland, including demographics, symptoms, exercise performance and survival over two decades. The Swiss Pulmonary Hypertension Registry started in 1998 and data has been collected ever since. We found a significant increase of age at diagnosis over the years in our registered patients and there was an increasing number of males leading to an equal gender distribution in the last

TABLE 3 Baseline characteristics of patients with CTEPH according to time periods of diagnosis

Periods	2001–2005	2006–2010	2011–2015	2016–2019	*p*-value
Demographics					
Number of patients	59	131	104	89	
Female (%)	31 (53)	51 (56)	54 (50)	45 (51)	0.991
Age (years)	63 ± 12	65 ± 13	64 ± 14	65 ± 14	0.601
BMI (kg/m^2)	26 ± 4	26 ± 5	28 ± 6	28 ± 6	0.221
Classification					**<0.001**
CTEPH—not further classified	52 (88)	123 (94)	78 (75)	31 (35)	
CTEPH—surgically accessible	4 (7)	3 (2)	9 (9)	36 (40)	
CTEPH—surgically not accessible	3 (5)	3 (2)	9 (9)	17 (19)	
CTEPH—persistent after PEA	0 (0)	2 (2)	8 (8)	5 (6)	
Hemodynamics and vital signs					
Heart rate (bpm)	75 ± 14	79 ± 13	80 ± 14	77 ± 15	0.338
mPAP (mmHg)	44 ± 13	44 ± 11	42 ± 13	40 ± 10	0.200
PAWP (mmHg)	11 ± 5	12 ± 5	12 ± 5	11 ± 4	0.560
RAP (mmHg)	8 ± 5	10 ± 5	9 ± 5	8 ± 4	**0.023**
PVR (WU)	9 ± 4	9 ± 6	8 ± 6	7 ± 4	**0.032**
CI (L/min/m^2)	2.3 ± 0.5	2.4 ± 0.7	2.5 ± 0.7	2.5 ± 0.6	0.128
Arterial oxygen saturation (%)	92 ± 3	92 ± 5	92 ± 6	91 ± 7	0.528
Mixed venous oxygen saturation (%)	61 ± 9	62 ± 10	62 ± 11	63 ± 8	0.501
Functional class and exercise capacity					
NYHA	2.9 ± 0.6	2.7 ± 0.9	2.8 ± 0.7	2.7 ± 0.6	0.609
NYHA (%)					**0.022**
I	2 (3)	2 (2)	4 (4)	2 (2)	
II	11 (19)	27 (21)	19 (18)	23 (26)	
III	27 (46)	49 (37)	45 (43)	27 (30)	
IV	6 (10)	17 (13)	10 (10)	4 (5)	
Not classified	13 (22)	36 (27)	26 (25)	33 (37)	
6MWD (m)	359 ± 104	404 ± 145	349 ± 155	409 ± 141	0.331

Note: Data are given as mean ± SD or numbers (%). In bold: significant *p*-values ($p < 0.05$) tested by χ^2 (categorical variables) or ANOVA (continuous variables).
Abbreviations: 6MWD, 6-min walking distance; ANOVA, analysis of variance; B

diagnostic period. mPAP and PVR significantly decreased while survival substantially increased over the consecutive time periods. PAH patients showed significantly poorer survival than those with CTEPH independent of the time of diagnosis and the prognosis was better for women compared to men. Most patients were treated with mono- or double therapy and an increasing number of CTEPH patients underwent PEA.

Looking at the proportion of the different diagnoses, it can be stated that while PAH had the highest representation in 2001–2015, the proportion of CTEPH patients overtakes PAH from 2016 to 2019 possibly indicating an increased awareness of chronic thromboembolic diseases. Despite changing PH-classifications over time, the last change in 2018[8] kept the main structure of five diagnostic groups, so that we think that no more than a minority of patients classified before 2018 would have a different diagnosis today.

Our data show that mean age at diagnosis has clearly increased over the last years, linear regression

TABLE 4   Treatment at last visit

Periods Overall patients Number of patients	Overall 1427	2001–2005 269	2006–2010 499	2011–2015 439	2016–2019 220	Missing (%)	*p*-value
Therapy at last visit							
Monotherapy	544 (39)	107 (40)	216 (43)	155 (36)	66 (34)	2.2	**0.05**
Double therapy	375 (27)	84 (31)	148 (30)	109 (25)	34 (18)	2.2	**0.003**
Triple therapy incl. iv/sc	96 (7)	30 (11)	37 (7)	16 (4)	13 (7)	2.2	**0.002**
Pulmonary arterial hypertension **Number of patients**		**136**	**190**	**165**	**69**	**(%)**	
Therapy at last visit							
Monotherapy	208 (37)	54 (40)	76 (40)	61 (37)	17 (25)	0.0	0.129
Double therapy	199 (36)	42 (31)	68 (36)	67 (41)	22 (32)	0.0	0.315
Triple therapy incl. iv/sc	60 (11)	18 (13)	24 (13)	9 (6)	9 (13)	0.0	0.079
Chronic thromboembolic pulmonary hypertension **Number of patients**	**383**	**59**	**131**	**104**	**89**	**(%)**	
Therapy at last visit							
Monotherapy	154 (44)	21 (36)	55 (42)	42 (43)	36 (57)	8.4	0.095
Double therapy	101 (29)	23 (39)	50 (38)	22 (22)	6 (10)	8.4	**<0.001**
Triple therapy incl. iv/sc	15 (4)	6 (10)	7 (5)	1 (1)	1 (2)	8.4	**0.029**
PEA (incl. PEA & death)	94 (25)	9 (15)	21 (16)	29 (28)	35 (40)		

Note: Data are given as numbers (%). In bold: significant *p*-values ($p < 0.05$) tested by χ^2 (categorical variables) or ANOVA (continuous variables).

Abbreviations: ANOVA, analysis of variance; iv, intravenous; PEA, pulmonary endarterectomy; sc, subcutaneous.

showing a highly significant, but weak trend, with a coefficient of 1.96 years and $p < 0.001$. This finding can be explained by the large in-group variability underlying our large study population. This is true over all PH groups and for PAH, but not for CTEPH patients, where the mean age remained stable and potentially signifies, that referring doctors think of and diagnose PAH also in advanced and potentially comorbid age groups in more recent years. At the same time, hemodynamics of PAH patients slightly improves over time, with a significantly lower PVR and a trend toward a decreasing mPAP. This change in patients characteristics toward older patients, with less severe pulmonary vascular disease has already been observed in our registry in 2012[17] and is in line with other European registries.[1,22–26] It can be stated that the trend is continued, for example age at diagnosis has further increased since 2012 from 63 ± 15 to 66 ± 14 years in 2016–2019 and mPAP and PVR have further decreased to 41 ± 11 mmHg and 7 ± 4 WU. An analysis of the COMPERA registry showed an inverse relationship between mPAP and age at diagnosis, suggesting that elderly patients become symptomatic at a lower mPAP as the capacity of the right ventricle to pump against high PVR decreases with age.[24] Although we did not analyze our data stratified by age, the increasing age at diagnosis together with the less severe hemodynamics but stable high functional class (NYHA III), support the statement of the COMPERA registry, that elderly patients become symptomatic at an earlier stage in disease progression.

The distribution of females and males is almost equal in Switzerland nowadays with a female to male ratio of 1.1:1 overall, 1.3:1 in PAH and 1:1 in CTEPH, contradicting earlier findings at the beginning of the century in the REVEAL registry, where Badesch et al. found a 4.1:1 female to male ratio in idiopathic PAH.[27,28] The balancing of gender in PH has already been established at our centers in 2012 by Mueller-Mottet et al.[17] as well as in other comparable European registries such as COMPERA,[24] who are also linking it to the increase in age at diagnosis. Elderly patients seem to present a different phenotype of PH, were both genders are equally affected and hemodynamics tend to be less severe compared to younger patients. One explanation could be that PH in the elderly is partly caused by an age-dependent decrease in right ventricular function in relation to the relative increase in right ventricular afterload, which is equal to both genders.
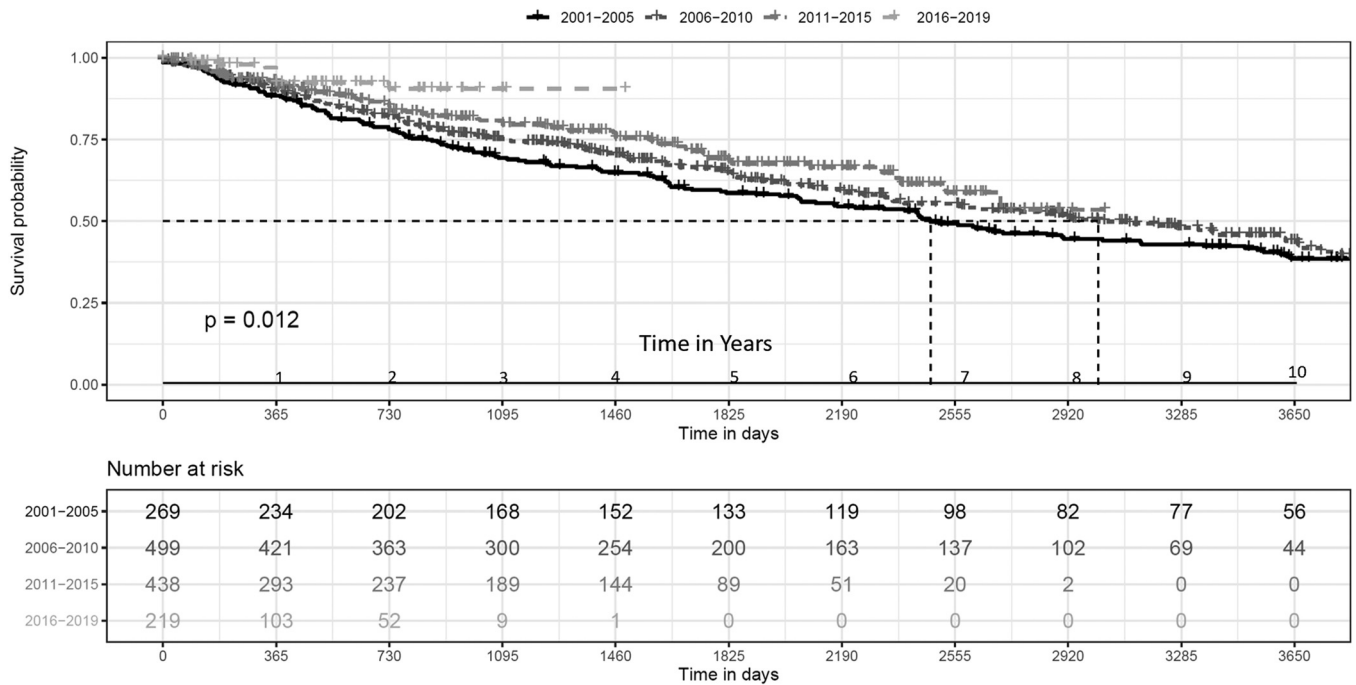
FIGURE 2 Kaplan–Meyer survival curve and number at risk for all patients stratified by time period of diagnosis. The different curves represent the different time periods of diagnosis. The dashed lines indicate 50% survival and the corresponding *p*-value refers to the comparison of median-survival by log-rank test. Number at risk are presented in a table below the survival curves. The timeline is presented in days and years, respectively
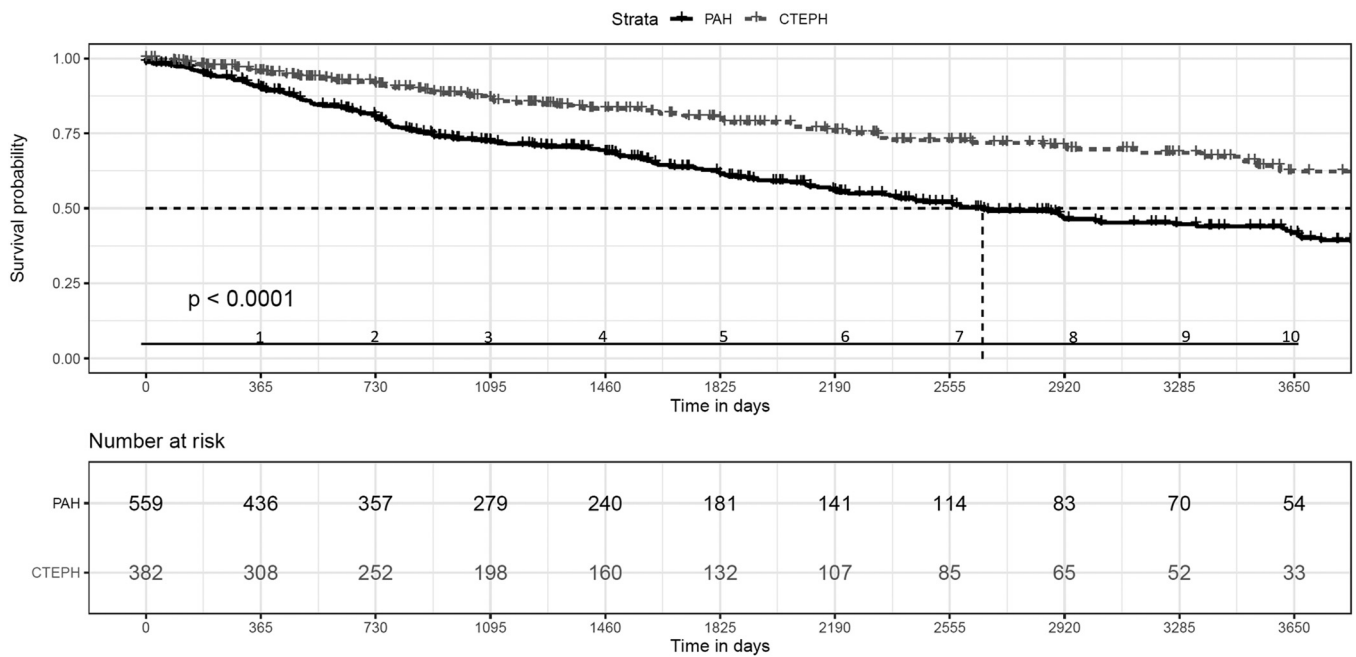

FIGURE 3 Kaplan–Meyer survival curve and number at risk comparing pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH), independently of time periods. The dashed lines indicate 50% survival and the corresponding *p*-value refers to the comparison of median-survival by log-rank test. Numbers at risk are presented in a table below the survival curves. The timeline is presented in days and years, respectively

TABLE 5 Cox-analysis of transplant-free survival after diagnosis of pulmonary hypertension

Dependent variable = transplant-free survival	Univariate analysis				Multivariate analysis (p < 0.001)			
		95% CI				95% CI		
	Hazard ratio	Lower	Upper	*p*-value	Hazard ratio	Lower	Upper	*p*-value
Time period (in reference to 2001–2005)								
2006–2010	0.91	0.74	1.13	0.408	0.87	0.70	1.08	0.207
2011–2015	0.73	0.56	0.96	**0.023**	0.71	0.54	0.94	**0.015**
2016–2019	0.42	0.23	0.81	**0.009**	0.46	0.24	0.89	**0.021**
PH-group (in reference to PAH)								
PH left heart disease	0.98	0.74	1.30	0.907	0.80	0.60	1.06	0.115
PH lung disease	1.74	1.35	2.23	**<0.001**	1.13	0.87	1.48	0.361
CTEPH	0.54	0.41	0.69	**<0.001**	0.39	0.30	0.51	**<0.001**
PH miscellaneous	0.96	0.57	1.59	0.859	0.89	0.53	1.48	0.657
Age (years)	1.03	1.02	1.04	**<0.001**	1.03	1.02	1.04	**<0.001**
Sex (in reference to male)								
Female	0.62	0.51	0.74	**<0.001**	0.62	0.51	0.75	**<0.001**
NYHA (in reference to I)								
II	0.73	0.38	1.42	0.363	0.64	0.33	1.25	0.193
III	1.41	0.75	2.67	0.279	1.12	0.59	2.12	0.724
IV	1.99	1.03	3.85	**0.040**	1.43	0.74	2.78	0.292
Not classified	1.11	0.57	2.13	0.761	0.87	0.45	1.68	0.672

Note: Bold values indicate the significance of $p < 0.05$. Data calculated by Cox regression analysis. $n = 1425$.

Abbreviations: CI, confidence interval; CTEPH, chronic thromboembolic pulmonary hypertension; NYHA, New York Heart Association functional class; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

However, the pathophysiology of PH in elderly people is not yet fully researched and needs to be further elucidated as already suggested in the COMPERA analysis.[24]

Survival analysis of the present cohort showed increasingly better survival over time, despite the increase in age. Overall, 3-year survival increased from 69% (95% CI 64%–75%) in 2001 to 91% (85%–97%) in 2016–2019. Additionally, Cox-regression showed time period of diagnosis to be an independent predictor of survival, even when adjusted for age at diagnosis, gender, and PH-groups. However, one must consider that not all patients in the incident period 2016–2019 have reached the 3-year follow-up and were therefore censored. Still, the increase in survival is already shown in earlier time periods, such as 2011–2015 (Table S2). Accordingly, survival of registered patients with both PAH and CTEPH has increased over time, while PAH patients reveal poorer survival than those with CTEPH independently of time periods. However, our data show considerably higher survival probabilities in both groups than previously reported by Hurdman et al. in 2012 (PAH: 95% vs. 68%, CTEPH 93% vs. 59%, respectively).[1] This increase in survival might be explained by earlier diagnosis of less advanced pulmonary

vascular disease due to increased awareness, introduction of new treatment possibilities and, for CTEPH the establishment of a PEA-center in Zurich, Switzerland.

Most patients in Switzerland are treated with mono- or double therapy. Combination therapy, such as combining phosphodiesterase-5-inhibitors and endothelin receptor antagonists, is proven to reduce clinical worsening and increase exercise capacity.[11,13,14] There has been a substantial increase in CTEPH-patients undergoing PEA. While in 2001–2005 only 15% of CTEPH patients were operated, in 2016–2019 its proportion raises to 40%. However, overall, only 25% patients in the registry have been surgically treated for CTEPH. This is less than in other European registries, such as the Scandinavian or German registry, where 33% and 50.3% of CTEPH patients were operated,[25,29] even though the baseline characteristics are comparable to our own and other European registries.[15] However, only in the incident period 2016–2019 more patients were classified into operable or nonoperable CTEPH, reflecting increasing awareness of this distinction, also due to the establishment of a PEA-center in Zurich with growing activity since 2014 and a regular national CTEPH board since 2018, so that we can
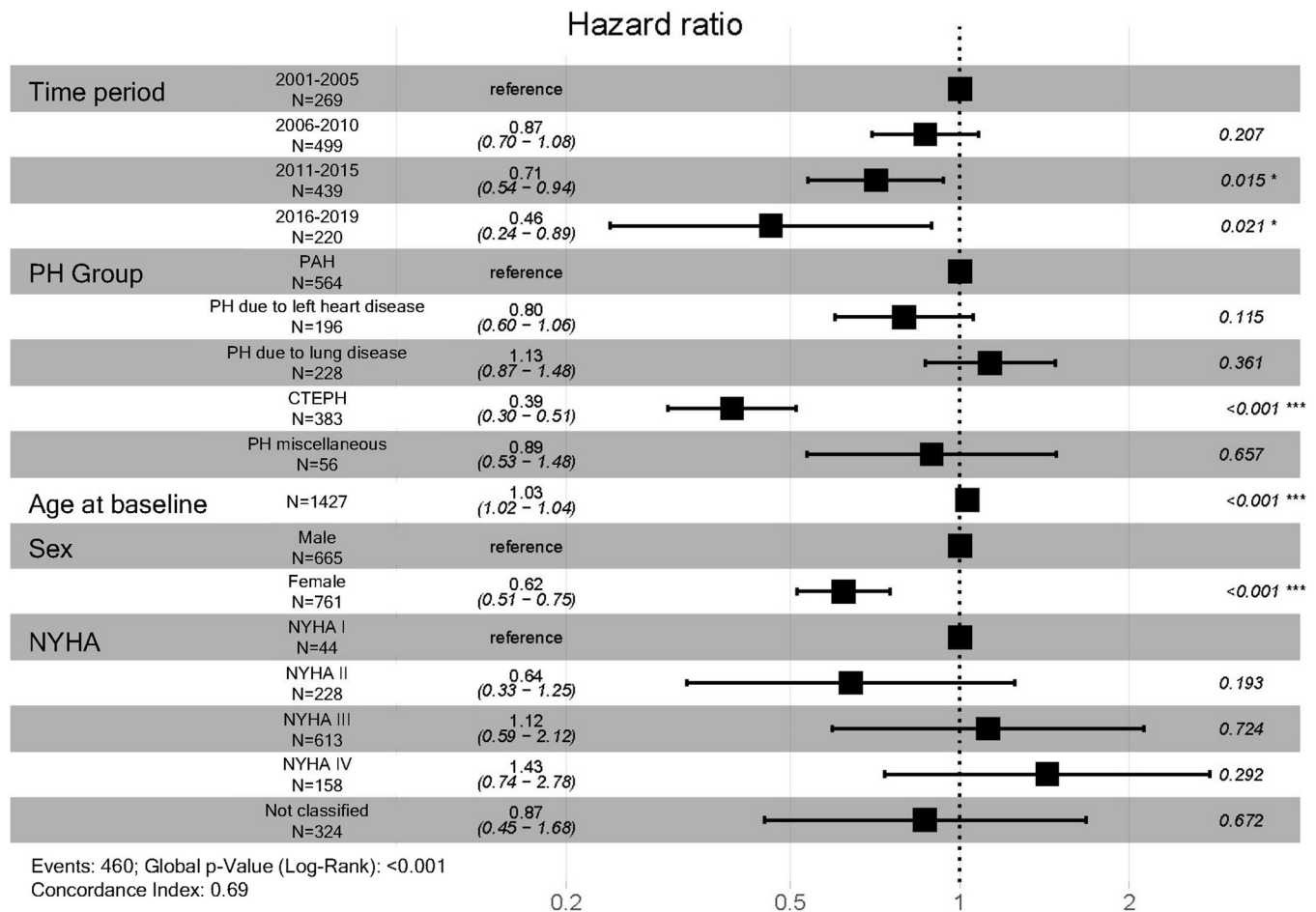
FIGURE 4 Hazard ratios by Cox regression are illustrated for time periods (in reference to 2001–2005), pulmonary hypertension (PH) groups (in reference to pulmonary arterial hypertension [PAH]). CTEPH, chronic thromboembolic pulmonary hypertension; NYHA, New York Heart Association class

expect more patients being surgically treated at tertiary centers in the near future.

The limitations of this study can be associated with the registry design. Although registries have the benefit of providing real-life clinical data, the data may be less comprehensive. As not all patients follow the same schedule, registry data is often incomplete and prone to potential bias and confounders and thus, any statistical analysis has to be interpreted with caution and is of exploratory nature. The observation of a decrease in PH incidence, while at the same time CTEPH incidence seems to be increasing, may reflect a national trend for treating PH patients in nontertiary centers or even private practices instead of specialized PH-centers, while CTEPH is more often diagnosed and treated at specialized centers leading to a bias in our registry. Sadly, patients not treated at specialized centers may miss the chance of advanced therapies or of taking part in clinical trials, which is especially regrettable regarding the excellent survival of patients treated and registered in Swiss

PH-centers. A further limitation concerns the short observational period in the last group, which thus can only be included in survival estimates but not life-tables. Despite some limitations, registry data can provide insight into real clinical data, and is useful to describe population characteristics, burden of illness and evaluation of guideline implementation.[22] Further analysis is needed to evaluate predictors of survival according to risk stratification at baseline or follow-up visits and assessing reasons for increased survival.

CONCLUSION

To conclude, this 20-year survey involving 1427 patients of the Swiss Pulmonary Hypertension Registry is in line with other European registries, showing a shift in the phenotype of PH with older patients in a more balanced gender distribution, presenting less severe hemodynamics, but high functional class, and increasing survival. It can be

speculated that the less severe hemodynamics are the consequence of a better disease awareness leading to earlier diagnosis of symptomatic patients also in a potentially comorbid elderly population.

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CONFLICT OF INTERESTS

Dr. Lichtblau reports personal fees from Boehringer-Ingelheim, personal fees from MSD, outside the submitted work. Dr. Lador reports personal fees from Actelion, personal fees from MSD, grants and personal fees from Orpha Swiss, outside the submitted work. Prof. Schwerzmann reports personal fees from Orpha Suisse, personal fees from MSD, personal fees from Actelion Janssen, outside the submitted work. Prof. Ulrich reports grants and personal fees from Actelion SA, personal fees from MSD SA, grants and personal fees from Orpha Swiss, personal fees from Novartis SA, grants from Swiss National Science Foundation, grants from Zurich Lung, from null, outside the submitted work. The remaining authors declare that there are no conflict of interests.

ETHICS STATEMENT

All participants gave written informed consent upon registration in the registry. The clarification of responsibility conducted by the Cantonal Ethics Review Board concluded that no further ethical considerations must be made before analysis (BASEC-Nr. Req-2019-00662).

AUTHOR CONTRIBUTIONS

Paula Appenzeller, Mona Lichtblau, Stéphanie Saxer, Silvia Ulrich contributed to data acquisition, analysis and interpretation and drafting of the manuscript. Mona Lichtblau, Stéphanie Saxer, Silvia Ulrich contributed to the conception and design of the study, interpretation of the data, drafting and critical review of the manuscript. Mona Lichtblau, Stéphanie Saxer, Silvia Ulrich, Charlotte Berlier, John-David Aubert, Andrea Azzola, Jean-Marc Fellrath, Thomas Geiser, Frederic Lador, Susanne Pohle, Isabelle Opitz, Markus Schwerzmann, Hans Stricker, Michael Tamm contributed to critical revision of the manuscript and provided final approval of the version to be published.

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