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1 **Various Factors Contribute to Death in Patients with Different Types of Pulmonary**
2 **Hypertension: A Retrospective Pilot Study from a Single Tertiary Center**

3

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25

26 **Abstract**

27 **Background:** A few studies have focused on the cause of death from different types of
28 pulmonary hypertension (PH). This study aimed to systematically analyze the primary and
29 secondary causes of death and compare the profiles between different PH groups.

30 **Methods:** The contribution of PH to death was assessed in precapillary PH (i.e., group 1
31 [pulmonary arterial hypertension], group 3 [PH associated with lung disease], and group 4
32 [chronic thromboembolic PH]) using specific criteria; death was classified into three
33 categories: PH death (death due to PH only), PH-related death, and PH-unrelated death.
34 Disorders other than PH that contributed to death were analyzed, and mortality profiles were
35 compared between groups.

36 **Results:** Eighty deceased patients with PH were examined (group 1, n=28; group 3, n=39;
37 and group 4, n=13). The contribution of PH to death was significantly different between the
38 three groups. “PH death” was most common in group 1 (61%), “PH-related death” in group 3
39 (56%), and “PH-related death” and “PH-unrelated death” in group 4 (38% for both). The
40 highest contributing factor to death other than PH was respiratory failure in group 3 and
41 malignant disease in group 4.

42 **Conclusions:** Significant variations in the causes of death were observed in groups 1, 3, and
43 4 PH patients. In addition to PH, respiratory failure and malignant disease significantly
44 contributed to death in group 3 and group 4 PH, respectively. Understanding the precise death
45 cause may be important in achieving better outcomes in PH patients.

46

47 **Keywords:** right heart failure, sudden death, cancer, respiratory failure

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50

51 **Abbreviations:**

52 PH: Pulmonary hypertension, PAH: pulmonary arterial hypertension; CTEPH: chronic
53 thromboembolic PH, ILD: interstitial lung disease, CTD: connective tissue disease, SSc:
54 systemic sclerosis, PPH: primary PH, BMI: body mass index, WHO: World Health
55 Organization, BNP: brain natriuretic peptide, PaO₂: partial pressure of oxygen, PaCO₂: partial
56 pressure of carbon dioxide, FVC: forced vital capacity, FEV1: forced expiratory volume in 1
57 second, DLco: carbon monoxide diffusing capacity, Kco: transfer coefficients, RHC: right
58 heart catheterization, HR: heart rate, MPAP: mean pulmonary artery pressure, PAWP:
59 pulmonary arterial wedge pressure, RAP: right atrium pressure, CO: cardiac output, CI:
60 cardiac index, PVR: pulmonary vascular resistance; Echo: echocardiography, CMR:
61 cardiovascular magnetic resonance imaging, TRPG: transtricuspid pressure gradient, TAPSE:
62 tricuspid annulus plane systolic excursion; ERA: endothelin receptor antagonists, NO: nitric
63 oxide, PG: prostaglandin, DOAC: direct oral anticoagulant

64

65 **1. Introduction**

66 Pulmonary hypertension (PH) is defined as a mean pulmonary arterial pressure ≥ 25
67 mmHg and categorized into five classes according to etiology and hemodynamic properties
68 [1]. Recently, the management of PH has greatly improved; in particular, the
69 management/outcome of pulmonary arterial hypertension (PAH) (group 1 PH) and chronic
70 thromboembolic PH (CTEPH) (group 4 PH) has progressed notably [2–6].

71 Right heart failure is believed to be the most common cause of death in PAH and
72 CTEPH. However, most publications that document the outcomes of patients with
73 PAH/CTEPH have not reported in detail why and how the patients died [2–4]. Interestingly, a
74 report by Tonelli et al. revealed that disorder(s) other than PAH contributed to mortality in
75 more than half of the study cohort [7]. In fact, patients with PAH/CTEPH are expected to
76 experience increasing longevity with time, owing to advances in treatment; thus, diseases
77 other than PH are likely to become more important for patient survival.

78 In contrast to PAH and CTEPH, the survival rate of patients with PH associated with
79 lung disease (group 3 PH) remains dismal [8,9]. Importantly, patients with group 3 PH
80 exhibit characteristics that are different from those with PAH/CTEPH; they tend to be older
81 and more hypoxemic, and to have a longer smoking history. Thus, patients with group 3 PH
82 are likely to have a disease-specific cause of death; however, in comparison with other PH
83 types, only a few studies have focused on the cause of death in these patients.

84 Recognition of the comprehensive profile of the cause of death in patients with each
85 PH type is important in clinical practice, because it allows clinicians to focus on aspects that
86 will improve the survival rate of these patients. This pilot study from a single PH tertiary
87 center aimed to examine not only the primary cause, but also the concurrent potential causes
88 of death other than PH, and compare the results between patients with group 1, 3, and 4 PH.

89

90 **2. Patients and methods**

91 This retrospective study included all patients who were diagnosed with PH at the
92 respiratory department of Hokkaido University Hospital and died from January 2001 to
93 December 2020. PH was diagnosed and managed based on 2015 guidelines [1,10,11]. Our
94 hospital is the largest PH center in our prefecture and is one of the high-volume PH centers
95 listed on the website of the Japanese Pulmonary Circulation and Pulmonary Hypertension
96 Society (<http://jpcphs.org/link/index.php>). In this study, patients with PH due to left heart
97 disease (group 2 PH) were excluded, because the database analyzed in the present study
98 included precapillary PH cases. Consequently, a complete baseline and follow-up dataset for
99 patients with group 2 PH was not available, which precluded inclusion of this subgroup.
100 Patients with PH due to miscellaneous causes (group 5 PH) were also excluded, because of
101 the small number of patients. Patients with pulmonary veno-occlusive disease or with
102 pulmonary capillary hemangiomatosis were classified into group 1, according to a recent
103 classification system [11]. Patients with PH and both connective tissue disease and interstitial
104 lung disease (ILD) were classified into group 3, if (i) computed tomography revealed
105 combined pulmonary fibrosis and emphysema, (ii) ILD was deemed extensive (i.e., the ILD
106 area exceeded >30% of the total lung area by gross evaluation), or (iii) the ILD area was
107 between 10% and 30% and the forced vital capacity was <70%, as reported by Goh et al.
108 [12].

109 The cause of death was determined using an algorithm modified from Tonelli et al.
110 [7]. Briefly, two PH physicians (a cardiologist and a pulmonologist) independently and
111 thoroughly reviewed medical records, including the medical history and results of general
112 and PH-specific evaluations. These two physicians first excluded cases with data deemed to
113 be insufficient for the determination of the cause of death. Subsequently, they classified the
114 contribution of PH to mortality into the following three categories: (i) PH was the direct and

115 only cause of death (PH death), (ii) both PH and other cause(s) contributed to death (PH-
116 related death), and (iii) death was caused by illness(es) other than PH (PH-unrelated death).

117 To elaborate, a death was considered to be due to PH (PH death) when patients died
118 irrespective of the presence/severity of any concomitant disease(s). Patients classified in this
119 category had moderate or advanced PH with high mean pulmonary arterial pressure and/or
120 reduced cardiac output and died suddenly or with symptoms/signs indicative of right heart
121 failure. In contrast, a death was deemed to be unrelated to PH when patients were considered
122 to have died although they did not have PH. Accordingly, patients in this category died of
123 malignant disease, respiratory/heart/hepatic/renal failure, or infectious disease, among other
124 causes. Finally, if death was not categorized into either of the previous two categories,
125 patients were considered to have died at least partly due to PH (PH-related death). When the
126 two physicians disagreed, a third physician, specialized in both cardiology and pulmonology,
127 determined the cause of death, and the three physicians reached a final consensus.

128 Furthermore, when a death was PH-related or PH-unrelated, the main cause of death
129 other than PH was classified into one of the following seven categories: respiratory failure
130 caused by factors other than PH, cardiovascular disease other than PH, hepatic disease,
131 infectious disease, malignant disease, renal disease, or miscellaneous.

132 Analysis was performed in accordance with the 1964 Declaration of Helsinki and its
133 later amendments. This study was performed according to the ethical standards of the
134 committee on human experimentation and was approved by the relevant Institutional Review
135 Board of Hokkaido University Hospital (approval no.: 016-0461, approval date: April 6,
136 2017). Owing to the retrospective nature of this study, informed consent was obtained using
137 the opt-out method.

138

139 ***2.1 Statistical analysis***

140 Background data are presented as medians with interquartile ranges. Differences
141 between groups 1, 3, and 4 PH were tested using the Wilcoxon rank-sum test for continuous
142 variables and the chi-squared test for categorical variables. The proportions of the cause of
143 death (PH death, PH-related death, and PH-unrelated death) were compared between the
144 three PH groups using the chi-squared test. For patients whose deaths were PH-related or PH-
145 unrelated, details of death were summarized for the three PH groups. To examine the possible
146 impact of systemic sclerosis (SSc) on the mortality profile, the cause of death was compared
147 between patients with or without SSc in groups 1 and 3 PH. Similarly, the cause of death was
148 compared between the three subsets of group 3 PH patients, i.e. those with restrictive lung
149 disease, obstructive lung disease, or combined pulmonary fibrosis and emphysema (CPFE).
150 We also analyzed the association between the profile of death and the five fundamental
151 parameters of PH; i.e., WHO: World Health Organization functional class (WHO-FC), serum
152 brain natriuretic peptide (BNP) concentration, mean pulmonary arterial pressure (MPAP),
153 cardiac index (CI), and pulmonary vascular resistance (PVR) acquired at the time of
154 diagnosis and their change between the initial and final evaluations. Finally, to compare the
155 survival curve between the three PH groups, Kaplan Meier analysis was conducted along
156 with the Log-rank test. $p < 0.05$ was considered statistically significant. Statistical analyses
157 were performed using JMP Pro 15.0.0 (SAS Institute Inc., Cary, NC, USA).

158

159 **3. Results**

160 During the study period, 98 out of 312 patients in our PH cohort died. Among them,
161 eight patients in groups 2 and 5, and 10 patients with medical data insufficient for
162 determination of the cause of death were excluded. Finally, a total of 80 patients were
163 included for analysis (Fig. 1). The characteristics of the study cohort are shown in Table 1.
164 Group 1 PH (n=28) included patients with idiopathic/heritable/drug-induced PAH (n=7),

165 connective tissue disease (CTD)-PAH (SSc-associated PAH (n=4), CTD-PAH (non-SSc)
166 (n=7), porto-PH (n=4), congenital heart disease-PAH (n=2), and pulmonary veno-occlusive
167 disease/pulmonary capillary hemangiomatosis (n=4). Group 3 PH (n=39) included patients
168 with restrictive lung disease (n=19 [SSc-CTD/non-SSc-CTD/non-CTD: 9/1/9], obstructive
169 lung disease (n=8), and CPFE (n=12 [SSc/non-SSc/non-CTD: 1/0/11]). Group 4 PH (n=13)
170 included patients with CTEPH (n=11) and other types (n=2). Among the 13 patients with
171 group 4 PH, only one patient underwent pulmonary endarterectomy (PEA) and none was
172 treated with balloon pulmonary angioplasty (BPA). Table 2 shows the medication used for
173 each group of patients.

174 As shown in Fig. 2, the causes of death were significantly different between the three
175 groups ($p=0.0063$). More than half of the patients (17/28, 61%) in group 1 PH died of PH,
176 which was higher than the proportions observed in group 3 PH (21%) and group 4 PH (23%).
177 In group 3 PH, PH-related deaths was the most common cause of death (56%), which was
178 higher than in group 1 PH (25%) and group 4 PH (38%).

179 Table 3 and Fig. 3 show the contribution of the seven-disease categories to PH-related
180 (n=34) and PH-unrelated (n=18) deaths. The distribution varied significantly between the
181 three PH groups ($p=0.0002$). Respiratory failure contributed more to mortality in group 3 PH
182 (71%) than in group 1 PH (36%) and group 4 PH (30%). In group 4 PH, malignant disease at
183 least partly contributed to death in 60% (6/10) of the cases, which was higher than in group 1
184 PH and group 3 PH.

185 Fig. 4 shows no significant differences in the mortality profile with or without SSc in
186 group 1 PH. In contrast, in group 3 PH, patients with SSc died due to PH more frequently
187 (6/10, 60%) than patients without SSc (2/29, 7%). Among the three subgroups of group 3 PH
188 patients (those with restrictive lung disease, obstructive lung disease, or CPFE), there were no
189 significant differences in the cause of death ($p=0.22$).

190 Table 4 shows the associations between the cause of death and five fundamental
191 parameters of PH (WHO-FC, BNP, MPAP, CI, and PVR). Group 1 PH patients who died of
192 PH-death tended to have an increase in BNP during follow-up more commonly (13/17) than
193 the PH-related death group (4/7) and PH-unrelated death group (0/3) ($p=0.04$ by chi-squared
194 test). In contrast, in group 3 PH, patients who died of PH-death had a significantly higher
195 baseline BNP level than those who died of PH-related and PH-unrelated death ($p=0.009$ by
196 Wilcoxon rank-sum test). In group 4 PH, there were no significant associations between the
197 mortality profile and the five clinical parameters.

198 Analysis of all 80 PH patients showed that those who died of respiratory failure were
199 older and more hypoxemic at diagnosis, and had lower BNP concentration, lower MPAP, and
200 lower PVR compared with those who died of causes other than respiratory failure (Table 5).
201 In contrast, analysis of each PH group showed that patients who died of respiratory failure
202 had lower MPAP in group 1 PH, lower BNP in group 3 PH, and higher rate of hypoxia at
203 diagnosis in group 4 PH, compared with those who did not have respiratory failure as the
204 cause of death.

205 Fig. 5 shows the Kaplan-Meier curves of the patients with the three PH groups.
206 Patients with group 3 PH tended to die sooner than patients in other PH groups, however, the
207 difference did not show statistical significance.

208

209 **4. Discussion**

210 In this study, the cause of death was examined in patients with group 1, 3, and 4 PH
211 using dedicated criteria. Unlike prior studies, we focused on “non-PH” causes of death, even
212 if they contributed to death secondarily or concurrently to PH. The major findings of this
213 analysis are three-fold: (i) Patients with group 1 PH died from PH in 61% of the cases, which
214 is higher than the other two groups. (ii) In group 3 PH, the majority of deaths was “PH-

215 related,” and the most prevalent cause of death was respiratory failure. (iii) In group 4 PH,
216 approximately 40% of deaths were PH-unrelated. Among the 10 PH-related or PH-unrelated
217 deaths, 6 were due to malignant disease.

218

219 ***4.1 Cause of death in group 1 PH***

220 According to the Patient Registry for the Characterization of Primary PH by the
221 National Heart, Lung, and Blood Institute, the cause of death in patients with primary PH
222 (PPH) was directly related to PPH in 74% of the cases [2]. Similarly, in 1999, before PH-
223 specific drugs became available in Japan, patients with PPH died directly from PPH in 76%
224 of the cases [13]. These studies had indicated that three-quarters of patients with PPH died
225 directly from PH. In contrast, in a recent study on the cause of death in patients with PAH,
226 44% of the patients died directly of PAH [7]. Another recent study reported a similarly low
227 rate of PAH patients dying of PAH (45%) [15]. In the present study, 61% of the patients in
228 group 1 died of PH. This rate decreased to 58% when only PAH cases were analyzed by
229 excluding four patients with pulmonary veno-occlusive disease. Taken together, recent
230 progress in the treatment of PAH not only prolonged patient survival, but also decreased the
231 contribution of PAH to death.

232 The causes of death other than PH varied substantially in PAH subtypes. For example,
233 among the four patients with porto-PH, two died at least partly of liver disease. Moreover, in
234 11 PAH patients who had comorbid CTD, causes of death varied, including respiratory
235 failure, infectious disease, and severe hemorrhage. Notably, SSc was unlikely to have
236 affected the mortality profile in group 1 PH patients, because we found no significant
237 differences in the cause of death between patients with or without SSc (Fig. 5). In contrast,
238 recent publications have reported a subset of “atypical” group 1 PH patients [14], which have
239 characteristics of group 2 or group 3 PH and show a different clinical course from that of

240 “typical” PAH patients. Although “atypical” group 1 PH patients were not included in our
241 study, the importance of individualized patient management in PAH is likely to increase
242 further in the future. Finally, group 1 PH patients that died of PH had a greater increase in
243 BNP concentration during follow-up, indicating that monitoring BNP may predict the cause
244 of death and thus, help to guide optimal patient management.

245

246 ***4.2 Cause of death in group 3 PH***

247 Studies have demonstrated that the prognosis of patients with group 3 PH is worse
248 than that of patients with group 1 or group 4 PH [4,9,15], likely due to the underlying lung
249 disease. Indeed, a recent study reported that the leading cause of death in 546 patients with
250 group 3 PH was respiratory failure [15]. In another small study including patients with
251 idiopathic pulmonary fibrosis with elevated mean pulmonary arterial pressure, 74% (17/23)
252 of deaths were related to idiopathic pulmonary fibrosis progression [16]. Consistent with
253 these findings, the present study showed that the underlying lung disease was the major cause
254 of death, rather than PH, in group 3 PH patients. These findings emphasize the need for
255 careful management of the background lung disease in patients with group 3 PH.

256 In our study, 21% (8/39) of patients with group 3 PH died directly of PH without
257 substantial deterioration of the underlying lung disease. Interestingly, 6 (75%) of these 8
258 patients had SSc, whereas only 4 (13%) patients had SSc among the remaining 31 patients
259 who died of PH-related or -unrelated causes (Fig. 5). This finding suggests that comorbid SSc
260 is predictive of future PH death, rather than death due to ILD, even if a patient is classified in
261 group 3 PH. Notably, patients who died due to respiratory failure had lower BNP level than
262 those who did not die, suggesting a possible role of BNP in predicting the future cause of
263 death and in optimal management in this group.

264

265 ***4.3 Cause of death in group 4 PH***

266 The outcomes in group 4 PH have been reported in previous studies [4,15], some of
267 which have analyzed the cause of death. For example, Gall et al. analyzed the causes of 459
268 deaths in patients with CTEPH and reported that right/left heart failure was the most frequent
269 cause (64%), followed by malignant disease (9%) and infection (7%) [15]. Similarly, another
270 large investigation on CTEPH documented that among 127 deaths, the most common cause
271 of death was right heart failure or perioperative complications (54%), followed by malignant
272 disease (7%) [17]. These publications, along with other studies [18–21], emphasized the
273 importance of malignant disease as the second most frequent cause of death in patients with
274 CTEPH. In line with these results, malignant disease at least partly contributed to death in
275 60% (6/10) of cases in group 4 PH in our study, which was substantially higher than in group
276 1 PH (0%) and group 3 PH (13%). Notably, in three of these six patients, malignant disease
277 was diagnosed after diagnosis of group 4 PH. This finding emphasizes the importance of
278 continuous workups for the possibility of malignant disease during follow-up, as well as at
279 the time of diagnosis in group 4 PH patients.

280

281 ***4.4 Difficulties in accurately determining the cause of death***

282 The main strength of this study was the detailed and systematic analysis of the cause
283 of death among PH types. We chose the method reported by Tonelli et al. [7] because, to the
284 best of our knowledge, it is the most systematic and objective method for the analysis of the
285 cause of death in patients with PH. Of note, however, Tonelli et al. determined the cause of
286 death prospectively, whereas we conducted this study in a retrospective manner. In addition,
287 determining the cause of death remained challenging even with the use of this method. For
288 example, in cases of PH due to ILD, progression of ILD often triggers hypoxemia, which, in
289 turn, induces hypoxic vasoconstriction, PH deterioration, and subsequent right heart failure.

290 Moreover, sudden death in patients with severe PH is usually considered PH death. However,
291 the possibility of other diseases, such as acute coronary syndrome, arrhythmia, and stroke
292 cannot be ruled out as the causes of death.

293

294 **4.5 Limitations**

295 This study had several limitations. First, this is a single-center study and the number
296 of PH cases is limited. We, thus, consider the present investigation as a pilot study, and our
297 results cannot be directly extrapolated to different PH patient cohorts. However, recognizing
298 the exact cause of death is critically important to improve the survival outcome in patients
299 with PH. Our results stress the need for detailed evaluation on the cause of death in future
300 studies and registries on PH. Second, this study was conducted retrospectively. As a result, 10
301 PH cases were excluded because of insufficient information. In this regard, prospective
302 studies with a prespecified algorithm for determining the cause of death are required. Third,
303 the possible effect of treatment was not considered. For example, differences in the use of
304 PAH drugs, the treatment strategy for underlying disease(s), and indication of balloon
305 pulmonary angioplasty and pulmonary endarterectomy in group 4 PH patients could have
306 significantly affected the results. However, in our hospital, PEA was conducted consistently
307 at a rate of approximately one surgery per year during the study period, and BPA was
308 initiated only recently, after completion of the study period. Therefore, the two treatment
309 modalities were unlikely to have significantly affected the results. However, the cause of
310 death is expected to substantially change with the development of PH treatment. Fourth,
311 autopsy was conducted in only 11 out of 80 cases in this study. The association of PH with
312 death was supported by autopsy in these cases (PH death, n=7; PH-related death, n=4);
313 however, a higher number of autopsies would have enabled more accurate evaluation of the
314 cause of death. Finally, as discussed above, the methods used to determine the cause of death

315 in this study were not without flaws. In the future, more standardized methods must be
316 established and used in registries and clinical trials.

317

318 **5. Conclusion**

319 Using a specific method, this study showed that patients with groups 1, 3, and 4 PH
320 die from different causes. In short, the most prevalent cause of death was PH in group 1 PH
321 patients, respiratory failure in group 3 PH patients, and malignant disease in group 4 PH
322 patients. With expectations of further treatment progress and longer survival, more research
323 on the PH-type specific cause of death is anticipated, which will foster optimal follow-up and
324 improve outcomes in each PH patient group.

325

326

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329

330 **Conflicts of Interest**

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419

420 **Figure captions**

421

422 **Figure 1. Flow chart of the study cohort.**

423 PH: pulmonary hypertension, WHO: World Health Organization

424

425 **Figure 2. Cause of death in patients with WHO group 1, 3, and 4 PH.**

426 The proportion of PH deaths, PH-related deaths, and PH-unrelated deaths in each PH
427 type is shown. Proportions were significantly different between the three groups (chi-squared
428 test, $p=0.0063$). The most common cause of death was “PH death” in group 1 PH patients,
429 “PH-related death” in group 3 PH patients, and “PH-related death” and “PH-unrelated death”
430 equally in group 4 PH patients.

431 PH: pulmonary hypertension, WHO: World Health Organization

432

433 **Figure 3. Proportion of the cause of death in patients with PH who had PH-related or**
434 **PH-unrelated death.**

435 Cause of death other than PH in patients who died of PH-related death (group 1, $n=7$;
436 group 3, $n=22$; group 4, $n=5$) or PH-unrelated death (group 1, $n=4$; group 3, $n=9$; group 4,
437 $n=5$). The proportion differed between the three groups, as shown by the chi-squared test
438 ($p=0.0002$).

439 PH: pulmonary hypertension

440

441 **Figure 4. Proportion of the cause of death between patients with or without systemic**
442 **sclerosis in group 1 and 3 PH**

443 There were no significant differences in the mortality profile in group 1 PH patients
444 with or without SSc; in contrast, group 3 PH patients with SSc died due to PH at a higher rate
445 (6/10, 60%) than those without SSc (2/29, 7%).

446 PH: pulmonary hypertension; SSc: systemic sclerosis

447

448 **Figure 5. Kaplan Meier curves of patients with Group 1, 3, and 4 PH**

449 There were no significant differences between the three groups (p=0.11, Log rank
450 test; p=0.35, Wilcoxon's test).

451 PH: pulmonary hypertension

452

453 **Table 1. Characteristics of patients at diagnosis.**

	Total	Group 1	Group 3	Group 4	p-value
N	80	28	39	13	
Age, years	67.0 (53.9-71.6)	59.3 (37.5-70.7)*	69.2 (61.7-73.9)	65.8 (51.2-69.8)	0.0126
Female sex, n (%)	43 (53.8)	22 (78.6)	13 (33.3)	8 (61.5)	0.0009
BMI, kg/m²	21.1 (18.2-23.7)	21.0 (19.5-23.5)	21.4 (17.8-24.3)	19.9 (17.9-23.5)	0.897
WHO functional class[#]					
I/II/III/IV	0/8/45/12	0/2/14/2	0/3/24/9	0/3/7/1	0.3824
Smoking history[#]					
Pack years	19.5 (0-50)	4.8 (0-23)*	42 (0.25-78)	13 (0-43.1)*	0.0022
BNP concentration (pg/mL) [#]					
	195.1 (86.2-511.2)	294.8 (127.2-405.4)	106 (14.9-508.9)	309.4 (112.8-681.6)	0.0906
Arterial gas analysis[#]					
O₂, yes/no	23/32	3/14	19/12	1/6	0.0039
O₂ flow (L/min)	0 (0-2)	0 (0-0)*	1.25 (0-4)	0 (0-3)*	0.0048
PaO₂ (torr)	64.2 (53.3-78.7)	63.8 (51.6-81.7)	64.1 (57.4-90.5)	68.1 (56.9-72.2)	0.6213
PaCO₂ (torr)	37.9 (34.3-43.9)	35.4 (32.4-38.4)*	39.7 (36.3-50.7)	36.9 (24.6-37.9)*	0.0048
Pulmonary function test[#]					
%FVC (%)	88.1 (70.2-101.8)	88.5 (79.8-102.1)* **	78.3 (62.2-95.2)	102.3 (93.6-117.3)*	0.0026
%FEV1 (%)	79.8 (67.2-95.7)	86.2 (73.5-100.0)	75.5 (59.8-87.1)	81.8 (69.9-99.3)	0.0817
FEV1/FVC (%)	76.1 (67.5-85.4)	77.1 (70.8±82.7)	80.1 (65.6-88.7)	69.9 (62.8-78.6)	0.171
%DLco	30.3 (20.5-49.8)	39 (27-51.4)* **	24.2 (15.3-30.5)	70 (64.8-87.5)*	<0.0001
%Kco	42.7 (24.2-65.6)	48.1 (36.6-72.2)* **	30.1 (17.1-48.0)	68.4 (60.7-85.4)*	<0.0001
RHC at diagnosis[#]					
O₂ flow (L/min)	1 (0-3)	0 (0-0)*	3 (0.125-4)	0 (0-2)*	<0.0001
HR (bpm)	74.5 (65-83)	76.5 (64-83.5)	75 (64.5-85.5)	70 (65.5-79.5)	0.6469
MPAP (mmHg)	39 (33.5-50)	43 (36.5-54)*	37 (30-44)	45 (36.5-51.5)*	0.0232
PAWP (mmHg)	8 (5-10)	8 (4.5-10.5)	8 (5-10)	7 (5.5-10)	0.9375
RAP (mmHg)	5 (3-8)	7 (4-11)*	5 (2-7)	6 (5-8)*	0.0056
CO (L/min)	3.81 (3.12-4.49)	4.28 (3-4.89)**	3.81 (3.36-4.32)**	3.13 (2.46-3.9)	0.0283
CI (L/min/m²)	2.45 (2.11-2.93)	2.77 (2.02-3.42)**	2.48 (2.21-2.92)**	2.13 (1.69-2.32)	0.006

PVR (Wood Unit)	8.3 (6.0-10.8)	8.3 (6.2-11.4)	7.5 (5.5-10.6)	10.6 (8.7-15.6)*	0.0184
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Values are presented either as n, n (%), or median (interquartile range)

BMI: body mass index, WHO: World Health Organization, BNP: brain natriuretic peptide, PaO₂: partial pressure of oxygen, PaCO₂: partial pressure of carbon dioxide, FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second, DLco: carbon monoxide diffusing capacity, Kco: transfer coefficients, RHC: right heart catheterization, HR: heart rate, MPAP: mean pulmonary artery pressure, PAWP: pulmonary arterial wedge pressure, RAP: right atrium pressure, CO: cardiac output, CI: cardiac index, PVR: pulmonary vascular resistance

*p<0.05 vs. group 3, **p<0.05 vs. group 4, #Data could not be obtained for some patients

Table 2. Medication use in each patient group.

	Group 1	Group 3	Group 4	p-value
n	28	39	13	
PAH-specific drugs				
ERA				
Macitentan	4	5	1	1.0000
Ambrisentan	6	2	4	0.0214
Bosentan	7	5	2	0.4178
NO axis drugs				
Sildenafil	10	19	3	0.2435
Tadalafil	8	4	2	0.1560
Riociguat	1	0	1	0.1399
PG I2				
Beraprost	12	5	6	0.0066
Selexipag	2	1	0	0.7475
Epoprostenol	3	0	0	0.1070
Treprostinil, intravenous	0	0	0	
Treprostinil, subcutaneous	0	0	0	
Iloprost, inhaled	1	0	0	0.5125
Combination of PH drugs				
No/single/dual/triple	2/9/8/9	14/13/9/3	3/3/5/2	0.0426
Medications for comorbidities				
Immunosuppressant				
Steroid	8	12	2	0.5418
Other drug(s)	3	6	0	0.4028
Anticoagulation				
DOAC	1	1	2	0.2135
Warfarin	14	7	11	<0.0001

PAH: pulmonary arterial hypertension, ERA: endothelin receptor antagonists, PH: pulmonary hypertension, NO: nitric oxide, PG: prostaglandin, DOAC: direct oral anticoagulant

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458 **Table 3. Cause of death in patients with group 1, 3, and 4 PH**

	Group 1 (n=28)			Group 3 (n=39)			Group 4 (n=13)		
	PH-death	PH-related death	PH-unrelated death	PH-death	PH-related death	PH-unrelated death	PH-death	PH-related death	PH-unrelated death
n	17	7	4 (14%)	8	22	9 (23%)	3	5	5 (38%)
(%)*	(61%)	(25%)		(21%)	(56%)		(23%)	(38%)	
Respiratory failure (non-PH)		3	1		18	4		3	0
Malignancy		0	0		1	4		1	5
Cardiovascular disease (non-PH)		0	0		0	0		0	0
Renal disease		0	0		0	0		1	0
Infectious disease		1	1		2	1		0	0
Liver disease		1	1		0	0		0	0
Miscellaneous		2	1		1	0		0	0

*p = 0.0003 (between the three PH groups)

PH: pulmonary hypertension

460 **Table 4. Associations between five fundamental PH-related indices and the cause of death**

		Group 1 PH				Group 3 PH				Group 4 PH				
		PH-death	PH-related death	PH-unrelated death	p value	PH-death	PH-related death	PH-unrelated death	p value	PH-death	PH-related death	PH-unrelated death	p value	
WHO FC														
baseline	I/II/III/IV	0/0/9/1	0/1/4/0	0/1/1/1	0.16	0/0/4/3	0/2/14/5	0/1/6/1	0.77	0/0/3/0	0/0/2/1	0/3/2/0	0.14	
change between baseline and the last evaluation					0.36						0.33			0.9
improved		0	0	0		1	0	0		1	0	1		
no change		7	2	2		3	11	6		1	2	2		
worsened		3	3	0		3	10	2		1	0	2		
BNP														
baseline		393(143-954)	295(169-353)	99(93-110)	0.06	611(245-1264)	57(13-167)	195(78-355)	0.009	114(112-919)	309(88-682)	507(191-1024)	0.68	
change between baseline and at the last evaluation					0.04						0.19			1.0
Increased		13	4	0		4	15	3		2	3	3		
Decreased		4	3	3		4	7	6		1	2	2		
MPAP														
baseline		47(41-54)	42(29-55)	37(29-56)	0.41	44(37-49)	37(32-44)	30(27-40)	0.05	53(37-63)	38(34-53)	45(37-49)	0.44	
change between baseline and at the last evaluation					0.79						0.88			0.21
Increased		5	2	1		1	5	2		0	2	0		
No change		0	0	0		1	2	0		0	0	0		
Decreased		4	4	1		4	10	2		1	1	4		
CI														
baseline		2.5(1.7-2.9)	3.5(2.7-3.6)	2.9(1.8-4.3)	0.14	2.5(1.9-3.2)	2.5(2.3-2.9)	2.6(2.2-3.0)	0.96	12.3(0.9-2.5)	2.3(2.1-2.3)	1.8(1.4-2.2)	0.42	

change between baseline and the last evaluation				1.0				0.61				0.21
Increased	4	2	1		3	12	2		0	2	4	
Decreased	4	3	1		3	5	2		1	1	0	
PVR												
baseline	9.9(7.3-	7.8(4.7-	4.2(3.6-	0.1	8.4(6.8-	7.9(5.5-	6.2(4.0-	0.12	13.3(7.9-	9.6(7.7-	12.9(9.0-	0.42
(Wood units)	14.0)	8.5)	15.0)		12.3)	10.6)	8.2)		41.6)	12.1)	17.7)	
change between baseline and the last evaluation				1.0				0.86				0.49
Increased	4	2	1		2	6	2		1	2	1	
Decreased	5	2	1		4	11	2		1	1	3	

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462 Values are presented either as n or median (interquartile range)

463 WHO: World Health Organization, BNP: brain natriuretic peptide, Echo: echocardiography, CMR: cardiovascular magnetic resonance imaging, FVC: forced vital capacity,

464 FEV1: forced expiratory volume in 1 second, DLco: carbon monoxide diffusing capacity, Kco: transfer coefficients, TRPG: transtricuspid pressure gradient, TAPSE:

465 tricuspid annulus plane systolic excursion, RHC: right heart catheterization, HR: heart rate, MPAP: mean pulmonary arterial pressure, PAWP: pulmonary arterial wedge

466 pressure, RAP: right atrium pressure, CO: cardiac output, CI: cardiac index, PVR: pulmonary vascular resistance

467 *p<0.05 vs. group 3, **p<0.05 vs. group 4, #Data could not be obtained for some patients

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Table 5. Comparison of the baseline characteristics between patients with and without respiratory failure that died

		Patients who died with respiratory failure (including cases in which respiratory failure partly contributed to death)	Patients who died without respiratory failure	p-value
Total number of patients (n=70)		n=29	n=41	
	age	69.1 (61.6-76.1)	63.6 (48.4-70.1)	0.01
	smoking (pack-years)	44.5 (29.8-66)	40 (15-60)	0.3
	oxygen therapy	27	43	0.45
	hypoxia at diagnosis	18	19	0.03
	BNP (pg/mL)	85.6 (13.7-158.4)	344.2 (133.6-802.5)	<0.0001
	MPAP (mmHg)	35 (29-39)	44 (37-51)	0.0002
	CI (L/min/m ²)	2.58 (2.2-3.0)	2.4 (1.9-2.8)	0.14
PVR (Wood units)	6.2 (5.3-10.5)	9.3 (6.9-12.8)	0.01	
Group 1 PH (n=28)		n=4	n=24	
	age	75 (40.3-79.7)	57 (37.5-68.7)	0.14
	smoking (pack-years)	12 (n=1)	24 (12-50) n=11	0.47
	oxygen therapy	3	19	0.56
	hypoxia at diagnosis	1	5	1
	BNP (pg/mL)	172.5 (13.1-299)	319.5 (128.8-631.2)	0.3
	MPAP (mmHg)	32 (26.8-37.3)	44 (40-54.5)	0.01
	CI (L/min/m ²)	3.2 (2.2-4.4)	2.67 (1.9-3.2)	0.29
PVR (Wood units)	5.1 (2.9-7.9)	8.5 (6.9-13.1)	0.07	
Group 3 PH (n=39)		n=22	n=17	
	age	68.5 (60.8-77.4)	69.3 (67-73.1)	0.9
	smoking (pack-years)	46.5 (29.9-78.5) n=14	46 (16.9-80.5)	0.77
	oxygen therapy	21	17	0.37
	hypoxia at diagnosis	15	12	0.95
	BNP (pg/mL)	57.3 (13.3-108.6)	383.3 (171.1-1008)	0.004
	MPAP (mmHg)	35.5 (28.5-40)	43 (33-47.5)	0.09
	CI (L/min/m ²)	2.6 (2.2-3.0)	2.4 (2.2-2.7)	0.41
PVR (Wood units)	6.6 (5.3-10.6)	7.6 (6.0-11.6)	0.28	
Group 4 PH (n=13)		n=3	n=10	
	age	68.3 (66.4-73.9)	59.7 (43-69.5)	0.15
	smoking (pack-years)	44 (n=1)	30 (13.3-52.9)	0.8
	oxygen therapy	3	7	0.28
	hypoxia at diagnosis	2	2	0.03
	BNP (pg/mL)	89.9 (86.2-560.6)	408.3 (118.3-831.6)	0.2
	MPAP (mmHg)	35 (32-55)	46.5 (37-50.8)	0.35
	CI (L/min/m ²)	2.3 (2.1-2.3)	2.1 (1.5-2.3)	0.45
PVR (Wood units)	9.6 (5.7-13.8)	11.7 (9.2-17.5)	0.35	

BNP: brain natriuretic peptide, WHO: World Health Organization, FC: functional class, MPAP: mean pulmonary arterial pressure, CI: cardiac index, PVR: pulmonary vascular resistance

472

**All patients with PH who died
between 2001 and 2020
(n=98)**

WHO Group 2 or 5 PH (n=8)

**Insufficient information for
determining the cause of death
(n=10)**

**Study population
(n=80)**









