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

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Abstract

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

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

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

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

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

Abbreviations:

PH: Pulmonary hypertension, PAH: pulmonary arterial hypertension; CTEPH: chronic thromboembolic PH, ILD: interstitial lung disease, CTD: connective tissue disease, SSc: systemic sclerosis, PPH: primary PH, BMI: body mass index, WHO: World Health Organization, BNP: brain natriuretic peptide, PaO_2: partial pressure of oxygen, $PaCO_2$: 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; Echo: echocardiography, CMR: cardiovascular magnetic resonance imaging, TRPG: transtricuspid pressure gradient, TAPSE: tricuspid annulus plane systolic excursion; ERA: endothelin receptor antagonists, NO: nitric oxide, PG: prostaglandin, DOAC: direct oral anticoagulant

1. Introduction

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

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

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

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

2. Patients and methods

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

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

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

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

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

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

2.1 Statistical analysis

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

3. Results

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

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

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

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

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

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

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

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

4. Discussion

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

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

4.1 Cause of death in group 1 PH

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

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

4.3 Cause of death in group 4 PH

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

4.4 Difficulties in accurately determining the cause of death

The main strength of this study was the detailed and systematic analysis of the cause of death among PH types. We chose the method reported by Tonelli et al. [7] because, to the best of our knowledge, it is the most systematic and objective method for the analysis of the cause of death in patients with PH. Of note, however, Tonelli et al. determined the cause of death prospectively, whereas we conducted this study in a retrospective manner. In addition, determining the cause of death remained challenging even with the use of this method. For example, in cases of PH due to ILD, progression of ILD often triggers hypoxemia, which, in 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 autopses 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

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

5. Conclusion

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

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Conflicts of Interest

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Figure captions

Figure 1. Flow chart of the study cohort.

PH: pulmonary hypertension, WHO: World Health Organization

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

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

PH: pulmonary hypertension, WHO: World Health Organization

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

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

PH: pulmonary hypertension

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

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

PH: pulmonary hypertension; SSc: systemic sclerosis

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

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

PH: pulmonary hypertension

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/m^2	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[#]					
O_2, yes/no	23/32	3/14	19/12	1/6	0.0039
O_2 flow (L/min)	0 (0-2)	0 (0-0)*	1.25 (0-4)	0 (0-3)*	0.0048
PaO_2 (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
$PaCO_2$ (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[#]					
O_2 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/m^2)	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

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

BMI: body mass index, WHO: World Health Organization, BNP: brain natriuretic peptide, PaO_2: partial pressure of oxygen, $PaCO_2$: 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

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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

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 (61%)	7 (25%)	4 (14%)	8 (21%)	22 (56%)	9 (23%)	3 (23%)	5 (38%)	5 (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

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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 (pg/mL)	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 (mmHg)	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 ($L/min/m^2$)	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 (Wood units)	9.9(7.3-14.0)	7.8(4.7-8.5)	4.2(3.6-15.0)	0.1	8.4(6.8-12.3)	7.9(5.5-10.6)	6.2(4.0-8.2)	0.12	13.3(7.9-41.6)	9.6(7.7-12.1)	12.9(9.0-17.7)	0.42
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	

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

WHO: World Health Organization, BNP: brain natriuretic peptide, Echo: echocardiography, CMR: cardiovascular magnetic resonance imaging, FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second, DLco: carbon monoxide diffusing capacity, Kco: transfer coefficients, TRPG: transtricuspid pressure gradient, TAPSE: tricuspid annulus plane systolic excursion, RHC: right heart catheterization, HR: heart rate, MPAP: mean pulmonary arterial 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 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

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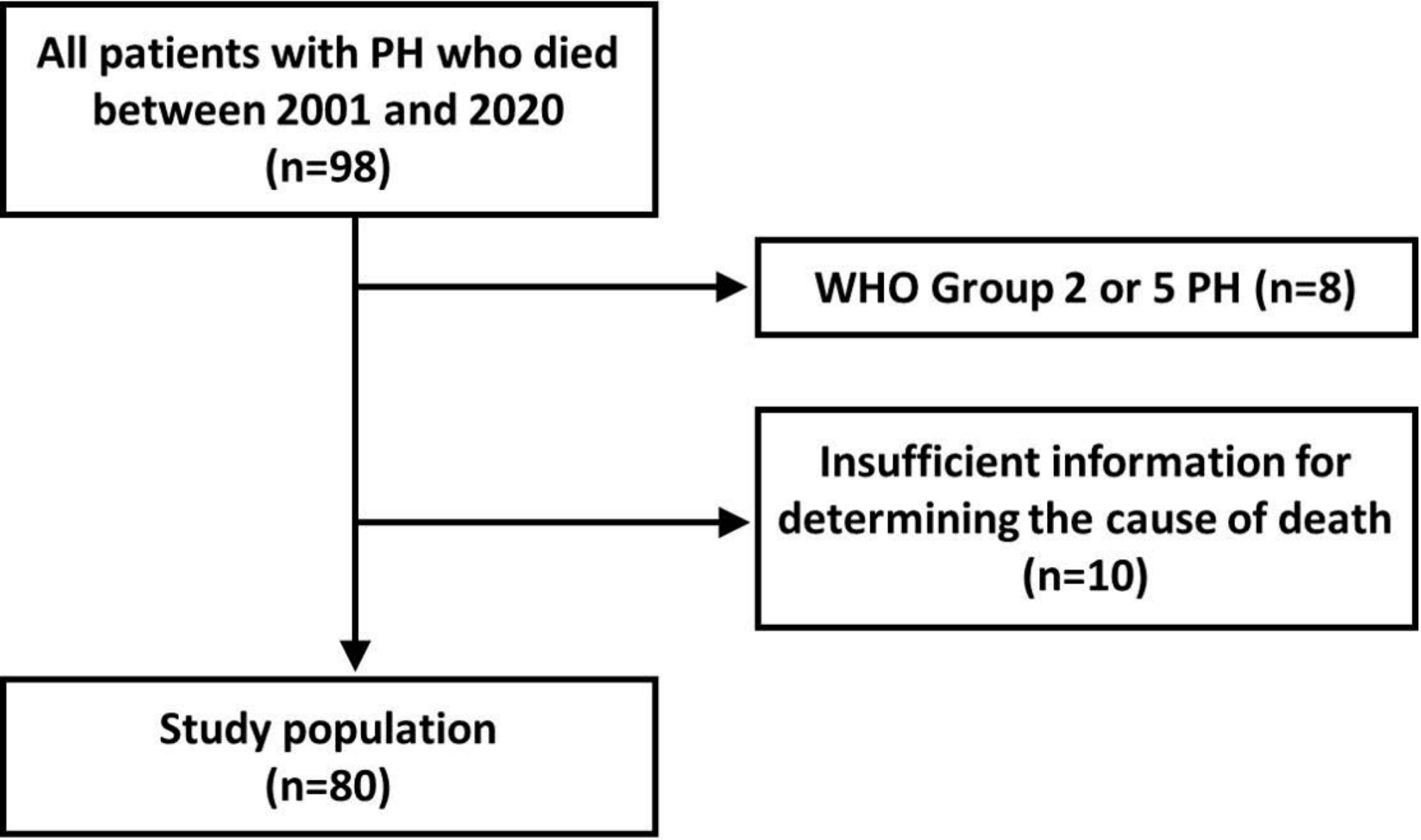
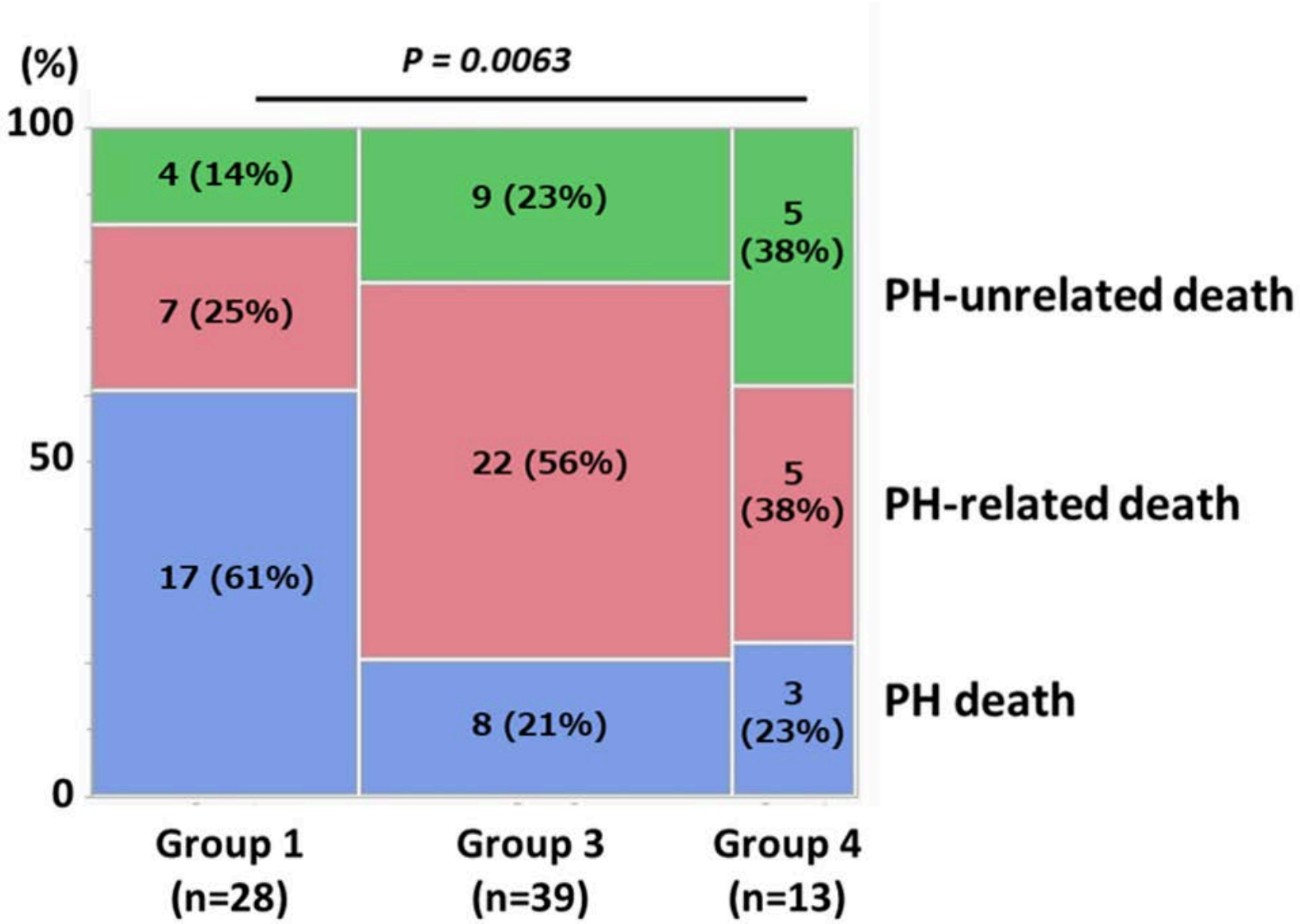
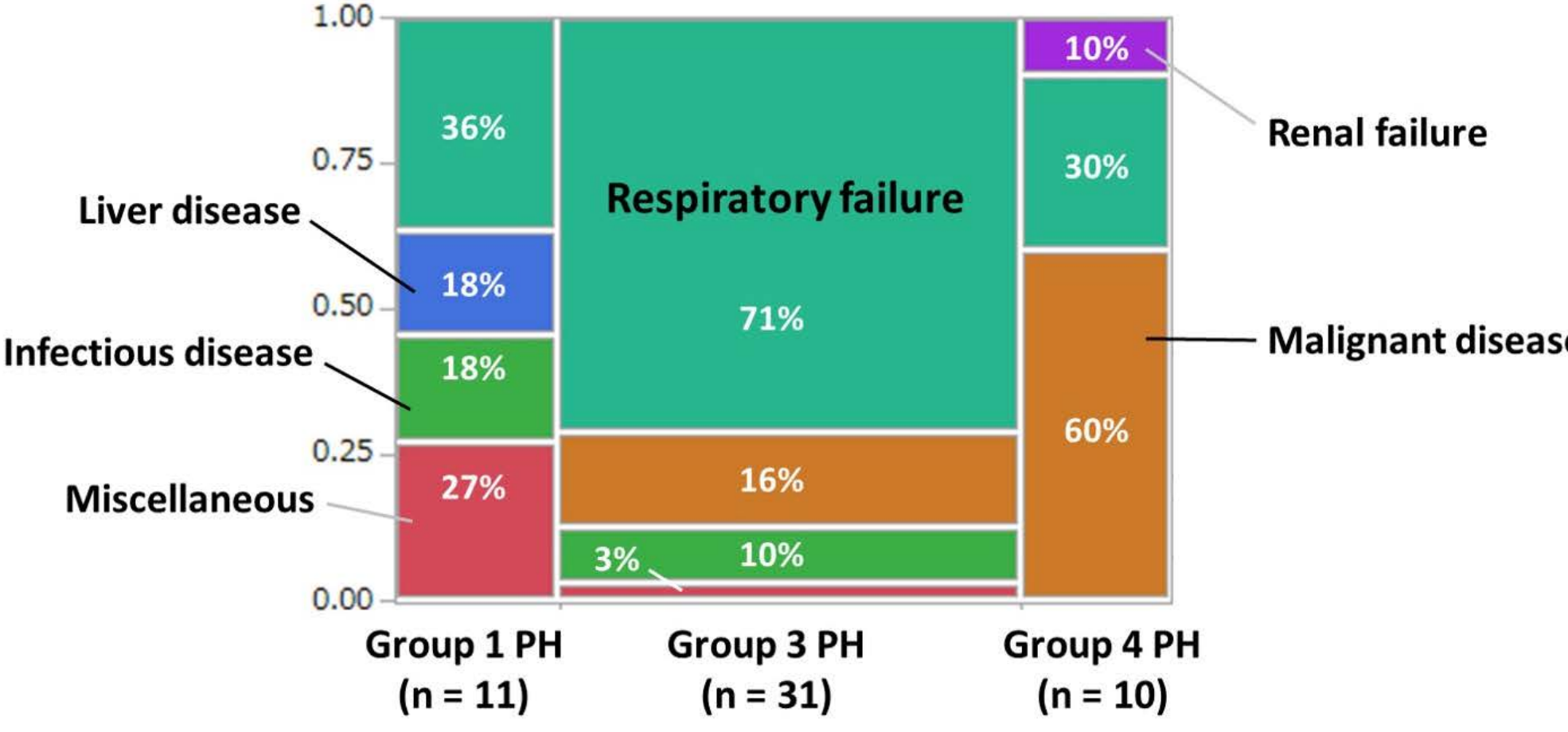
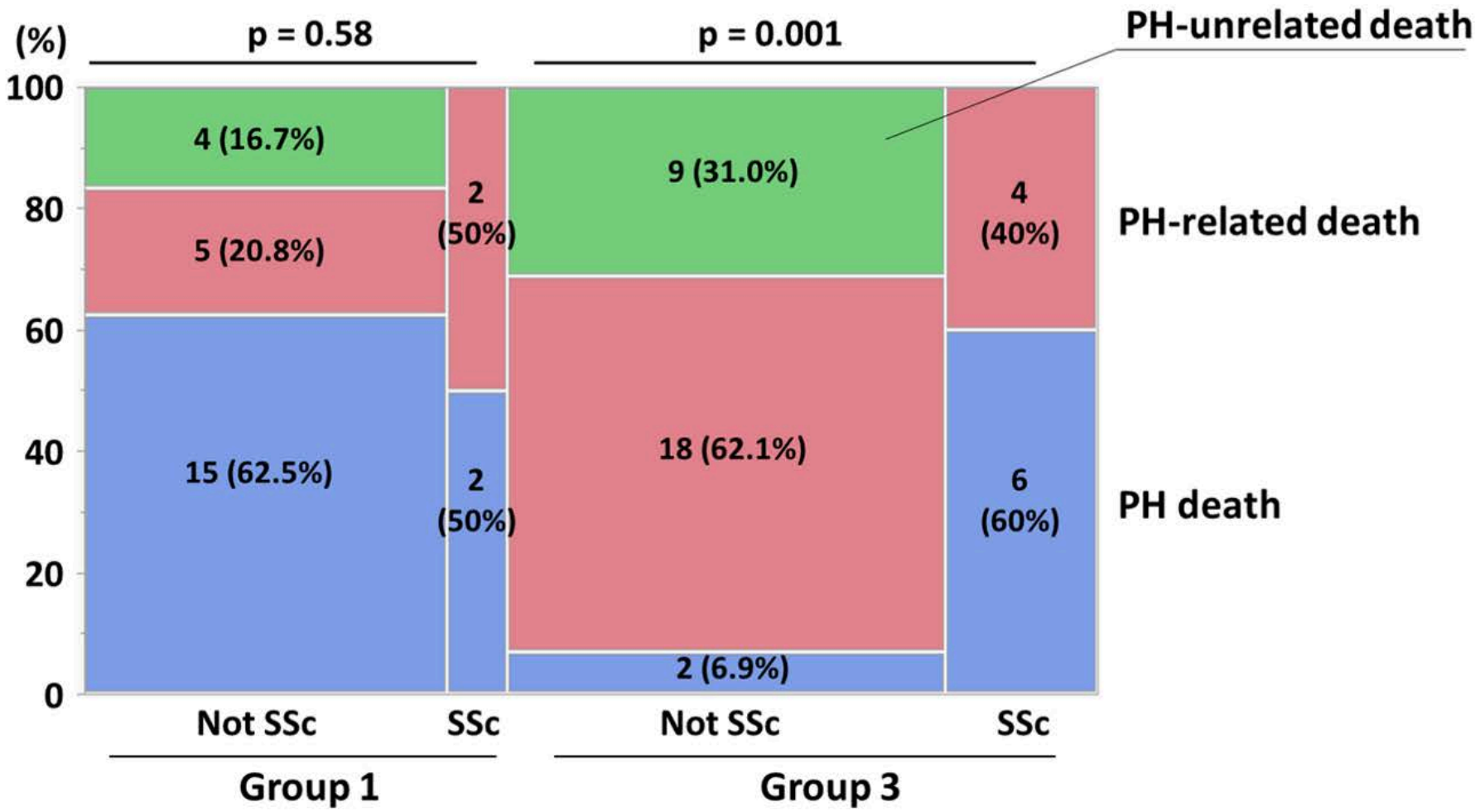
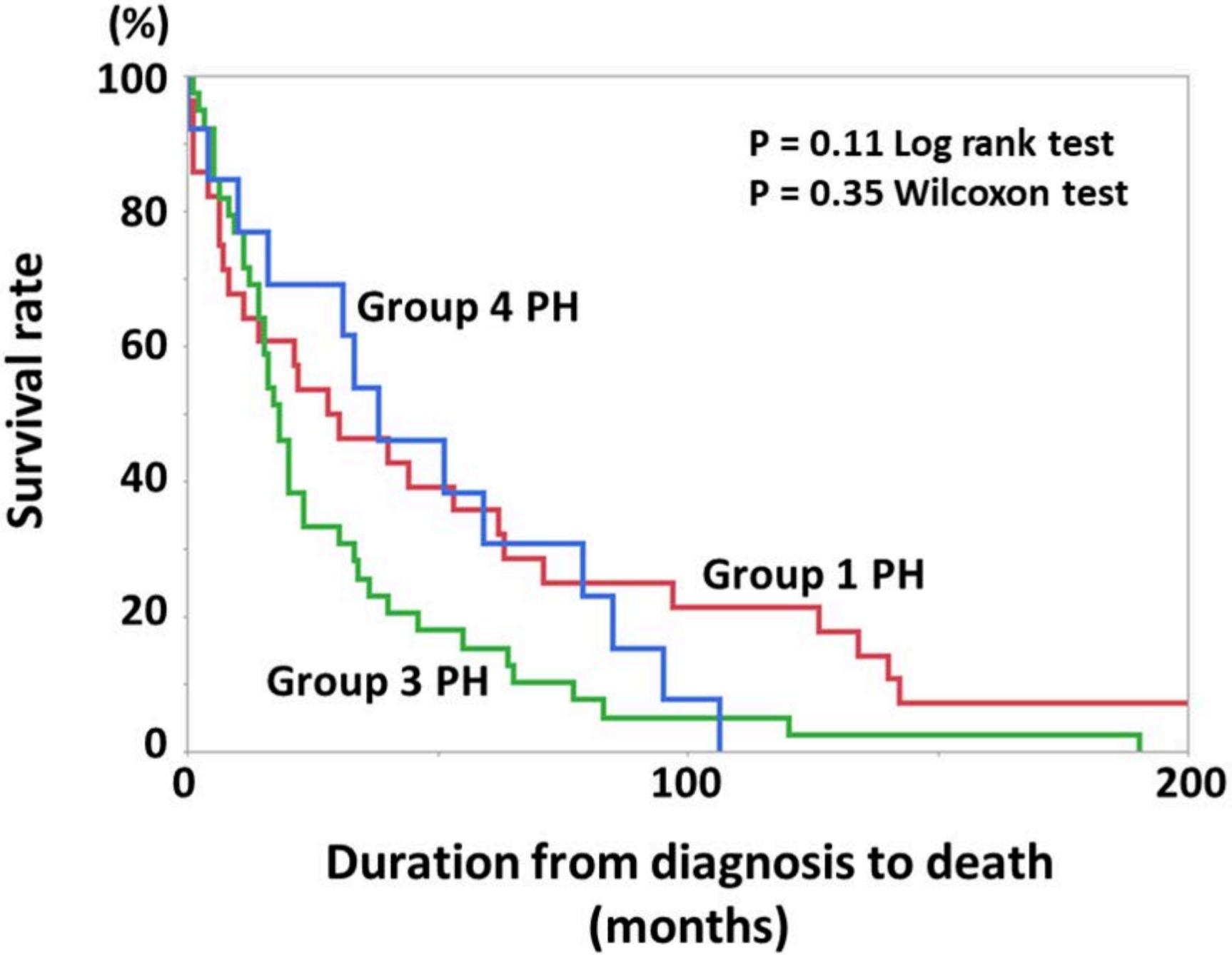

All patients with PH who died between 2001 and 2020 (n=98)
WHO Group 2 or 5 PH (n=8)
Insufficient information for determining the cause of death (n=10)
Study population (n=80)


(%)
P = 0.0063
100
50
0
4 (14%)
7 (25%)
17 (61%)
9 (23%)
22 (56%)
8 (21%)
5 (38%)
5 (38%)
3 (23%)
PH-unrelated death
PH-related death
PH death
Group 1 (n=28)
Group 3 (n=39)
Group 4 (n=13)


1.00
0.75
0.50
0.25
0.00
36%
18%
18%
27%
Respiratory failure
71%
16%
3%
10%
10%
30%
60%
Liver disease
Infectious disease
Miscellaneous
Renal failure
Malignant disease
Group 1 PH
(n = 11)
Group 3 PH
(n = 31)
Group 4 PH
(n = 10)


(%)
p = 0.58
p = 0.001
PH-unrelated death
100
80
60
40
20
0
4 (16.7%)
5 (20.8%)
15 (62.5%)
2 (50%)
2 (50%)
9 (31.0%)
18 (62.1%)
2 (6.9%)
4 (40%)
6 (60%)
PH-related death
PH death
Not SSc
SSc
Not SSc
SSc
Group 1
Group 3


(%)
100
80
60
40
20
0
Survival rate
P = 0.11 Log rank test
P = 0.35 Wilcoxon test
Group 4 PH
Group 1 PH
Group 3 PH
0
100
200
Duration from diagnosis to death
(months)