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

Junichi Nakamura[a], Ichizo Tsujino[a,b*], Hiroshi Ohira[a], Toshitaka Nakaya[a], Ayako Sugimoto[a], Takahiro Sato[a,b], Taku Watanabe[a], Masaru Suzuki[a], Masaru Kato[c], Isao Yokota[d], Satoshi Konno[a,b]

[a]Department of Respiratory Medicine, Faculty of Medicine, Hokkaido University, Sapporo, Japan, 060-8638

[b]Division of Respiratory and Cardiovascular Innovative Research, Faculty of Medicine, Hokkaido University, Sapporo, Japan, 060-8638

[c]Department of Rheumatology, Endocrinology and Nephrology, Faculty of Medicine and Graduate School of Medicine, Hokkaido University, Sapporo, Japan, 060-8638

[d]Department of Biostatistics, Graduate School of Medicine, Hokkaido University, Sapporo, Japan, 060-8638

**Corresponding author:**

Ichizo Tsujino

Division of Respiratory and Cardiovascular Innovative Research, Faculty of Medicine, Hokkaido University

N15, W7, Kita-ku, Sapporo, Hokkaido 060-8638, Japan

Phone number: 81-11-706-5911, Fax number: 81-11-706-7899

Email: itsujino@med.hokudai.ac.jp

Word count: 3,449

**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.


## Acknowledgments

The authors thank Editage (www.editage.com) for English language editing.


## Conflicts of Interest

Ichizo Tsujino, Takahiro Sato, and Satoshi Konno received research funding from Nihon Shinyaku Co Ltd. Nippon Boehringer Ingelheim Co., Ltd. and Mochida Pharmaceutical Co., Ltd. IY reports grants from KAKENHI, AMED, and Health, Labour and Welfare Policy Research Grants, research fund by Nihon Medi-Physics, and speaker fees from Chugai Pharmaceutical Co, AstraZeneca plt, Japan Tabacco Pharamaceutical Division, and Nippon Shinyaku Co, not related to the submitted work.


## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

**References**

[1] Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J. 2015;46:903–75. https://doi.org/10.1183/13993003.01032-2015.

[2] D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med. 1991;115:343–9. https://doi.org/10.7326/0003-4819-115-5-343.

[3] Tamura Y, Kumamaru H, Satoh T, Miyata H, Ogawa A, Tanabe N, et al. Effectiveness and outcome of pulmonary arterial hypertension-specific therapy in Japanese patients with pulmonary arterial hypertension. Circ J. 2017;82:275–82. https://doi.org/10.1253/circj.CJ-17-0139.

[4] Hurdman J, Condliffe R, Elliot CA, Davies C, Hill C, Wild JM, et al. Aspire registry: Assessing the spectrum of pulmonary hypertension identified at a REferral centre. Eur Respir J. 2012;39:945–55. https://doi.org/10.1183/09031936.00078411.

[5] Farber HW, Miller DP, Poms AD, Badesch DB, Frost AE, Muros-Le Rouzic E, et al. Five-year outcomes of patients enrolled in the REVEAL Registry. Chest. 2015;148:1043–54. https://doi.org/10.1378/chest.15-0300.

[6] Delcroix M, Lang I, Pepke-Zaba J, Jansa P, D'Armini AM, Snijder R, et al. Long-term outcome of patients with chronic thromboembolic pulmonary hypertension: Results from an international prospective registry. Circulation. 2016;133:859–71. https://doi.org/10.1161/CIRCULATIONAHA.115.016522.

[7] Tonelli AR, Arelli V, Minai OA, Newman J, Bair N, Heresi GA, et al. Causes and circumstances of death in pulmonary arterial hypertension. Am J Respir Crit Care Med. 2013;188:365–69. https://doi.org/10.1164/rccm.201209-1640OC.

[8] Rubin LJ, American College of Chest Physicians. Diagnosis and management of pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. Chest. 2004;126 (suppl.):7S–10S. https://doi.org/10.1378/chest.126.1_suppl.7S.

[9] Tanabe N, Taniguchi H, Tsujino I, Sakamaki F, Emoto N, Kimura H, et al. Multi-institutional retrospective cohort study of patients with severe pulmonary hypertension associated with respiratory diseases. Respirology. 2015;20:805–12. https://doi.org/10.1111/resp.12530.

[10] Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC) , European Respiratory Society (ERS), International Society of Heart and Lung Transplantation (ISHLT), Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2009;34:1219–63. https://doi.org/10.1183/09031936.00139009.

[11] Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53. https://doi.org/10.1183/13993003.01913-2018'.

[12] Goh NS, Desai SR, Veeraraghavan S, Hansell DM, Copley SJ, Maher TM, et al. Interstitial lung disease in systemic sclerosis: A simple staging system. Am J Respir Crit Care Med. 2008;177:1248–54. https://doi.org/10.1164/rccm.200706-877OC.

[13] Okada O, Tanabe N, Yasuda J, Yoshida Y, Katoh K, Yamamoto T, et al. Prediction of life expectancy in patients with primary pulmonary hypertension. A retrospective nationwide survey from 1980–1990. Intern Med. 1999;38:12–6. https://doi.org/10.2169/internalmedicine.38.12.

[14] Opitz CF, Hoeper MM, Gibbs JS, Kaemmerer H, Pepke-Zaba J, Coghlan JG, et al. Pre-capillary, combined, and post-capillary pulmonary hypertension: A pathophysiological continuum. J Am Coll Cardiol. 2016;68:368–78. https://doi.org/10.1016/j.jacc.2016.05.047.

[15] Gall H, Felix JF, Schneck FK, Milger K, Sommer N, Voswinckel R, et al. The Giessen Pulmonary hypertension Registry: Survival in pulmonary hypertension subgroups. J Heart Lung Transplant. 2017;36:957–67. https://doi.org/10.1016/j.healun.2017.02.016.

[16] Hamada K, Nagai S, Tanaka S, Handa T, Shigematsu M, Nagao T, et al. Significance of pulmonary arterial pressure and diffusion capacity of the lung as prognosticator in patients with idiopathic pulmonary fibrosis. Chest. 2007;131:650–6. https://doi.org/10.1378/chest.06-1466.

[17] Barco S, Klok FA, Konstantinides SV, Dartevelle P, Fadel E, Jenkins D, et al. Sex-specific differences in chronic thromboembolic pulmonary hypertension. Results from the European CTEPH registry. J Thromb Haemost. 2020;18:151–61. https://doi.org/10.1111/jth.14629.

[18] Corsico AG, D'Armini AM, Cerveri I, Klersy C, Ansaldo E, Niniano R, et al. Long-term outcome after pulmonary endarterectomy. Am J Respir Crit Care Med. 2008;178:419–24. https://doi.org/10.1164/rccm.200801-101OC.

[19] Ogino H, Ando M, Matsuda H, Minatoya K, Sasaki H, Nakanishi N, et al. Japanese single-center experience of surgery for chronic thromboembolic pulmonary hypertension. Ann Thorac Surg. 2006;82:630–6. https://doi.org/10.1016/j.athoracsur.2006.03.121.

[20] Aoki T, Sugimura K, Tatebe S, Miura M, Yamamoto S, Yaoita N, et al. Comprehensive evaluation of the effectiveness and safety of balloon pulmonary angioplasty for inoperable chronic thrombo-embolic pulmonary hypertension: Long-term effects and procedure-related complications. Eur Heart J. 2017;38:3152–9. https://doi.org/10.1093/eurheartj/ehx530.

[21] Kim NH, Lang IM. Risk factors for chronic thromboembolic pulmonary hypertension. Eur Respir Rev. 2012;21:27–31. https://doi.org/10.1183/09059180.00009111.

**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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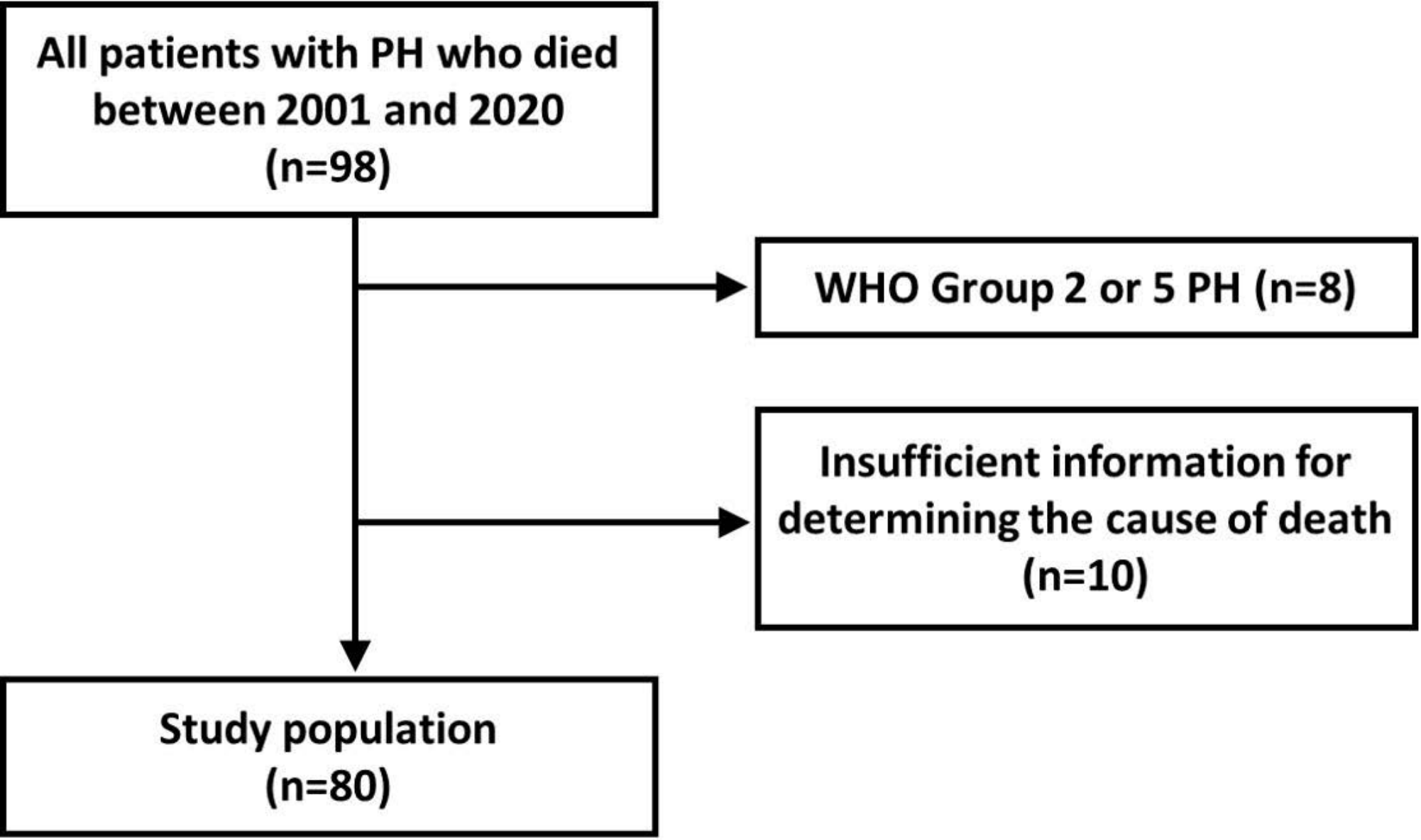
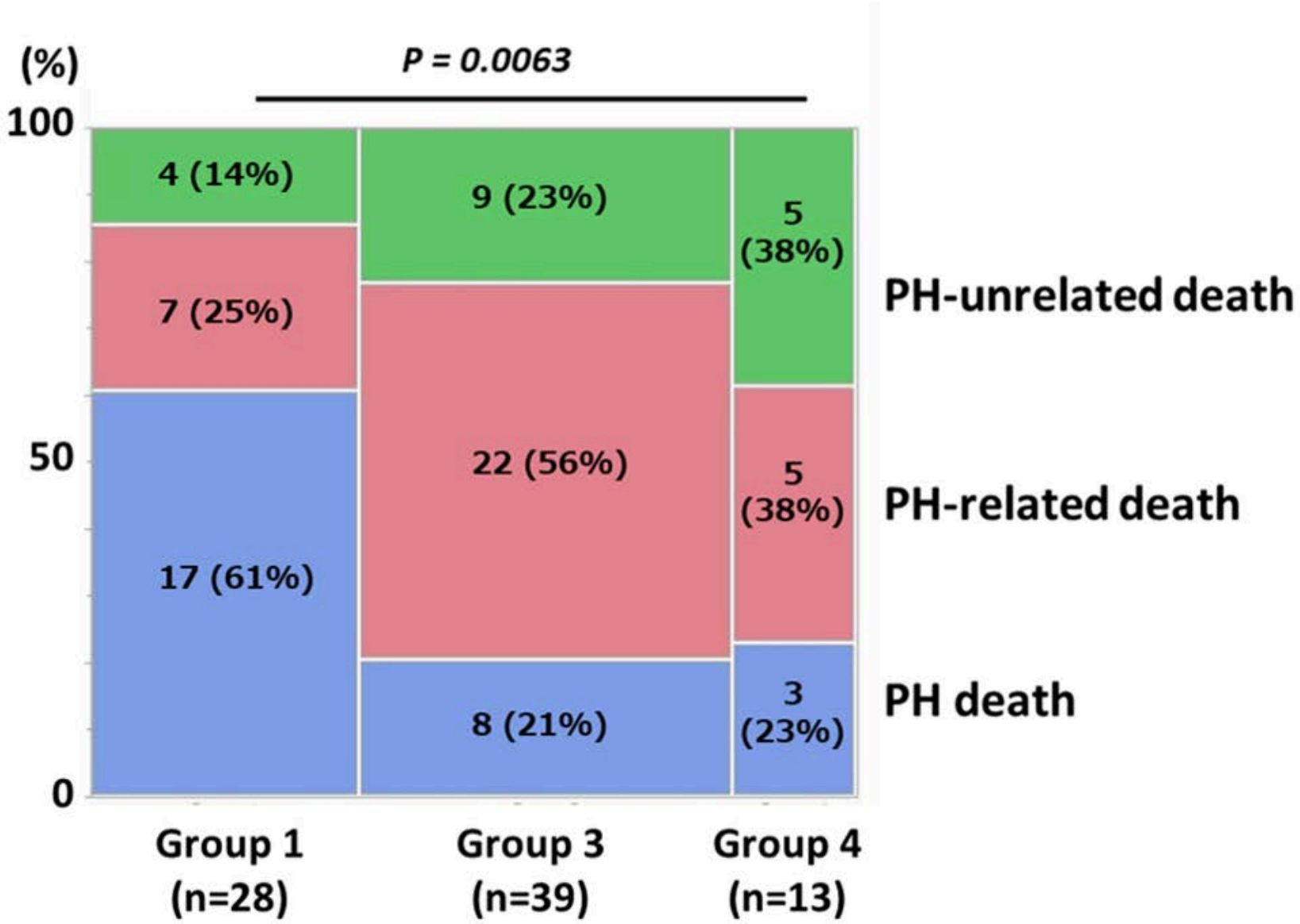
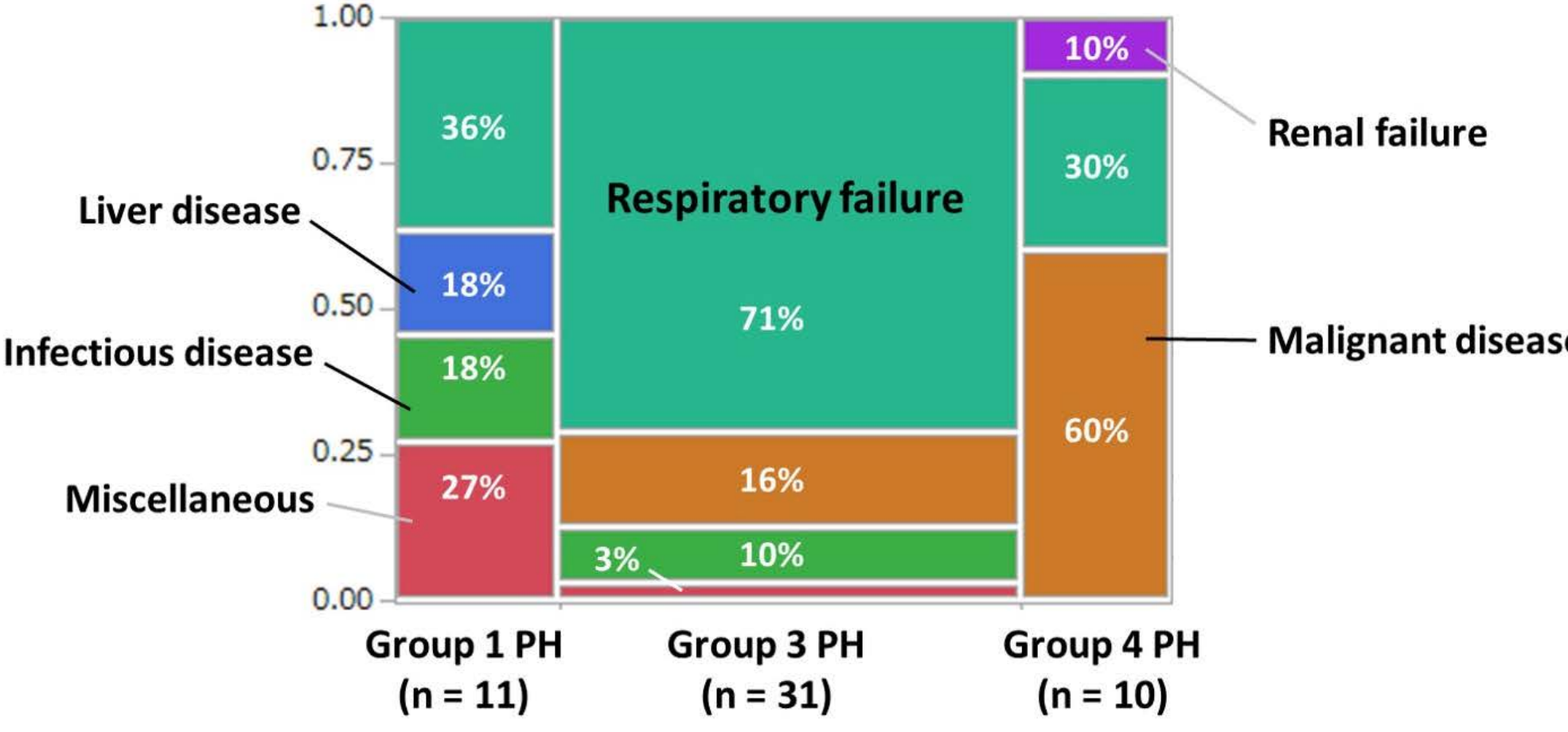
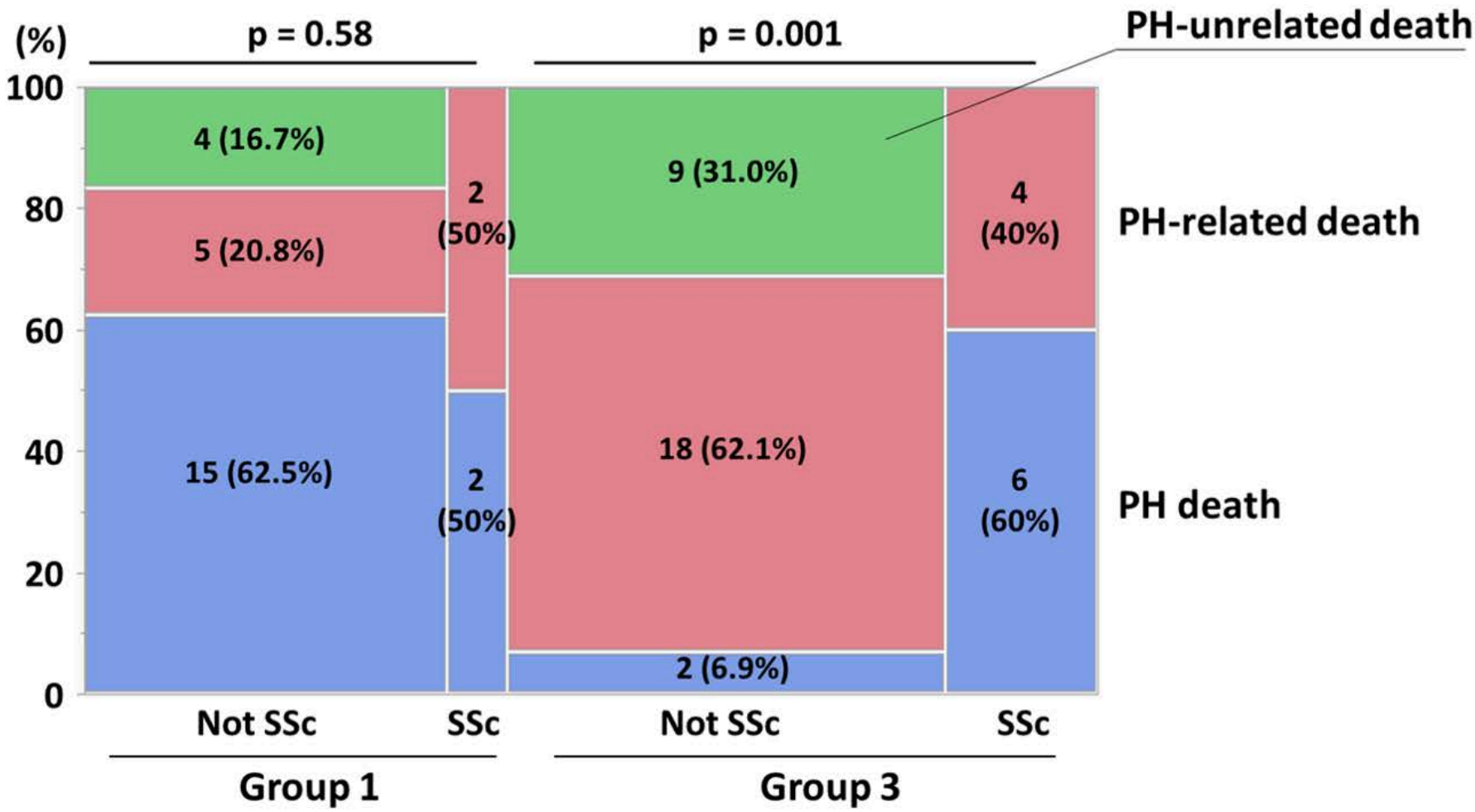
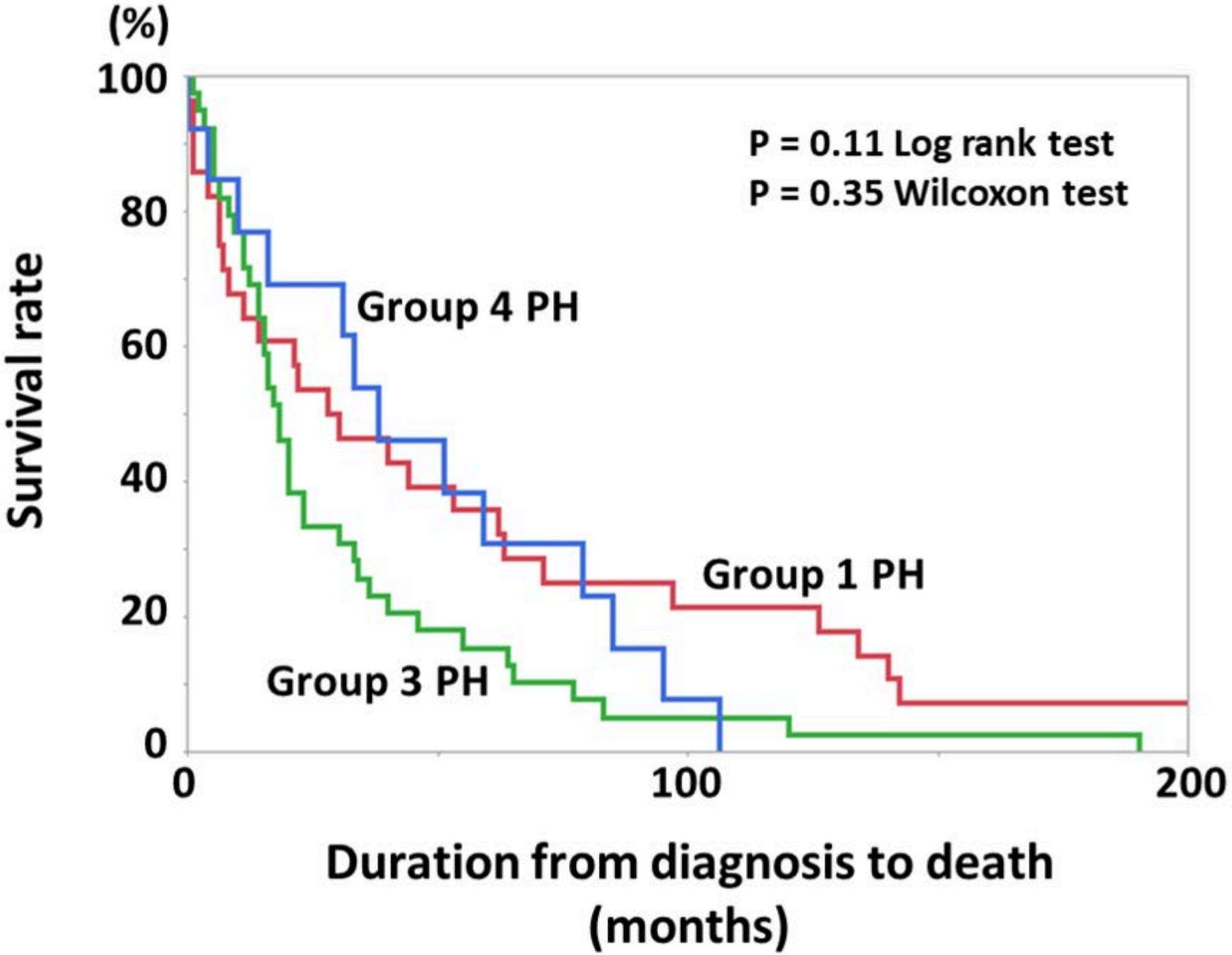

All patients with PH who died between 2001 and 2020 (n=98)
WHO Group 2 or 5 PH (n=8)
Insufficient information for determining the cause of death (n=10)
Study population (n=80)


(%)
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)