Understanding the current status of patients with pulmonary hypertension during COVID-19 outbreak: a small-scale national survey from China

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Abstract
Pulmonary hypertension is a chronic disease developing progressively with high mortality. Pulmonary hypertension patients need persistent medical care; however, limited reports focused on them when there was an outbreak of coronavirus disease 2019 in China. This national survey was aimed to evaluate the overall condition of pulmonary hypertension patients during this period. A questionnaire regarding the living condition of pulmonary hypertension patients during coronavirus disease 2019 was designed by pulmonary hypertension diagnostic experts in Wuhan Asia Heart Hospital. Pulmonary hypertension patients and their family members were invited to participate in this survey online. One-hundred twenty pulmonary hypertension patients and 23 family members participated in the survey; 64.8% (n = 87) participants came from Hubei, and others were from 15 other provinces; 98.6% (n = 141) participants were in home quarantine; 65.8% (n = 79) were pulmonary arterial hypertension associated with congenital heart disease; and 76.7% (n = 92) patients proclaimed their heart function was well maintained at class I or II. One (0.8%) patient was confirmed severe acute respiratory syndrome coronavirus 2 infection. Two (1.7%) patients were hospitalized due to heart function worsening. Nearly 70% (n = 100) participants implied shortage in medications during coronavirus disease 2019 outbreak. A total of 24.2% (n = 29) patients indicated that medications were discontinued due to the insufficient supply. Most of the participants stayed optimistic on either coronavirus disease 2019 outbreak or their pulmonary hypertension disease, and 61.7% (n = 74) patients would go to the hospital for follow-up immediately after outbreak. These preliminary data show pulmonary hypertension patients are able to avoid severe disease when they are in home quarantine. Medication supplement is important for pulmonary hypertension patients when their heart function is well maintained. In addition, there might be increasing requirements of medical care for pulmonary hypertension patients after the outbreak.

Keywords
coronavirus disease 2019 (COVID-19), pulmonary hypertension, medical care

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Introduction
Pulmonary hypertension (PH) is a chronic and progressive lung disease caused by multiple differing etiologies. Increasing pulmonary vascular resistance led to overloading of the right ventricle and eventually death.¹

PH is characterized by a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest. In addition to the treatment of relieving symptoms, targeted therapy aiming to improve heart function extended three-year survival of pulmonary arterial hypertension (PAH) from 39% to 75%.²,³

Coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China, in last December.⁴ Studies observed severe damage in the lung, which raised
the hypothesis that PH patients might be more vulnerable than others. Subsequently, the whole country was placed in lockdown to prevent the spread of the disease, which potentially could compromise PH patient care. All these factors made PH patients a potentially vulnerable group. Hereby, we designed a questionnaire for PH patients to understand their disease condition, mental condition, medication supplement, and requirements in medical care during COVID-19 outbreak. The survey would provide general information for future medical care and support to PH patients in such conditions.

Methods

Design and participants

The study was conducted by experts from Congenital Heart Disease Center at Wuhan Asia Heart Hospital in Wuhan in collaboration with other PH centers and unofficial patients groups. Patients diagnosed with PH and their families were considered for the survey. PH was defined as mPAP ≥ 25 mmHg at rest. All diagnosis was made according to right heart catheter examination.

A small-scale national online survey was performed. PH patients and one of their family members were invited to participate in the survey via Quick Response (QR) code. All answers were listed in non-medical descriptions and reviewed by unprofessional individuals for better understanding. No personal information was included. The study protocol and questionnaire were reviewed and approved by the Ethics Committee of Wuhan Asia Heart Hospital (2020-S-002). Participants were given informed consent during the survey.

The questionnaire was designed by experts on PH in Wuhan Asia Heart Hospital, Wuhan, China. To understand the status of PH patients during COVID-19 outbreak in China, the questions were designed to cover the following issues: (1) basic clinical information of the patients, including age, gender, medical history of PH, and current heart function; (2) physical and mental conditions associated with COVID-19; and (3) details of the medications they were using and requirements for medical care if any. Questions were designed in single choice and multiple choices. “Yes” or “No” were offered for most questions, and answers other than choices were required to fill. The questionnaire is still open for recruitment (questionnaire in Supplement). Here, we present the preliminary data from the first respondents.

Statistical analysis

Baseline characteristics are presented as number for categorical data, and mean ± standard deviation or median with interquartile range as appropriate for continuous data. Percentage is applied for illustrating constitution. Comparison was made between variables using Student’s t-test or Wilcoxon signed-rank test for continuous variables regarding their distributions and with the χ² test for categorical variables. A p-value of < 0.05 was considered as statistically significant. All statistical analyses were performed with SPSS 23.0 (IBM Corp, Armonk, NY).

Results

Participants

Over 300 individuals were invited to participate in this survey. A total of 120 PH patients and 23 family members from 16 provinces responded from 1 March 2020 to 11 March 2020. All questionnaires were included in final analysis. A total of 64.8% (n = 87) participants were from Hubei, among which 29.9% (n = 26) were from Wuhan; 13.3% (n = 19) were from Henan, 7.0% (n = 10) from Anhui, and 18.9% (n = 27) came from other 13 provinces (as shown in Fig. 1). Both patients and their family members completed the survey in 13 families; however, we failed to identify them due to the design. Table 1 shows general information of the participants. Overall participants were aged 32.3 ± 11.5 years. A total of 61 patients suffered PH more than seven years. Three family participants did not know PH history of their relatives. Possibly due to the different etiology, CHD-PH contributed most in PH groups (79, 65.8% in patients; 13, 56.5% in family participants; p < 0.001).

New onset symptoms

A total of 98.6% (n = 141) participants were in home quarantine during COVID-19 outbreak. Table 1 shows the majority of participants (121, 84.6%) felt not much change on disease progress. Surprisingly, most patients were with less severe symptoms as 46.9% (n = 67) participants proclaimed New York Heart Association heart functional class I and 44 (30.8%) were class II. A total of 83.3% (n = 100) patients and 91.3% (n = 21) family participants reported the disease progression was the same as before. Fatigue and less active was more reported in patients (20% vs 0, p = 0.026); however, cough was common in both patients and family participants (5.8% vs 13.0%, p = 0.203) (as shown in Fig. 2). Symptoms in “Others” included not sleeping well, chest pain, aching pain in limbs, and catching a cold but recovered. There were three (2.5%) patients hospitalized during COVID-19 outbreak, two of them were because of heart failure and one was due to pneumonia. None of the family participants reported death of patients. Actually, three patients passed away by 11 March 2020. One of the patients died due to an unexpected fall and unable to go to hospital during outbreak. Two died from worsening of PAH. All deaths were reported by family privately, and not included in the survey.

Fever is an important symptom indicating COVID-19. In our survey, 5.0% (n = 6) patients had fever with highest temperature of 39.8°C. One patient was confirmed
SARS-CoV-2 infection, and two patients reported COVID-19 related symptoms (cough) in their families. All family participants denied COVID-19 related symptoms in either themselves or patients.

**Medications**

Bosentan, Ambrisentan, Tadalafil, and Sildenafil were most commonly used medications for target therapy (as shown in Fig. 3). Specifically, Ambrisentan was preferred in 57.5% ($n = 69$) patients and 60.9% ($n = 14$) family participants. A total of 21.6% ($n = 26$) patients and 26.1% ($n = 6$) family participants chose Chinese generic Ambrisentan because of the lower price in Chinese generic medication. There were 17 patients enrolling in clinical trial and using Macitentan for free. Patients were more sensitive to the shortage of medications than family participants ($62, 51.7\%$ vs 4, 17.4\%, $p = 0.003$). There were 26.6% participants (29 in patients; 9 in family participants) who thought they had enough medications by the time of survey, when it was at least 40 days after national lockdown (as shown in Fig. 4a). A total of 40.0% ($n = 48$) patients were able to buy more medications with great effort; however, 24.2% ($n = 29$) discontinued one or more medications. There were 10 (7.0%) patients changing their medications without consulting their doctors (as shown in Fig. 4a), two of which previously took Macitentan. A total of 100 participants (69.9%) thought they had medications shortage during COVID-19 outbreak (as shown in Fig. 4b).

**Psychological conditions**

Over 20.0% patients ($n = 29$) and family participants ($n = 6$) had panic, but most of them (89, 62.2%) thought protection was important (as shown in Fig. 5a). Though 48.3% ($n = 58$) patients and 39.1% ($n = 9$) family participants felt bad due to the disease, more than 70% (85 in patients; 18 in family participants) participants still kept optimistic at the same time (as shown in Fig. 5b).

**Further requirement in medical care**

Both PH patients and their families requested further medical care despite of a lack of clear clinical worsening according to our survey. A total of 11.7% ($n = 14$) patients and 26.1% ($n = 6$) family participants would like to contact their
also encourage patients to be more positive.

soon as possible, which was similar to patients. pants would ask their relatives with PH go to the hospital as preferred hospitalization; and 60.9% (n = 17) family participants would go to the hospital for follow-up immediately after public transportation was available, eight of whom preferred hospitalization; and 60.9% (n = 14) family participants would ask their relatives with PH go to the hospital as soon as possible, which was similar to patients. Additionally, 73.9% (n = 17) family participants would also encourage patients to be more positive.

Discussion

The outbreak of COVID-19 changed most people’s life in last winter. Specifically, patients with chronic diseases might suffer from the high risk of COVID-19 and uncontrolled existing diseases at the same time. PH patients require sustained medical care similar to other chronic diseases. Any interruption in medications may result in clinical worsening and death. However, their living condition during COVID-19 was unknown. Our small-scale national survey brought an insight to this group. The results of the questionnaire indicated that the incidence of COVID-19 was not higher in PH patients according to our survey. Regardless of incidental cough and fever in our patients, only one patient was confirmed SARS-CoV-2 infection. Medication insufficiency was the most common problem in our patients as nearly 70% participants implied their medications shortage during COVID-19 outbreak. A total of 24.2% patients discontinued medications, and 7.0% patients changed their medications without consulting their doctor. A total of 98.6% participants stayed at home during outbreak, and most of them were not depressed by either PH or COVID-19 according to our survey. However, further requirements in medical care might significantly increase due to the high desire of follow-up, even hospitalization, from both patients and their families when COVID-19 outbreak is over.

In early studies, COVID-19 patients often stayed in Wuhan for a while or had a history of exposure to confirmed cases. Family cluster was also observed in several cases. There were 18.2% (n = 26) participants from Wuhan in our study, which might be the result of hospital location, and one of the patients groups were from Hubei. None of them reported COVID-19, neither in patients nor in family participants. Person-to-person transmission is confirmed in COVID-19, and lockdown in Wuhan began in 24 January 2020 to prevent further spread of this infectious disease. A total of 98.6% of our patients and their families were in home quarantine during COVID-19 outbreak, which might be a key factor that prevented our patients being infected. Previous studies showed 32–51% patients with COVID-19 had existing diseases, such as diabetes, hypertension, and other cardiovascular diseases. Males were more vulnerable. Mean age of the patients were 49–55 years from different study cohort. Our participants were 33 years old at mean age, which was much younger than previous COVID-19 patients. Our study cohort consisted of 80% females, which was quite different from the proportion of COVID-19. In addition, most of our patients were CHD-PAH and maintained a fairly well heart function. Therefore, the younger age, more females, different etiology, and better cardiac function in our PH patients might result in a lower incidence of COVID-19.

Similar to any other chronic diseases, PH patients have to take life-time medications, and most of them had higher medication adherence. Bosentan was first used in PAH in 2002, and it significantly improved six-minute walk distance and heart function. Since then, targeted treatment has extended more than half of patients’ life to three or even five years. Combination therapy recommended in recent years has further reduced adverse events and slowed down the PH progression. In our study, patients took Ambrisentan more than Bosentan partly due to the lower price in Chinese generic medication. A total of 17 patients were taking Macitentan for free. Treprostinil was used in very few patients because of the high price and inconvenience of

| Table 1. General information of participants. | Patients | Family members |
|---------------------------------------------|---------|----------------|
| Participants (n)                            | 120     | 23             |
| Female (n, %)                               | 95 (79.2%) | 15 (65.2%)    |
| Age (year)                                  | 33.7 ± 8.4 | 34.8 ± 12.9   |
| Patient history (year)                      | 32 (29–38) | 17 (10–43)    |
| NYHA class (n, %)                           |         |                |
| I                                           | 51 (42.5%) | 16 (69.6%)    |
| II                                          | 41 (34.2%) | 3 (13.0%)     |
| III                                         | 28 (23.3%) | 3 (13.04%)    |
| IV                                          | 0       | 0              |
| No idea                                     | NA      | 3 (13.0%)     |
| PH group (n, %)                             |         |                |
| iPAH                                        | 25 (20.8%) | 5 (21.7%)     |
| CTD-PAH                                     | 9 (7.5%) | 3 (13.0%)     |
| CHD-PAH                                     | 79 (65.8%) | 13 (56.5%)   |
| PH-lung disease                             | 4 (3.3%) | 0              |
| CTEPH                                       | 0       | 2 (8.7%)      |
| PH (do not know group)                      | 3 (2.5%) | 0              |
| New onset symptoms (n, %)                   |         |                |
| Nothing, same as before                     | 100 (83.3%) | 21 (91.3%)   |
| Fatigue and less active                     | 24 (20.0%) | 0              |
| Cough                                       | 7 (5.8%) | 3 (13.0%)     |

CHD-PAH: pulmonary arterial hypertension associated with congenital heart disease; CTEPH: chronic thrombotic embolism pulmonary hypertension; CTD-PAH: pulmonary arterial hypertension associated with connective tissue disease; iPAH: idiopathic pulmonary arterial hypertension; NA: not applicable; NYHA: New York Heart Association; PH: pulmonary hypertension.
intravenous application. Luckily, 40.0% of patients were able to continue their medications with great effort during the national lockdown. Different from other cardiovascular diseases, PH target medications are expensive and unavailable in small cities, which might result in the shortage of medications in our PH patients. The lockdown in cities additionally prevented patients from getting supplement. Nearly 30% of patients either discontinued their medications or changed without consultation. We have tried to help some of our patients to buy medications; however, shutdown of most public transportations made the process very difficult. We could hardly predict the prognosis of those who changed their treatment for less than 40 days. An interruption of treatment around three days might be tolerated, but clinical worsening might happen due to the discontinuation of medications. Patients preferred clinic visiting to consult doctors for any modification. Our patients showed higher desire to contact their doctors even though we had provided online consultation before the survey.

Mental condition of PH patients has aroused attentions in recent years. Their concerns about the invasive examination, disease progression, and social interactions may directly impact their tolerance to treatment. The outbreak of COVID-19 brought an unexpected crisis first in Wuhan, then spread to other cities. Surprisingly, our PH patients and their families were mostly not panicking during the outbreak. They were overall positive and optimistic even though there were shortages on their medications. The reasons for such response might be as follows: first, most PH patients stayed at home which was familiar and comfort for them. Second, there were not many clinical worsening in our patients. Their disease condition was mostly constant during

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**Fig. 2.** New onset symptoms. Incidences of new onset symptoms based on multiple in questionnaire are presented. Most patients and family participants reported unchanged in disease progression. Fatigue and less active were more reported in patients (20% vs 0, \( p = 0.026 \)). “Others” included sleep not well, chest pain, aching pain in limbs, and catching a cold but recovered.

**Fig. 3.** Medication utilization of PH patients. Utilization of medications is illustrated in percentage according to the answers from patients and family participants respectively. Bosentan, Ambrisentan, Tadalafil, and Sildenafil were most commonly used medications; 57.5% \((n = 69)\) patients and 60.9% \((n = 14)\) family participants chose Ambrisentan while using other medications.
the outbreak, which maintained their optimism. Third, we, the doctors, were active in patients groups, including being available for consultation online, and offering assistance for medication supplement. All these might be helpful to reduce their anxiety.

Our results provided preliminary view in living condition of PH patients during COVID-19 in China; however, several limitations in our study need to be addressed: first of all, there were only 120 PH patients participating in the survey. The small-scale survey might give us some general information, which also might bring bias in some aspects. The results might highlight CHD-PAH, due to that CHD-PAH contributed most in the study population. Further study should try to include more patients to get more details. The questionnaire was designed to generate the information from both patients and their family members; however, we failed to match patients with their family members from the beginning. Studies could avoid such mistakes and focus on patients more. Second, the survey was started 35 days after Wuhan lockdown and lasted 10 days. Most PH patients might be still stable in such a short time. Studies conducted later or longer might observe more clinical worsening and anxiety in patients and their families. Although no death was reported in our survey, three patients passed away.
based on our knowledge. Neither patients nor their families would participate in the survey if they were in critical condition. Therefore, our results might be more optimistic than real world. Follow-up to the real mortality has been initiated. Third, there were many uncertainties in online survey. We involved a question to estimate whether participants were seriously taking the survey. The result showed 86.7% patients and 91.0% family participants went through the survey carefully, which indicated there might be misunderstanding and incorrect answers.

Our small-scale national survey first investigated the living condition of PH patients during COVID-19. As the disease is spreading all over the world, doctors should be aware that PH patients could be vulnerable to COVID-19 if they are in good protection. Sustaining medical care, including medication supplement, is important for PH patients at this time. COVID-19 might impact PH patients psychologically other than physically. Higher hospitalization even death might been seen when the outbreak is over.

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Ethical approval
The study was reviewed and approved by the Ethics Committee of Wuhan Asia Heart Hospital (2020-S-002).

Author contributions
H.Z. and X.Z. designed the study. G.Z., B.J., X.D., Q.Q., M.Y., and X.W. collected data. X.Z. and M.Y. performed the statistical analysis. X.Z. and X.D. wrote the manuscript. H.Z. and G.Z. reviewed and edited the manuscript. All authors read and approved the final manuscript.

Conflict of interest
The author(s) declare that there is no conflict of interest.

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Supplemental material
Supplemental material for this article is available online.

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