

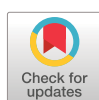


The paradox of pulmonary arterial hypertension in Italy in the COVID-19 era: is risk of disease progression around the corner?

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Abstract

Objective The coronavirus disease 2019 (COVID-19) outbreak has led to significant restrictions on routine medical care. We conducted a multicentre nationwide survey of patients with pulmonary arterial hypertension (PAH) to determine the consequences of governance measures on PAH management and risk of poor outcome in patients with COVID-19.

Materials and methods The present study, which included 25 Italian centres, considered demographic data, the number of in-person visits, 6-min walk and echocardiographic test results, brain natriuretic peptide/N-terminal pro-brain natriuretic peptide test results, World Health Organization functional class assessment, presence of elective and non-elective hospitalisation, need for treatment escalation/initiation, newly diagnosed PAH, incidence of COVID-19 and mortality rates. Data were collected, double-checked and tracked by institutional records between March 1 and May 1, 2020, to coincide with the first peak of COVID-19 and compared with the same time period in 2019.

Results Among 1922 PAH patients, the incidences of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and COVID-19 were 1.0% and 0.46%, respectively, with the latter comparable to

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that in the overall Italian population (0.34%) but associated with 100% mortality. Less systematic activities were converted into more effective remote interfacing between clinicians and PAH patients, resulting in lower rates of hospitalisation (1.2% *versus* 1.9%) and related death (0.3% *versus* 0.5%) compared with 2019 ($p < 0.001$). A high level of attention is needed to avoid the potential risk of disease progression related to less aggressive escalation of treatment and the reduction in new PAH diagnoses compared with 2019.

Conclusion A cohesive partnership between healthcare providers and regional public health officials is needed to prioritise PAH patients for remote monitoring by dedicated tools.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic has led to remarkable global morbidity and mortality [1], causing significant restrictions on routine medical care to comply with public health guidance on public exposure and to help preserve or redirect limited resources [2]. Accordingly, cardiovascular societies have released position statements that predominantly focus on the provision of care, balancing essential heart care services while reducing exposure and preserving healthcare resources to address the pandemic [3–5]. However, focusing on rare disease position statements becomes a challenge without robust data available for inspection. Unfortunately, patients with pulmonary arterial hypertension (PAH) are at increased risk of adverse outcomes, the majority resulting at intermediate- and high-risk [6]. Delays in treatment escalation in such patients would be detrimental. Similarly, reduced access to diagnostic testing could lead to a high burden of undiagnosed naïve patients that would further delay time to treatment. Although there will be a myriad of competing demands in the clinical arena, this risk may warrant the prioritisation of PAH patients as healthcare systems return to normal capacity [7].

Determining the consequences of governance measures on PAH management and the risk of poor outcome in patients with PAH who acquire severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is crucial to determine what mitigation measures are required in the community. Therefore, we undertook a multicentre nationwide survey of PAH patients among the Italian Pulmonary Hypertension Network (iPHNET) between March 1 and May 1, 2020, to coincide with the first peak of COVID-19 in Italy.

Methods

Population and study design

This was a multicentre, observational, nationwide survey conducted in consecutive PAH patients treated and managed in 25 centres participating in the iPHNET during the COVID-19 outbreak, between March 1 and May 1, 2020. The same data were also collected for the equivalent interval (March 1 to May 1) in 2019 for comparative purposes.

Eligible patients were ≥ 18 years old, with idiopathic, heritable or drug- and toxin-induced PAH, connective tissue disease-associated PAH, congenital heart disease PAH, portal-PAH and HIV-PAH. The diagnostic work-up of PAH conformed to the European Respiratory Society/European Society of Cardiology (ERS/ESC) guidelines [8] with the typical haemodynamic profile of precapillary pulmonary hypertension (defined by a mean pulmonary artery pressure ≥ 25 mmHg, a pulmonary artery wedge pressure ≤ 15 mmHg and a pulmonary vascular resistance ≥ 3 Wood Units) and a diagnostic algorithm including pulmonary function tests, ventilation/perfusion lung scan, computed tomography scan and echocardiography.

Treatments were prescribed and follow-up scheduled in accordance with international guidelines, with repeated risk assessment over time based on the ERS/ESC guidelines score [8] and the REVEAL 2.0 score [9].

For each included patient, demographic data, the number of in-person visits, 6-min walk tests (6MWTs), echocardiographic tests and brain natriuretic peptide/N-terminal pro-brain natriuretic peptide (BNP/NT-proBNP) tests available and World Health Organization (WHO) functional class assessment were collected in the two time periods; the presence of elective hospitalisation for right heart catheterisation (RHC), non-elective hospitalisation and need for treatment escalation/initiation were also recorded. Finally, patients with newly diagnosed PAH, the incidence of SARS-CoV-2 infection and the mortality rates among both infected and non-infected PAH patients were recorded.

The study complied with the Declaration of Helsinki and was approved by the Institutional Review Board for human studies of the Policlinico Umberto I – Sapienza University of Rome (coordinator centre EC-Protocol n.683/14).

Data collection, search strategy and quality of data

At each site, a coordinating investigator was responsible for identifying the whole cohort of patients followed in the two time periods, 2019 and 2020. Patients managed by each centre were securely tracked through the local database used for drugs prescription and distribution, because all of the iPHNET centres are prescriber-identified centres from the Italian Health System. Because drugs are delivered on a monthly basis, each centre was able to use an active search to correctly identify those patients with a COVID-19 diagnosis. Data were collected at single centres from the institutional records that were used for the prospective follow-up of PAH patients, using a case report form provided by the coordinating centre. Patient-related information and data on in-person visits, hospital admission and drug prescriptions were cross-checked against records of catheterisation laboratories and/or hospital wards of the same institution. When hospital electronic records of admissions were not available, investigators were asked to verify data with their Department of Management. Data were finally checked for missing or contradictory entries by the coordinator centre of Rome.

Statistical analysis

Continuous data are expressed as mean±SD or median (interquartile range), and categorical data are expressed as counts and proportions. Two-group comparisons were done with unpaired, two-tailed t-tests for means if the data were normally distributed or with Wilcoxon's rank-sum tests if the data were not normally distributed. Chi-squared or Fisher's exact tests were used to analyse the categorical data. No missing data were captured according to the robust data collection strategy.

Results

Study cohort characteristics

Among 25 Italian centres, a total of 1922 PAH patients were treated during the first COVID-19 outbreak, between March 1 and May 1, 2020. Patients' characteristics are shown in table 1. The majority of patients had a diagnosis of idiopathic PAH (n=700; 36.4%), the mean age was 56 years and 1245 (64.8%) were women. Almost half of the patients were in WHO functional classes III–IV (43.0%) with impaired exercise capacity. All patients were treated with targeted therapy according to ERS/ESC guidelines.

TABLE 1 Characteristics of PAH patients and referral centres

Characteristic	Finding
Centres	25
iPHNET	25
Centre location:	
North Italy	10
Central Italy	5
South Italy	9
Health-system prescribers	25
Patients	1922
Age, years	58±11
Female sex	1245 (64.7)
Caucasian race, %	100
PAH subgroup	
Idiopathic	700 (36.4)
Drug induced	21 (1.1)
CTD	151 (7.8)
CHD	436 (22.6)
HIV	59 (3.0)
Portopulmonary	81 (4.2)
Other	210 (10.9)
WHO functional class	
I–II	1096 (57)
III–IV	826 (43)

Data are presented as n, n (%) or mean±SD. PAH: pulmonary arterial hypertension; iPHNET: Italian Pulmonary Hypertension Network; CTD: connective tissue disease; CHD: coronary heart disease; HIV: human immunodeficiency virus; WHO: World Health Organization.

Downsizing of systematic activities in PAH

Systematic activities for 1922 PAH patients between March 1 and May 1, 2020, were compared with those for 1967 PAH patients managed in the same period in 2019. A total of 250 patients attended one in-person visit during the 2020 2-month period, which was a 71.4% reduction on the equivalent period in 2019 ($p<0.0001$), when 875 patients attended one in-person visit (figures 1 and 2). The majority of the in-person visits were registered for patients in WHO functional classes III–IV ($n=158$, 66.7%). This contrasted with the equivalent period in 2019, when the visits were equally distributed between patients with different WHO functional classes.

Nine patients attended two in-person visits and no patients attended three or more visits; this was significantly higher in 2019, with 70 patients attending two visits and 15 attending three or more ($p=0.0001$).

A total of 1672 patients did not visit in person in the 2020 2-month period, which was a 31.4% increase on the equivalent period in 2019 ($p=0.0001$).

Similarly, 88 6MWTs and 240 echocardiographic tests were registered, which was a 84.2% and 70.9% reduction, respectively, on the equivalent period in 2019, when 558 and 824 tests were performed, respectively ($p<0.001$).

With respect to biomarkers, BNP/NT-proBNP data were available for only 153 patients, considering both in-person visits and remote visiting, which corresponds to a 76.7% reduction in available tests compared with the equivalent period in 2019 ($n=657$; $p<0.001$).

A total of 1682 patients did not perform tests in the 2020 2-month period, which is a 29.4% increase on the equivalent period in 2019 ($p=0.0001$).

Concerning elective hospitalisation for RHC periodic evaluation, 27 procedures were performed during the COVID-19 outbreak, corresponding to an 80.8% reduction on the equivalent period in 2019 ($p<0.001$) (figures 2 and 3).

Finally, only 14 patients were newly diagnosed with PAH between March 1 and May 1, 2020, corresponding to a 72.5% reduction on the equivalent period in 2019 ($p<0.001$) (figures 2 and 4).

Withdrawal of in-person-directed medical management and outcomes

The hospitalisation rate for heart failure in patients treated between March 1 and May 1, 2020, was 1.2%, which was significantly lower than that in the equivalent period in 2019 (1.9%; $p<0.001$). This

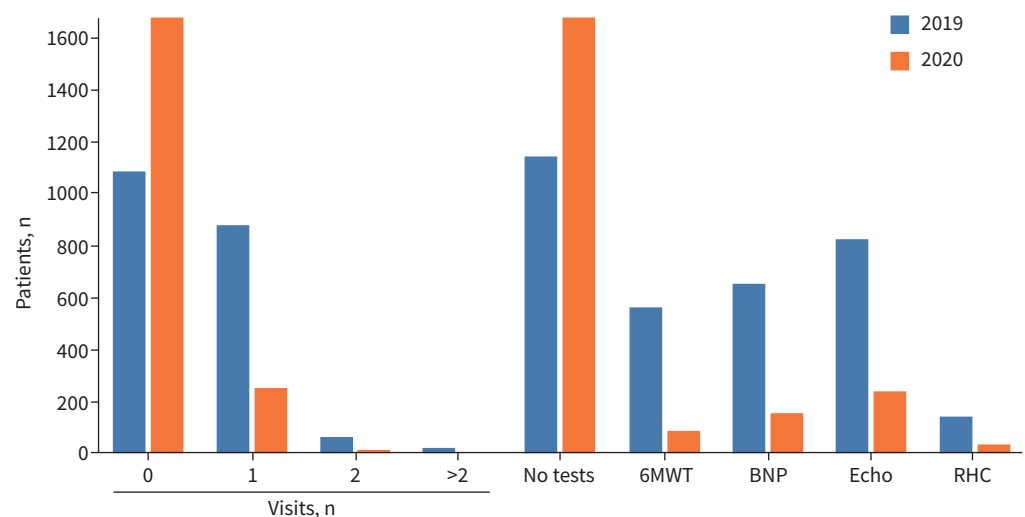


FIGURE 1 Systematic activities and relevant tests between March 1 and May 1, 2020, compared with the equivalent period in 2019. Overall number of pulmonary arterial hypertension patients performing in-person visits and tests are shown. 6MWT: 6-min walk test; BNP: N-terminal pro-brain natriuretic peptide; Echo: echocardiogram; RHC: right heart catheterisation.

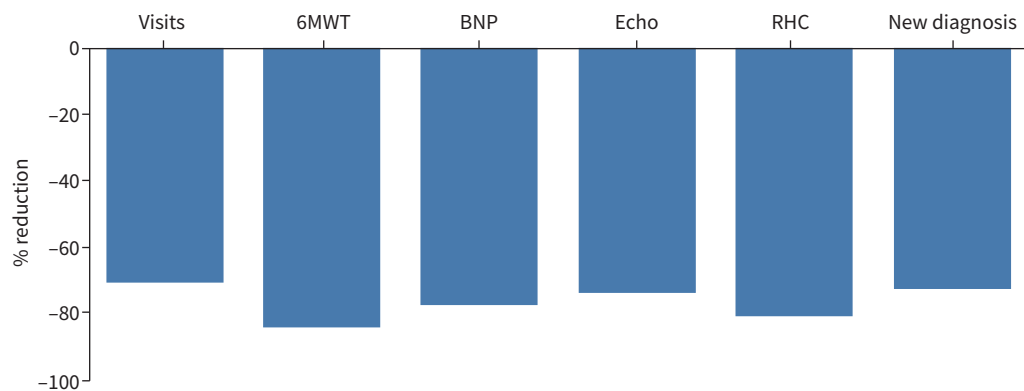


FIGURE 2 Reduction in systematic activities and relative tests for pulmonary arterial hypertension patients between the two time periods. Percentage reduction from 2019 and 2020 has been reported. 6MWT: 6-min walk test; BNP: N-terminal pro-brain natriuretic peptide; Echo: echocardiogram; RHC: right heart catheterisation.

corresponds to a 36.1% reduction in hospitalisation for heart failure, from 36 patients in 2019 to 23 patients in 2020. Additionally, patients during the COVID-19 outbreak were less likely to receive elective sequential add-on therapy compared with the equivalent period in 2019 (n=24, 1.2% versus n=97, 5.0%; p<0.001), while higher rates were observed for sequential add-on therapies in patients hospitalised for heart failure (n=15, 65.2% versus n=15, 41.6%; p<0.001) (figures 3 and 4).

Finally, all cause mortality (not including COVID-19) was lower among PAH patients between March 1 and May 1, 2020, compared with the previous year (n=6, 0.3% versus n=10, 0.5%; p<0.001) (figure 3).

Incidence of SARS-CoV-2 infection and outcomes

Between March 1 and May 1, 2020, 20 PAH patients received a diagnosis of SARS-CoV-2 infection (1.0%), while nine patients had a diagnosis of COVID-19, corresponding to an incidence of 0.46%. The latter patients were admitted to hospital and received noninvasive or invasive ventilation at any time during hospitalisation and all of them died within 30 days from presentation (figure 3).

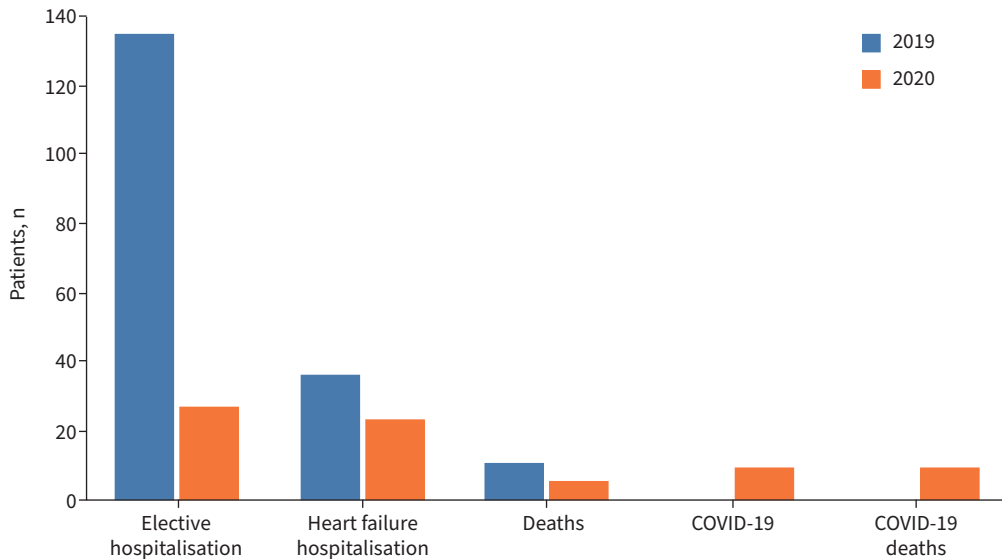


FIGURE 3 Hospitalisation for heart failure and mortality rates for non-infected pulmonary arterial hypertension (PAH) patients from March 1 to May 1 2020 compared with the equivalent period in 2019. COVID-19 PAH patients are reported in separate histograms.

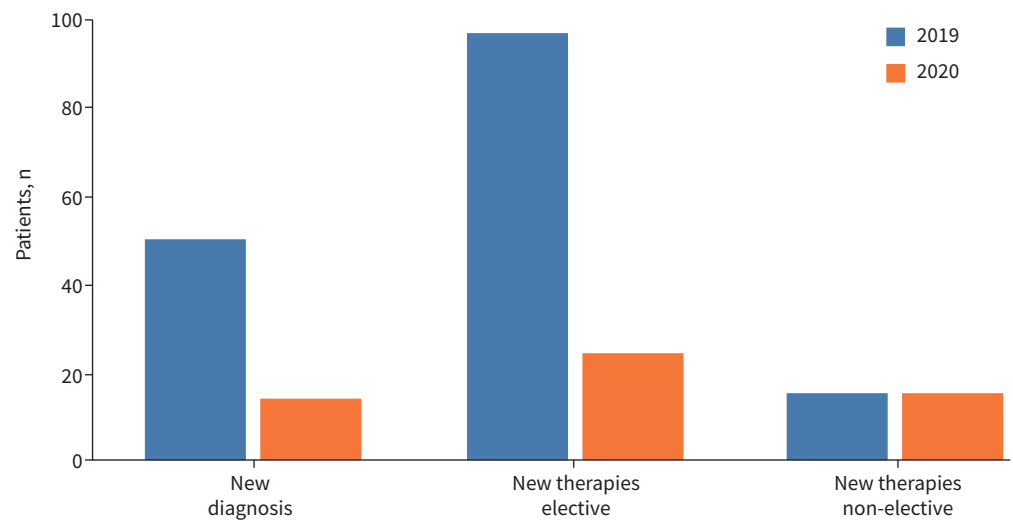


FIGURE 4 Number of new pulmonary arterial hypertension diagnoses, elective sequential add-on therapies and non-elective sequential add-on therapies from March 1 to May 2, 2020, compared with the equivalent period in 2019.

With regards distribution throughout the country, in North Italy the incidence of COVID-19 among PAH patients in the study period was 0.87% (seven cases), while in Central and South Italy it was 0.17% (one case) and 0.14% (one case), respectively.

Discussion

To accurately understand the risk of COVID-19 and inform decision- and risk-matrices going forward, the iPHNET community undertook an audit of patients with PAH between March 1 and May 1, 2020, to coincide with the first peak of COVID-19 within Italy. These data represent the largest assessment of the impact of SARS-CoV-2 infection on patients with PAH to date based on patient-level information.

The main finding of the present study was the significant decrease in the number of PAH outpatient visits and PAH-related tests across Italy during the COVID-19 outbreak. Indeed, case volumes of outpatient clinics downsized to 20–30% during the pandemic of the equivalent period in the previous year. The second unexpected finding to emerge from our study, and shown for the first time, is the low morbi-mortality rates in the PAH cohort despite the apparent toned-down level of care from the previous year. Finally, we found an exceptionally low incidence of COVID-19 among PAH patients in contrast to those with other chronic lung and heart diseases, but still with a very high mortality rate.

Identifying the mechanisms behind the unusual behaviour of a severe disease like PAH in relation to COVID-19 is beyond the scope of the present study. Nevertheless, it is tempting to speculate that a number of factors, rather than a unique determinant, contributed to the phenomenon.

Chronic diseases like PAH are considered to be fragile clinical conditions; therefore, close monitoring of specific sets of parameters, largely included in current European and US risk scores, positively influences patient outcomes, reducing intercurrent acute events and related hospitalisations, when applied in clinical practice [8, 10, 11]. Tragically, COVID-19 has placed an enormous strain on the healthcare systems of nations in which it has spread widely, and the disease has specific implications on clinical practice. In Italy the Government established a stepwise strategy starting from the complete lockdown of initial foci in Northern Italy on February 20, 2020, and subsequent adoption of progressively more stringent lockdown measures for the entire nation as of March 8, 2020 [12]. All systematic activities at centres, including elective hospitalisation and procedures, were cancelled and non-urgent outpatient visits were discouraged. Although the degree of disruption to usual practice varied across regions owing to differences in population density, rates of community spread, time to peak disease burden and resource availability, institutions were stretched in an effort to preserve resources and avoid exposure of patients to the hospital environment, where COVID-19 has been more prevalent. In PAH centres, patients' scheduled clinic visits

were postponed, leading to a dramatic reduction in the number of overall outpatient visits compared with the previous year. Periodic risk assessment through the European and REVEAL score tools were often unfeasible; 6MWTs and pro-BNP measurement were largely unavailable to clinicians. Elective hospitalisation for RHC needed to be postponed multiple times, again causing a significant reduction in the number of procedures compared with the same period of the previous year. These data are in agreement with the estimates of cumulative data from a large cross-sectional anonymous survey of programme directors at accredited pulmonary hypertension centres in the USA [13] and from an international survey [14], and confirm the substantial impact of COVID-19 on clinical operations at centre level.

It would be expected that downsizing these systematic activities would significantly increase hospitalisations for heart failure and negatively impact on patients' outcomes, leading to higher mortality rates when compared to standard of care. However, this was paradoxically not the case for PAH, as evidenced by lower mortality rates compared with the same period of the previous year and even lower hospitalisation rates for right heart failure.



FIGURE 5 Schematic illustration of remote interfacing between clinicians and pulmonary arterial hypertension (PAH) patients following less systematic activities during the COVID-19 outbreak. WHO: World Health Organization.

In our opinion, this could be at least in part related to the great changes that the last two decades have witnessed in Italy in the field of PAH. While the pandemic was evolving, without predetermined planning, networking among clinicians and the sharing of experiences between high- and low-volume centres throughout the country brought many benefits that allowed clinicians to reassure and maintain doctor–patient relationships and promoted the adoption of similar procedures with key features of programmes for periodic follow-up and patient support [15]. As a result, close communication with patients became a prime characteristic of all pulmonary hypertension centres, a critical issue to ensure ongoing delivery of optimal cardiac care, with less systematic activities encouraging more effective remote interfacing between clinicians and PAH patients (figure 5). Because all procedures that were originally scheduled for the next 2 months were cancelled, patients were subsequently categorised and reprioritised in the majority of centres. Given the limitations of telemedicine among PAH centres, a large proportion of outpatients received a follow-up call within 1–2 weeks of the initial encounter to ensure they were stable prior to scheduling future check-ins according to their tier of risk. According to common sense, patients known to be low risk and found to be stable on a phone-call basis were managed conservatively and in-person visits were postponed until a safer date. For patients known to be intermediate risk, case decisions were individualised, taking into account the risk of COVID-19 exposure *versus* the risk of a delay in disease progression recognition and treatment escalation, and usually resulting in check-in calls every 1–3 months. By contrast, high-risk patients usually received at least weekly or biweekly check-in calls and when possible were offered the option to keep the original appointment, especially in Central and South Italy where the spread of COVID-19 was less pressing. In cases where there was a likelihood of rapidly worsening symptoms, an intervention was deemed urgent and patients were hospitalised under safe, controlled procedures when possible or, more frequently, as in North Italy, through the emergency department.

This empirical approach requires close and attentive follow-up of patients at a future date to identify disease progression that potentially occurred during the COVID pandemic. Indeed, less aggressive escalation of treatment was recorded in the 2020 period compared with 2019.

A further important finding from our study covers the unknown incidence of acquired SARS-CoV-2 infection and COVID-19 among PAH patients in Italy. Indeed, the risk for patients with PAH has not yet been quantified because patients with uncommon diseases may not be accurately reported with specific diagnostic information in the administrative healthcare datasets that are used for large observational studies. The incidence of SARS-CoV-2 infection, reported for the first time in an Italian PAH cohort, was 1.0%, while the incidence of COVID-19 was very close to that reported for the overall Italian population in the same period (0.46% *versus* 0.34%) [16], and similar to the estimated rate in the US PAH population (0.29%) [13]. With regards the distribution throughout the regions of the country, in North Italy the incidence of COVID-19 among PAH patients during the study period was 0.87% (seven cases), very close to that reported in the general population (0.76%). Similar results were found for Central Italy, with 0.17% (one case) *versus* 0.20%, and South Italy, with 0.14% (one case) *versus* 0.11%. Our observation is in contrast with other studies that have identified patients with chronic diseases, *e.g.* diabetes mellitus, ischaemic heart disease and other non-PAH chronic pulmonary diseases, as a vulnerable group with a high incidence of COVID-19 with a poor outcome [17–21], including a case–control study conducted in Italy [22]. In Tuscany (Central Italy), between March and April 2020, a higher incidence of COVID-19 infection was found among patients with chronic diseases such as diabetes mellitus, ischaemic heart disease and chronic obstructive pulmonary disease compared with the general population: 0.32%, 0.38% and 0.43%, respectively [22]. An increased risk of COVID-19 infection was shown in patients with chronic diseases even adjusting for age, sex and other comorbidities.

This result may partially reflect the self-isolation chosen by many patients during the pandemic, leading to apparent protection from COVID-19. In addition, because the vast majority of patient–physician interactions during the COVID-19 outbreak were remote, clinicians from PAH centres provided clear guidance on when to request phone consultations or urgent in-person evaluations to minimise risk of transit-related and hospital-related infection. Frequent, transparent communication gave patients confidence that their care was not being neglected, avoiding in-person attempts to get in touch with the clinical team. Finally, we may further consider the reduced angiotensin converting enzyme 2 (ACE-2) expression shown in PAH [23], the contrasting viral entry mechanism, and the potential protective effects of PAH-targeted therapies against SARS-CoV-2 infection as suggested by some authors [24, 25].

Nevertheless, these data demonstrate that patients with PAH are at increased risk of death following hospitalisation for COVID-19, with 100% mortality rates, in keeping with data already reported for other severe chronic diseases [26–28].

The final, not unexpected, finding from our study was the dramatic reduction in the number of new PAH diagnoses across Italy during the COVID-19 pandemic. This was in line with other diseases, even when acute conditions were considered as acute coronary syndromes [29, 30], and mainly reflects patients' fear of contagion, especially after the media reported the infection spread across hospitalised patients and healthcare personnel due to the lack of appropriate personal protection equipment at an early stage of the pandemic. A further explanation is related to the shift-based allocation of clinicians needed to operate in other hospital COVID areas. This might have induced an attitude towards deferral of less urgent cases at the healthcare system levels with a consequent reduction in referral to PAH centres of patients with suspected PAH. This may have led to delays in patients' treatment initiation with important prognostic implications in the near future.

Interestingly, when written in Chinese the word crisis (*weiji*) is composed of two characters. One represents danger (*wei*), while the other opportunity or crucial point (*ji*). Our National Health System has speculated on implementing telemedicine many times over the last two decades. Now that the Loosened Health Insurance Portability and Accountability Act (HIPAA) [31] rules have enabled the use of alternative modes of patient communication, such as personal phones for medical calls, e-mailing and web conferencing applications to facilitate a video encounter, the benefits now outweigh the risks and the Italian Government can use this opportunity to enhance and support the conversion of local hospital administration from traditional visits to telehealth visits [32, 33]. Indeed, telehealth applications are one of the main goals of the Recovery Plan of the Italian Government [34], in accordance with the Annual Sustainable Growth Strategy of the European Committee, where remote devices will be implemented and expanded throughout the country.

Strengths and limitations

Owing to the retrospective nature of the data collection, recall bias might have led to under-selection of PAH patients at each centre. However, this is mitigated by the official requirement for PAH-treatment prescription that occurs on a personal basis [33], allowing each centre to know the exact number of patients managed. Therefore, this turns out to be a strength of the present study compared with other studies on largely prevalent chronic diseases.

Conclusions

We believe these data demonstrate the importance of multicentre collaboration to collect data to understand the consequences of emerging threats to patients with PAH. Our results show low incidence of COVID-19 among PAH patients, but high risk of mortality, in keeping with other chronic diseases. Equally important, paradoxically less systematic activities encouraged more effective remote interfacing between clinicians and patients, allowing lower rates of hospitalisation for heart failure and mortality compared with the previous year, and potentially reducing the risk of patient infection. However, a high level of attention is needed to avoid the potential risk of disease progression in the near future related to the less aggressive escalation of treatment and the reduction in new PAH diagnoses compared with 2019. Thus, we strongly suggest that PAH continues to be regarded as a high frailty condition and that patients follow national self-isolation guidelines for vulnerable individuals and are prioritised within the Recovery Plan policy document for remote monitoring by dedicated tools through a cohesive partnership with regional public health.

As the medical community gains more experience dealing with the various issues raised by the COVID-19 pandemic, the present study represents an opportunity to exchange experiences and best practices.

Conflict of Interest: All authors have nothing to disclose.

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