Early View

Original research article

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

Short title: PAH in the COVID-19 era in Italy

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Abstract

Objective: The coronavirus disease-2019 (COVID-19) oubreak has led to significant restrictions on routine medical care. We conducted a multicenter nationwide survey of PAH patients aiming at determining the consequences of the Governance measures on PAH management and risk of poor outcome in patients with COVID-19.

Meterials and Methods: Demographic data, number of in-person visits, 6-minutes walk and echocardiographic tests, BNP/NT-proBNP tests, WHO functional class assessment, presence of elective and non-elective hospitalization, need for treatment escalation/initiation, newly diagnosed PAH, incidence of COVID-19 and mortality rates were considered in the present study including 25 Italian centers. Data were collected, double checked and tracked by institutional records, between the 1ˢᵗ March and 1ˢᵗ May 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 incidence of SARS- CoV-2 infection and COVID-19 was 1.0% and 0.46%, respectively, the latter comparable to 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 allowing lower rates of hospitalization and related death compared with 2019 (1.2% and 0.3% vs 1.9% and 0.5%, respectively; $p<0.001$). 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 diagnosis compared with 2019.

Conclusion: Cohesive partnership of health care providers with regional public health officials is needed to prioritize PAH patients for remote monitoring by dedicated tools.

Summary
COVID-19 showed low incidence among PAH patients, but high mortality rates. High level of attention is needed to avoid in the near future the potential risk of disease progression.

Keywords: pulmonary arterial hypertension, COVID-19, SARS-CoV-2, infection, mortality, hospitalization.

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, the cardiovascular societies have released position statements that predominantly focus on the provision of care balancing essential heart care services while reducing exposure and preserving health care resources to address the pandemic (3-5). However, focusing on rare disease position statements become 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 the treatment escalation of such patients would be detrimental. Similarly, reduced access to diagnostic testing would lead to a high burden of undiagnosed naïve patients that will further delay time to treatment. Although there will be a myriad of competing demands in the clinical arena, this risk may warrant the prioritization of PAH patients as health care systems return to normal capacity (7).

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

Methods

Population and study design

This is a multicenter, observational, nationwide survey conducted in consecutive PAH patients, treated and managed in 25 centers participating to the Italian Pulmonary Hypertension Network (iPHNET) during the COVID-19 outbreak, between 1st March and 1st May 2020. The same data were also collected for the equivalent time-interval 1st March to 1st May 2019 for comparative purposes.

Eligible patients were ≥ 18 years old, with idiopathic, heritable or drug- and toxin-induced PAH, connective tissue disease PAH, congenital heart disease PAH, portal-PAH, and HIV-PAH. The diagnosic work-up of PAH conformed to the ESC/ERS guidelines (8) with the typical hemodynamic profile of precapillary pulmonary hypertension (defined by a mean pulmonary artery pressure-mPAP ≥ 25 mmHg, a pulmonary artery wedge pressure -PAWP ≤15 mmHg, and a PVR ≥ 3 Wood Units) and a diagnostic algorithm including pulmonary function tests, ventilation/perfusion lung scan, computer 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, 6MWTs, echocardiographic tests, BNP/NT-proBNP tests available and WHO functional class assessment were collected in the two time-periods; the presence of elective hospitalization for RHC, non-elective hospitalization, need for treatment escalation/initiation were also recorded.

Finally, newly diagnosed PAH patients, the incidence of SARS- CoV-2 infection and mortality rate of 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 center 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 center were safely tracked through the local database used for drugs prescription and distribution, as all of the iPHNET centers are prescriber-identified centers from the Italian Health System. As drugs are delivered on a monthly basis, each center was able to correctly identify those patients with a COVID-19 diagnosis by an active search. Data were collected at single centers from their institutional records that were used for the prospective follow-up of PAH patients, using a case report form provided by the coordinating center. Patient-related information and data on in-person visits, hospital admission and drugs prescription were cross-checked against records of catheterization laboratories and/or hospital wards of the same institution. When hospital electronic records of admissions were not available, investigatiors were asked to verify data with their Department of Management. Data were finally checked for missing or contradictory entries by the coordinator center of Rome.

Statistical analysis

Continuous data are expressed as mean ± standard deviation or median and interquartile range (IQR), 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 square or Fisher's exact tests were used to analyze the categorical data. No missing data were captured according to the robust data collection strategy.

Results

Study cohort characteristics

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

Down-sizing of systematic activities in PAH

Systematic activities for 1922 PAH patients between 1st March and 1st May 2020 were compared with those for 1967 PAH patients managed in the same period 2019. A total of 250 patients performed one in-person visit during the 2020 two-months period, with a 71.4% reduction compared with the equivalent period in 2019 (p < 0.0001), when 875 patients were

visited (figure 1, 2). The majority of the in-person visits were registered for patients in WHO functional class III-IV (158, 66.7%), in contrast with the equivalent period in 2019, when the visits were equally distributed between patients with different WHO functional class.

Nine patients performed 2 in-person visit and none $\geq$ 3 visits, while a significantly higher percentage was registered in 2019, respectively, 70 and 15 patients (p=0.0001).

A total of 1672 patients did not perform an in-person visit in the 2020 two-months period, whith a 31.4% increase compared with the equivalent period in 2019 (p=0.0001).

Similarly, a total of 88 6MWTs and 240 echocardiographic tests were registered, with a 84.2% and 70.9% reduction, respectively, compared with 2019, when 558 and 824 tests were performed, respectively (p<0.001).

Respect to biomarkers, the BNP/NT-proBNP was available only for 153 patients, considering both in-person visits and remote visiting, corresponding to a 76.7% reduction of the available tests compared with the equivalent period 2019 (657)(p<0.001).

A total of 1682 patients did not perform tests in the 2020 two-months period, whith a 29.4% increase compared with the equivalent period in 2019 (p=0.0001).

Concerning elective hospitalization for RHC periodic evaluation, 27 procedures were performed during the COVID-19 outbreak, corresponding to an 80.8% reduction compared with the equivalent period in 2019 (p<0.001) (figure 2, 3).

Finally, the number of newly diagnosed PAH patients decreased down to 14 between 1st March and 1st May 2020, corresponding to a 72.5% reduction compared with the equivalent period in 2019 (p<0.001)(figure 2, 4).

Withdrawal of in-person-directed medical management and outcomes

The hospitalization rate for heart failure of patients managed between March 1st and May 1st 2020 was 1.2%, resulting significantly lower compared with the equivalent period 2019 (1.9%; p< 0.001). This corresponds to a 36.1% reduction in hospitalization for heart failure, from 36 patients in 2019 to 23 in 2020. Additionally, patients during the COVID-19 outbreak were less likely to receive elective sequential add-on therapy compared with the equivalent period 2019 (24, 1.2% vs 97, 5.0%, p<0.001), while higher rates were observed for sequential add-on therapies in hospitalized patients for heart failure (15, 65.2% vs 15, 41.6%, p<0.001)(figure 3,4).

Finally, a lower proportion of PAH patients died for all cause mortality (not COVID-19) from March 1st and May 1st 2020 compared with the previous year (0.3% (6) vs 0.5% (10), p<0.001)(figure 3).

Incidence of SARS- CoV-2 infection and outcomes

Between March 1st and May 1st 2020, 20 PAH patients received a diagnosis of SARS- CoV-2 infection (1.0%), while 9 patients had a diagnosis of COVID-19, corresponding to an incidence of 0.46%. The latter patients were admitted to hospital and received non-invasive

or invasive ventilation at any time during hospitalization and all of them died up to 30 days from presentation (figure 3).
Considering regions distribution throughout the Country, in the North of Italy the incidence of COVID-19 among PAH patients in the study period was 0.87% (7 cases), while in the Central and in the South of Italy, respectively, 0.17% (1 cases) and 0.14% (1 case).

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 the 1st of March and 1st of May 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 is the significant decrease in the number of PAH out-patient 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 compared with the equivalent period of the previous year. The second unexpected finding emerged from our study for the first time is the low morbi-mortality rates in the PAH cohort in spite of 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 other chronic lung and heart diseases, but still with very high mortality rate.

The identification of the mechanisms that brought to such unusual behavior for a severe disease as PAH are beyond the scope of the present study. Nevertheless, it is tempting to speculate that probably a number of factors, rather than a unique determinant, contributed to the phenomenon.

Chronic diseases as PAH are considered a fragile clinical condition, therefore sustaining the close monitoring of specific sets of parameters, largely included in current European and U.S. risk scores, positively influences patient's outcomes, reducing intercurrent acute events and related hospitalizations when applied in clinical practice (8,10,11). Tragically, COVID-19 has placed an enormous strain on the health care systems of the nations where it has spread widely, with specific implications of the disease on clinical practice. In Italy the Government established a stepwise strategy starting from the complete lockdown of initial foci in Northern Italy on February 20th 2020 and subsequent adoption of progressively more stringent lockdown measures of the entire Nation as of March 8th(12). All systematic activities at centers, including elective hospitalization and procedures, were cancelled and nonurgent outpatient visits were discouraged. Although the degree of disruption to usual practice varied across regions due to differences in population density, rates of community spread, time to peak disease burden, and resource availability, institutions were pulled in an effort to preserve resources and avoid exposure of patients to the hospital environment, where COVID-19 has been more prevalent. In PAH centers patients scheduled for clinic visits were postponed until a future date, leading to a dramatic reduction of the overall outpatient visits compared with the previous year. Periodic risk assessment through the European and REVEAL score-tools were often unfeasible; 6MWT and pro-BNP were largely unavailable to clinicians. Elective hospitalization for RHC needed to be postponed multiple times, again with significant reduction 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 program directors at accredited PH centers in the U.S. (13) and from an international survey (14), and definitely confirm the substantial impact of COVID-19 on clinical operations at centers level.

Therefore, down-sizing these systematic activities would expect to significantly increase hospitalization for heart failure and negatively impact on patients' outcome leading to higher mortality rate when compared to standard of care. However, this was paradoxically not the case for PAH, as resulted from lower mortality rates compared with the same period of the previous year and even lower hospitalization rates for right heart failure.

In our opinion, this could be at least in part related to the great changes that the last two decades have been witnessed in Italy in the field of PAH. While the pandemic was evolving, without predetermined planning, networking among clinicians and sharing experiences between high- and low-volume centers throughout the Country brought to a virtuous circle allowing retain existing patients and promoting referral of similar procedures with key features of programs for periodic follow-up and patients support (15). As a result a close communication with patients became a paramount characteristic of all PH centers, a critical issue to ensure ongoing delivery of optimal cardiac care, allowing less systematic activities to become more effective remote interfacing with patients (figure 5). As all procedures that were originally scheduled for the next 2 months were canceled, patients were subsequently categorized and reprioritized in the majority of centers. Given the limitations of telemedicine among PAH centers, a great proportion of outpatient received a follow-up call within 1 to 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, for patients known to be at low risk and found to be stable on a phone-call basis, a conservative approach was undertaken postponing an in-person visit until a safer date will become available. For patients known to be at intermediate risk, case decisions were individualized, taking into account the risk for COVID-19 exposure versus the risk for delay in disease progression recognition and treatment escalation, and usually ending in check-in calls every 1 to 3 months. In contrast, high risk patients received usually at least weekly or biweekly check-in calls and when possible were offered the option to keep the original appointment, especially in the Center and South of Italy were the COVID-19 spread was less pressing. In case of likelihood of rapidly worsening symptoms an intervention was deemed urgent and patients were hospitalized under safe-controlled procedures when possible or more frequently, as in the North of Italy, through the Emergency Department.
Nevertheless, such empirical approach will require a close and attentive follow-up of patients when a future date will become safer to recognize disease progression potentially occurred during the COVID pandemic. Indeed, less aggressive escalation of treatment was recorded in the latter period compared with 2019.
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, such a 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 administrative healthcare datasets which are used for large observational studies. The incidence of SARS- CoV-2 infection emerged for the first time in our cohort was found to be 1.0%, while the incidence of COVID-19 was very close to the one reported for the overall Italian population in the same period (0.46% vs 0.34%)(16), and similar to the estimated rate in the U.S. (0.29%) PAH population (13). Considering regions distribution throughout the Country, in the North of Italy the incidence of COVID-19 among PAH patients in the study period was 0.87% (7

cases), very close to the one reported in the general population (0.76%), as well as in the Central and in the South of Italy, respectively, 0.17% (1 case)(general population: 0.20%) and 0.14% (1 case)(general population: 0.11%). Our observation is in contrast with other studies which have identified chronic diseases, like diabetes mellitus, ischemic heart disease, and other non-PAH chronic pulmonary diseases, as a vulnerable group of patients at high incidence of COVID-19 with poor outcome (17-21), including a case-control study conducted in Italy (22). In Tuscany region (Central Italy), between March and April 2020, chronic diseases, as diabetes mellitus, ischemic heart disease, and COPD were found at higher incidence of COVID-19 compared with the general population, respectively, 0.32%, 0.38% and 0.43% (22). Chronic diseases showed an increased risk of COVID-19 even adjusting by age, sex and other comorbidities.

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

Nevertheless, these data demonstrate that patients with PAH are at increased risk of death following hospitalization for COVID-19, with 100% mortality rates, in keeping with data already reported for other severe chronic diseases (26,27,28).

Last but not least expected finding from our study was the dramatic reduction in the number of new PAH diagnosis across Italy during the COVID-19 pandemic. This was in line with other diseases, even when acute conditions have been considered as acute coronary syndromes (29,30), and mainly reflects patients fear of contagion, especially after the media shed light on the infection spread across hospitalized 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 a 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 consequent reduction of referral to PAH centers of suspected PAH patients. This may lead to potential delay in patient's 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 speculated on implementing telemedicine many times over the last two decades. Now that the Loosened Health Insurance Portability and Accountability Act (HIPAA)(31) rules 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, with benefits now outweighing risks, the Italian Government has finally the chance to enhance and support the local hospital administration to convert 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 to the Annual Sustainable Growth Strategy of the European Committee, where remote devices will be implemented and expanded throughout the Country.

Strengths and limitations

Due to the retrospective nature of the data collection recall bias might have led to under-selection of PAH patients at each center. However, this is mitigated by the official requirement for PAH-treatment prescription that occurs on a personal basis (33), allowing each center to know the exact number of patients managed. Therefore, it turns to be a strength of the present study among others on largely prevalent chronic diseases.

Conclusions

We believe these data demonstrate the importance of multicenter 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 became more effective remote interfacing with patients allowing lower rates of hospitalization for heart failure and of mortality compared with the previous year, and potentially reducing the risk of patient's infection. However, high level of attention is needed to avoid in the near future the potential risk of disease progression related to less aggressive escalation of treatment and the reduction in new PAH diagnosis compared with 2019. Thus, we strongly suggest that patients with PAH continue to be regarded as a high frailty condition and follow national self-isolation guidelines for vulnerable individuals and be prioritized 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.

Table 1. Characteristics of PAH patients and referral centers.

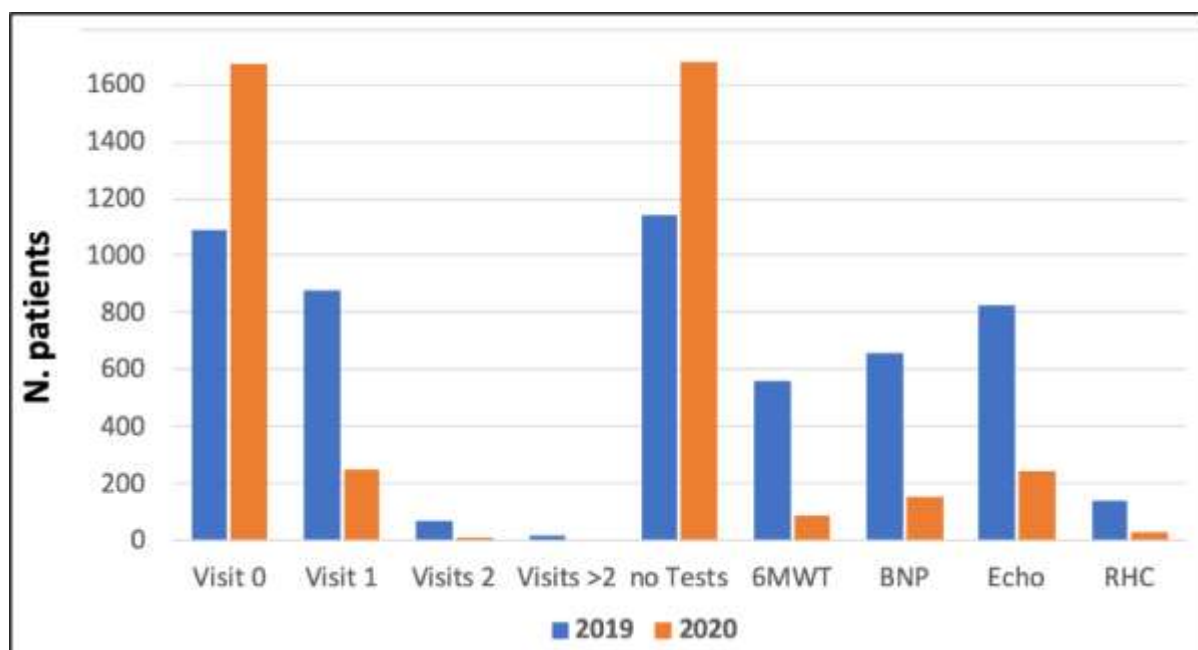|	
Number of Centers, n	25
iPHNET, n	25
Center Location:	
North Italy, n	10
Center Italy, n	5
South Italy, n	9
Health-System prescribers, n	25
Patients, n	1922
Age, years	58±11
Sex, F (%)	1245 (64.7)
Race - caucasian, %	100
PAH subgroups, %	
Idiopathic	700 (36.4)
Drug induced	21 (1.1)
CTD	151 (7.8)
CHD	436 (22.6)
HIV	59 (3.0)
Portopulmonary	81 (4.2)
Others	210 (10.9)
WHO functional class, %	
I-II	1096 (57)
III-IV	826 (43)

Figure 1. Systematic activities and relative tests between 1st March and 1st May 2020 compared with the equivalent period in 2019. Overall number of PAH patients performing 0, 1, at least one in-person visits, number of 6MWTs, echocardiograms, RHC, and NT-proBNP available are shown in the histogram. Blue (2019) and orange (2020).

Legend. 6MWT: 6-minutes walk test; *RHC*: right heart catheterization; *NT-proBNP*: pro-brain natriuretic peptide.
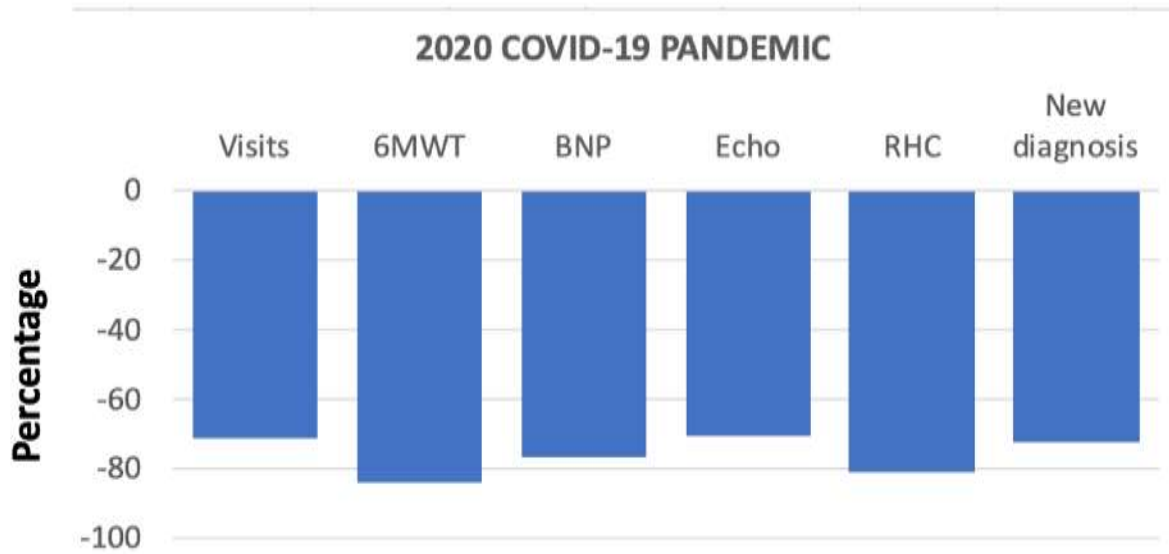
Figure 2. Reduction of systematic activities and relative tests for PAH patients between the two time-periods. Percentage reduction have been reported for different activities from 2019 and 2020.

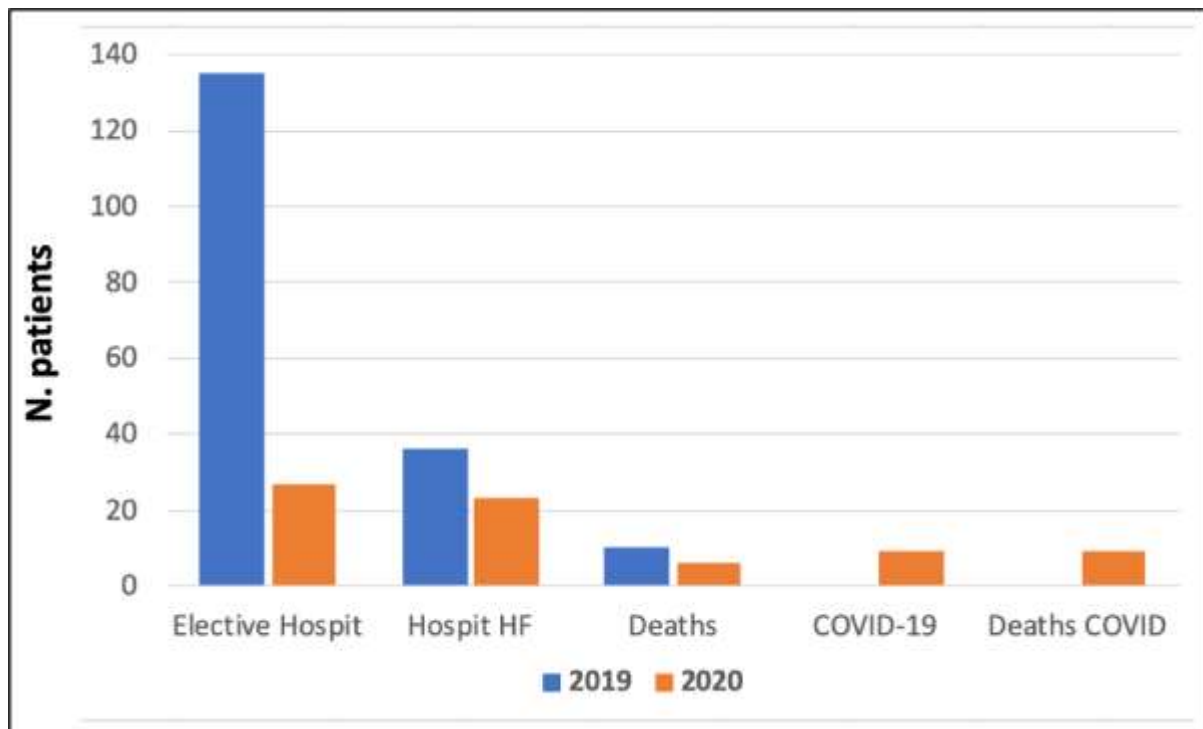Figure 3. Hospitalization for heart failure and mortality rates for non-infected PAH patients, from 1st March to 1st May 2020 compared with the equivalent period in 2019. COVID-19 PAH patients are reported as separated histograms.
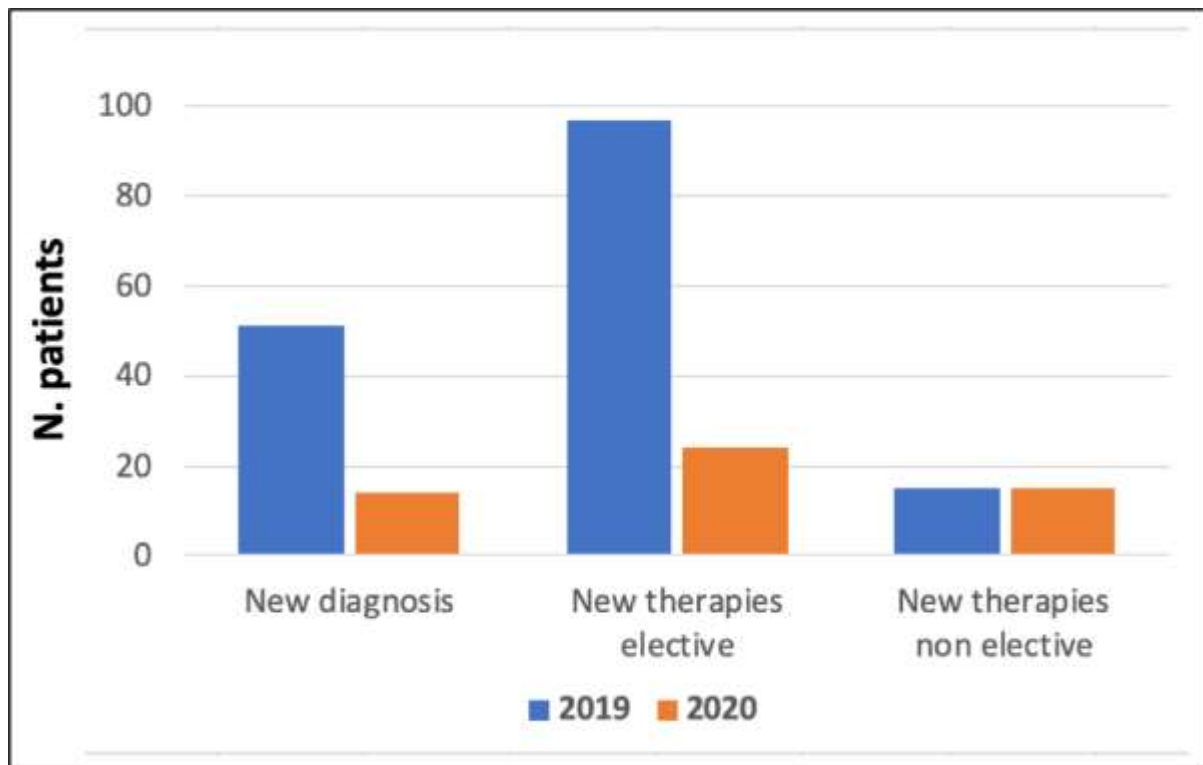
Figure 4. Number of new PAH diagnosis, elective sequential add-on therapies and non-elective sequential add-on therapies, from 1st March to 1st May 2020 compared with the equivalent period in 2019.

Covid-19 emergency

Non-urgent PAH systematic activities cancelled or postponed

follow-up call within 2 weeks of the initial encounter
to prioritize future check-ins

According to historical risk assessment
supported on a phone-call basis

(Medical judgement based on symptoms, vital signs, body weight, WHO functional class, lab tests)

LOW RISK   **INTERMEDIATE RISK**   **HIGH RISK**

Conservative approach
- Postponed visit until safer date
- Confirmation ongoing therapy

Individualized decision
- Balanced for risk exposure versus delay in disease progression
  → phone calls versus in-person visit

Active approach
- Weekly/biweekly phone calls
- In-person visit when possible
- Hospitalization through safe covid-free path when possible

Figure 5. Schematic illustration of remote interfacing between clinicians and PAH patients following less systematic activities during the COVID-19 outbreak.

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APPENDIX

The paradox of pulmonary arterial hypertension in Italy in the COVID-19 era: why less could be more

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