Trends in COVID-19-associated mortality in patients with pulmonary hypertension: a COMPERA analysis

Received: 20 Dec 2022
Accepted: 26 March 2023

To the Editor:

Patients with pulmonary hypertension (PH) have been among those affected heavily by the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Early case series reported case fatality rates ranging from 19–45% in small series of 11–70 patients with PH who contracted COVID-19 [1–4]. A prospective series of 211 French patients with various forms of PH, who developed COVID-19 between February 2020 and April 2021, found an overall case fatality rate of 24.6% [5].

The COVID-19 pandemic has changed over time. In many communities, there is now a background immunity due to vaccination programmes and previous infections, and treatment strategies have evolved. In addition, the Omicron variants of SARS-CoV-2, which have been the predominant virus strains in Europe since January 2022, are associated with a higher transmissibility but a lower mortality than previous variants [6].

To our knowledge, no data are available on mortality rates associated with COVID-19 among patients with PH in the most recent period of the pandemic. Therefore, we assessed the COMPERA (Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension) database to compare COVID-19-associated case fatality rates before and since January 2022.

COMPERA, a European PH registry (www.compera.org; ClinicalTrials.gov identifier NCT01347216) that captures data from patients with all forms of PH who receive PH medications, has prospectively collected information on SARS-CoV-2 infections since the beginning of the pandemic. About 80% of the patients enrolled into COMPERA are from Germany, with the rest from other participating countries (Austria, Belgium, Greece, Hungary, Italy, Latvia, Lithuania, the Netherlands, Slovakia, Switzerland and the UK). We identified adult patients with at least one SARS-CoV-2 infection confirmed by PCR or antigen testing up to 5 November, 2022. We compared the case fatality rates of patients with PH who developed COVID-19 between 1 January, 2020 and 31 December, 2021 (first period), and between 1 January and 31 October, 2022 (second period). 1 January, 2022 was used as cut-off date as this was when Omicron BA.1/2 became the predominant SARS-CoV-2 variants in Europe, to be replaced by the BA.4/5 variants during the summer months of 2022 (https://www.ecdc.europa.eu/en as of 20 October, 2022).

In November 2022, we also performed an internet-based survey among the COMPERA investigators who contributed ⩾10 cases to the present series to obtain information on the general vaccination status of their patients and their approach to using antiviral medications in 2022.

Categorical data are presented as number and percentage, and continuous data as median and first and third quartile (Q1, Q3). For group comparisons, Wilcoxon rank sum tests were used for continuous data, and Pearson's Chi-squared test was used for categorical data. A p-value ⩽0.05 was considered statistically significant. Incidence rates were calculated per 100 patient-years to adjust for the different lengths of the two periods. Case fatality rates were calculated as percentages and 95% Wilson confidence intervals (CI) based on patients who were diagnosed with COVID-19 in the respective time periods.

During the entire observation period, 392 SARS-CoV-2 infections were documented in 32 centres; the median number of documented SARS-CoV-2 infections per centre was 4, and 10 centres documented more

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In patients with pulmonary hypertension, the mortality rate associated with COVID-19 has declined sharply with the emergence of the Omicron variants https://bit.ly/42OMsfj

Cite this article as: Schmidt K-H, Milger K, Pausch C, *et al*. Trends in COVID-19-associated mortality in patients with pulmonary hypertension: a COMPERA analysis. *Eur Respir J* 2023; 61: 2202440 [DOI: 10.1183/13993003.02440-2022].

than 10 infections. The first period comprised 8474 patient-years, the second period 1313 patient-years. In the first period, 139 patients were diagnosed with COVID-19, *i.e.* the incidence rate was 1.6 per 100 patient years. In the second period, 253 patients were diagnosed with COVID-19, *i.e.* the incidence rate was 19.3 per 100 patient years. The characteristics of the patients who contracted COVID-19 during the two periods are shown in table 1. The patients who contracted COVID-19 in the second period were younger and had less functional impairment than the patients who contracted COVID-19 in the first period. The higher number of SARS-CoV-2 infections in the second period mirrored the spread of COVID-19 in Europe (https://www.ecdc.europa.eu/en as of 20 October, 2022).

In the first period, 28 of 139 patients died from COVID-19, resulting in a case fatality rate of 20.1% (95% CI 14.3–27.6%). In the second period, four of 253 patients died from COVID-19, resulting in a case

TABLE 1 Characteristics of patients with pulmonary hypertension (PH) diagnosed with COVID-19

	Jan 2020 to Dec 2021 (n=139)	Jan 2022 to Oct 2022 (n=253)	p-value
Age, years	73 (55, 80)	64 (49, 78)	0.0064
Age ⩾65 years	90 (64.7%)	125 (49.4%)	0.0049
Female	97 (69.8%)	163 (64.4%)	0.3361
BMI, kg·m^{-2}	27.8 (23.5, 31.5)	27.2 (23.0, 31.6)	0.8854
Interval between PH diagnosis and COVID-19, months	55 (20, 104)	62 (26, 107)	<0.0001
Type of PH			0.0715
Group 1	89 (64.0%)	170 (67.2%)	
Group 2	15 (10.8%)	14 (5.5%)	
Group 3	10 (7.2%)	19 (7.5%)	
Group 4	25 (18.0%)	41 (16.2%)	
Group 5	0 (0%)	9 (3.6%)	
6MWD, m	310 (218, 401)	401 (300, 480)	<0.0001
WHO FC III/IV	104 (74.8%)	141 (57.1%)	0.0008
NT-proBNP, ng·L^{-1}	587 (183, 2502)	400 (156, 1228)	<0.0001
Haemodynamics			
RAP, mmHg	8 (5, 11)	7 (4, 10)	0.3088
mPAP, mmHg	41 (33, 51)	43 (34, 54)	0.2454
PAWP, mmHg	10 (8, 13)	10 (7, 13)	0.1534
Cardiac index, L·min^{-1}·m^{-2}	2.2 (1.8, 2.8)	2.3 (1.8, 2.8)	0.9111
PVR, WU	7.3 (5.4, 10.3)	8.2 (4.9, 11.4)	0.4732
S_{vO_2}, %	66 (60, 70)	65 (60, 70)	0.8395
Comorbidities and risk factors			
Smoking history	33 (46.5%)	74 (46.8%)	1.0000
Arterial hypertension	76 (61.8%)	120 (51.7%)	0.0887
Coronary heart disease	29 (23.8%)	33 (14.5%)	0.0450
Diabetes mellitus	31 (5.6%)	37 (16.4%)	0.0566
Obesity (BMI ⩾30 kg·m^{-2})	55 (40.7%)	82 (32.5%)	0.1346
PH therapy and anticoagulants			
PDE5i	89 (64.0%)	171 (67.6%)	0.5473
sGCs	33 (23.7%)	53 (20.9%)	0.6090
ERA	67 (48.2%)	128 (50.6%)	0.7283
PPA	18 (12.9%)	42 (16.6%)	0.4157
Monotherapy	74 (53.2%)	126 (49.8%)	0.5856
Dual combination	41 (29.5%)	77 (30.4%)	0.9373
Triple combination	17 (12.2%)	35 (13.8%)	0.7701
Anticoagulants	74 (53.2%)	142 (56.1%)	0.7971

Categorical data are shown as n (%) of the respective population. Continuous data are depicted as median and first and third quartile (Q1, Q3). Values shown are from the last documented visits before the COVID-19 diagnosis except haemodynamic variables and comorbidities, which were obtained at PH diagnosis. When more than one infection occurred in an individual during one period (n=3), only the first one was considered. Patients who had COVID-19 in both periods (n=8) were counted once in each period. BMI: body mass index; 6MWD: 6-min walking distance; WHO FC: World Health Organization functional class; NT-proBNP: N-terminal fragment of pro-brain natriuretic peptide; RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; PAWP: pulmonary arterial wedge pressure; PVR: pulmonary vascular resistance; WU: Wood units; S_{vO_2}, mixed venous oxygen saturation; PDE5i: phosphodiesterase-5 inhibitors; sGCs: stimulator of soluble guanylate cyclase; ERA: endothelin receptor antagonists; PPA: prostacyclin pathway agents.

fatality rate of 1.6% (95% CI 0.6–4.0%). The high case fatality rate in the first period was consistent with previous series [1–5], while the risk of death from COVID-19 was substantially lower in the second period (OR 0.064, 95% CI 0.016–0.189).

The median (Q1, Q3) age of the patients who died from COVID-19 was 79 (74, 85) years in period 1, and 83 (81, 86) years in period 2. No deaths associated with COVID-19 occurred in patients <65 years of age. When restricting the analyses to patients ⩾65 years of age, we found that 28 of 90 (31.1%) died during the first period, and four of 125 (3.2%) died during the second period.

Our survey revealed that by the end of October 2022, more than 90% of the patients in COMPERA were immunised (by vaccination or previous infection) against SARS-CoV-2, and that most centres used antiviral medications only in patients considered at very high risk of death. When comparing our data with previous studies, it is important to bear in mind that we included patients with all forms of PH.

The present analysis has strength and limitations. Strengths include the prospective assessment of real-world data from a large multinational registry, which allows comparing trends in incidence and mortality. Our series is one of the largest to date to investigate the mortality risk associated with SARS-CoV-2 infection in patients with PH and, to our knowledge, the first to assess the mortality risk during the Omicron era in these patients. There are also several important limitations: 1) the possibility of missing information cannot be excluded; 2) while our survey revealed that the majority of the patients in COMPERA have been fully vaccinated against SARS-CoV-2 as recommended by the current European PH guidelines [7, 8], the immunisation status of the individual patients was unknown; 3) detailed information on the management of COVID-19, including management strategies and need for hospitalisation, was not available; and 4) we cannot exclude a possible ascertainment bias due to a proportionally higher fraction of patients with incomplete follow-up in the second period.

Despite these limitations, our data suggest that the case fatality rate of patients with PH who contracted COVID-19 has substantially declined in 2022 compared to the first 2 years of the pandemic. However, with individual level data on vaccination status and COVID-19 management not available, we are unable to determine the causes of this development. It is likely that our findings reflect the sum of a lower case fatality rate associated with the Omicron variants of SARS-CoV-2 compared with previous variants, plus increased immunity due to vaccination and previous infections, plus effects of medical therapies against SARS-CoV-2. In addition, the patients who contracted COVID-19 in the second period were younger, with less functional impairment and fewer comorbidities.

Despite these uncertainties, the sharp decline in COVID-19-associated case fatality rates among patients with PH is important for patients with PH and their caregivers, especially when the use of antiviral agents is discussed in patients with newly diagnosed SARS-CoV-2 infection. Nirmatrelvir–ritonavir, the most widely used antiviral agent, is contraindicated in combination with some of the most widely used PH drugs (sildenafil, tadalafil, bosentan and macitentan) due to relevant pharmacokinetic interactions [9]. Molnupiravir and remdesivir are probably safe, but our data suggest that antiviral treatment may not be needed in patients with PH who have no other risk factors of a serious disease course.

While somewhat reassuring, our findings are not to be interpreted as an “all-clear” signal. A case fatality rate of 1.6% is still substantial, reinforcing the continued need for vigilance and vaccination.

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Conflict of interest: K-H. Schmidt has received fees for lectures and educational events from Abbott, Janssen and MSD. K. Milger has received fees from Actelion, AstraZeneca, GSK, Janssen, MSD, Novartis and Sanofi-Avensis. C. Pausch has no disclosures. D. Huscher has received travel compensation from Shire. D. Pittrow has received fees for consultations from Actelion, Amgen, Aspen, Bayer, Biogen, Boehringer Ingelheim, Daiichi Sankyo, MSD, Novartis, Sanofi-Genzyme, Takeda, Viatris and Zambon. E. Grünig has received fees for lectures and/or consultations from Actelion, Bayer, Ferrer, GSK, Janssen, MSD and Orpha Care. G. Staehler has received honoraria for lectures and/or consultancy for Actelion, Bayer, GSK, Novartis and Pfizer. H. Gall reports personal fees from Actelion, AstraZeneca, Bayer, BMS, GossamerBio, GSK, Janssen-Cilag, Lilly, MSD, Novartis, OMT, Pfizer and United Therapeutics. O. Distler has/had consultancy relationship and/or has received research funding from 4 D Science, Actelion, Active Biotec, Bayer, Biogen Idec, Boehringer Ingelheim Pharma, BMS, ChemoAb, EpiPharm, Ergonex, espeRare foundation, GSK, Genentech/Roche, Inventiva, Janssen, Lilly, medac, MedImmune, Mitsubishi Tanabe, Pharmacyclics, Pfizer, Sanofi, Serodapharm and Sinoxa in the area of potential treatments of scleroderma and its complications, including PAH; and in addition, has a patent mir-29 for the treatment of systemic sclerosis licensed. D. Skowasch received fees for lectures and/or consulting and/or research support to institution from Actelion, Bayer, GSK, Janssen, MSD and Pfizer. M. Halank has received speaker fees and honoraria for consultations from Acceleron, Actelion, AstraZeneca, BerlinChemie, GSK, Janssen and MSD. H. Wilkens received fees for lectures and/or consultations from Actelion, Bayer, Biotest, Boehringer, GSK, Janssen, MSD, Pfizer and Roche. M. Held has received speaker fees and honoraria for consultations from Actelion, Bayer, Boehringer Ingelheim Pharma, GlaxoSmithKline, Janssen, MSD, Novartis, Pfizer, Nycomed, Roche and Servier. H. Klose has received speaker fees and honoraria for consultations from Actelion, Bayer, GSK, Janssen, MSD, Novartis, Pfizer and United Therapeutics. M.M. Hoeper has received fees for lectures and/or consultations from Acceleron, Actelion, AOP Health, Bayer, Ferrer, GSK, Janssen, MSD and Pfizer.

Support statement: This work was supported by the German Centre of Lung Research (DZL). COMPERA is funded by unrestricted grants from Acceleron, AOP Health, Bayer, Ferrer, Janssen, and OMT. These companies were not involved in data analysis or the writing of this manuscript.

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