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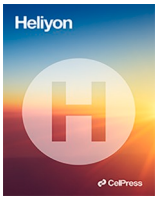

Research article

International trends in pulmonary hypertension mortality between 2001 and 2019: Retrospective analysis of the WHO mortality database

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ABSTRACT

Background: There are limited published data on mortality trends in pulmonary hypertension (PH) worldwide. The objective of this study was to assess the PH-related mortality and time trends in the general population over the past 20 years.

Material and methods: We used country-level PH mortality data from the World Health Organization (WHO) mortality database (2000–19), using the International Classification of Diseases, tenth revision (ICD-10) codes (I27.0, I27.2, I27.8, or I27.9). The average annual percentage changes (AAPCs) were calculated to describe mortality trends.

Results: Fifty-four countries were included in this study. Between 2017 and 2019, the average age-standardized death rates (per 100,000) were 0.80 and 0.87 for males and females, respectively. Joinpoint analyses revealed a decreasing PH mortality trend for the overall population from 2000 to 2019 (AAPC -3.2 [95% confidence interval (CI) −4.1 to −2.4]), which was consistent between males and females (males: AAPC -5.3 [95% CI –6.2 to −4.4], females: AAPC -1.7 [95% CI –2.4 to −0.9]). When the estimates were stratified by etiology, we found that the mortality rates from idiopathic pulmonary arterial hypertension (I27.0) and pulmonary heart disease (unspecified, I27.9) had decreased significantly, while the mortality rates in other secondary PH (I27.2) and other specified pulmonary heart diseases (I27.8) had significantly increased. In addition, there were substantial differences in mortality rates and time trends across countries.

Conclusion: Although an overall decrease in PH mortality trends over the past two decades, there were substantial differences across countries. For countries with high or rising mortality rates, more efforts are needed to reduce the mortality.

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Abbreviations

PH	Pulmonary hypertension
PAH	pulmonary arterial hypertension
WHO	World Health Organization
AAPC	average annual percentage change
CI	confidence interval
ASDR	age-standardized death rate
CTEPH	chronic thromboembolic pulmonary hypertension
ICD	International Classification of Diseases
LOESS	locally weighted scatter plot smoother
NYHA	New York Heart Association
BPA	balloon pulmonary arterioplasty
PEA	pulmonary endarterectomy

1. Introduction

Pulmonary hypertension (PH) is a life-threatening pulmonary vascular disease characterized by elevated resting mean pulmonary arterial pressure [1]. PH arises from a wide range of etiologies and its diagnosis depends on right-sided heart catheterization [2,3]. Although PH is less common than other vascular diseases such as coronary heart disease, it remains a substantial global health concern [4]. Estimates suggest that nearly 1% of the global population suffers from PH, with a prevalence rate of up to 10% among people aged 65 years and older [4]. The 3-year survival for pulmonary arterial hypertension (PAH), PH due to left heart disease, PH due to chronic lung disease, chronic thromboembolic PH (CTEPH), and miscellaneous PH was about 68%, 73%, 44%, 71%, and 59%, respectively [5].

Over the past 20 years, considerable efforts have been made to improve the identification, diagnosis, and treatment of PH [6]. A range of therapeutic regimens, such as molecular targeted therapies, pulmonary endarterectomy (PEA), and balloon pulmonary arterioplasty (BPA), have been shown to significantly improve quality of life and survival rates [7]. However, little is known about the PH-related mortality and time trends to this date [8]. Understanding the time trend of PH-related mortality not only helps to assess the effects of prevention and treatment strategies for PH but may also provide information to healthcare providers and policymakers for the efficient use of limited resources. Thus, the purpose of this study was to describe PH-related mortality and time trends based on the World Health Organization (WHO) mortality database.

2. Materials and methods

2.1. Data source

The WHO mortality database is a highly important data source for comparative epidemiological studies of cause-specific mortality, such as cancer, asthma, and idiopathic pulmonary fibrosis [9–11]. The database includes the number of deaths by country, year, sex, age group, and cause of death from 1950 to date, with the underlying cause of death coded according to the rules of the International Classification of Diseases (ICD). For our study, the crude number of PH deaths and the corresponding population data were extracted from the WHO mortality database (latest update: February 2023) for the years 2000–2019, using ICD-10 codes of I27.0 (primary PH), I27.2(other secondary PH), I27.8(other specified pulmonary heart diseases), or I27.9(pulmonary heart disease, unspecified) [12]. Primary PH, also known as idiopathic PAH, is used to categorize individuals with the pre-capillary PH of unknown origin [13]. The years after 2019 were excluded because of a high percentage of missing mortality data. Countries with $\geq$1 million inhabitants and $\geq$10 years of mortality data were selected. For those countries with missing reference populations in the WHO mortality database, we extracted data from the UN population database.

2.2. Statistical analysis

The crude mortality rates per 100,000 population were calculated by dividing the number of PH deaths by the corresponding population. Crude PH mortality rates were age-standardized using the WHO World standard population. We calculated the 3-year average age-standardized death rates (ASDRs) for 2017–2019 as the mortality at the end of the observation period. If data were missing, we calculated 2-year averages. Joinpoint regression analysis was used to estimate mortality trends in the overall population and each country [14]. The average annual percentage changes (AAPCs) and corresponding 95% confidence intervals (CIs) were calculated to describe time trends from 2000 to 2019. We stratified the analysis by sex(male and female) and etiologic classifications (I27.0, I27.2, I27.8, and I27.9) [15]. A locally weighted scatter plot smoother (LOESS) curve was used to describe smoothed curves of best fit for age-specific mortality trends [16]. Joinpoint analyses were performed using Joinpoint software (version 4.9.1.0) [17]. LOESS curves were performed using R software (version 3.6.3).

3. Results

Fifty-four countries met the inclusion criteria and were included in this study. Between 2000 and 2019, there were 491,287 deaths related to PH, of which 70,116 (14.3%) deaths were related to primary PH (I27.0), 153,017 (31.1%) deaths were related to other secondary PH (I27.2), 8674 (1.7%) deaths were related to other specified pulmonary heart diseases (I27.8), and 259,480 (52.3%) deaths were related to pulmonary heart disease (unspecified, I27.9).

3.1. Global PH mortality

During the study period, the crude mortality (per 100,000) for the overall population decreased by 23.3% from 2.10 in 2000 to 1.61 in 2019. At the end of the observation period (2017–2019), forty-five countries had available data and the highest ASDRs were observed in Georgia (ASDR = 9.12), Romania (ASDR = 5.41), and USA (ASDR = 1.45). The 3-year (2017–19) average annual crude mortality rates and ASDRs of each country are listed in Fig. 1 A and B.

3.2. Joinpoint regression analysis

Joinpoint analysis revealed a decreasing PH mortality trend for the overall population from 2000 to 2019 (AAPC -3.2 [95% CI –4.1 to −2.4]), which was consistent between males and females (males: AAPC -5.3 [95% CI –6.2 to −4.4], females: AAPC -1.7 [95% CI –2.4 to −0.9]) (Fig. 2A). When the estimates were stratified by etiology, we found that the mortality rates from primary PH (I27.0) and pulmonary heart disease (unspecified. I27.9) had decreased significantly in the past 20 years, while the mortality rates in other secondary PH (I27.2) and other specified pulmonary heart diseases (I27.8) had significantly increased (Fig. 2B). The AAPCs of primary PH (I27.0), other secondary PH (I27.2), other specified pulmonary heart diseases (I27.8), and pulmonary heart disease (unspecified, I27.9) were −7.8 [95% CI –9.2 to −6.3]), 6.7 [95% CI 6.3 to 7.2]), 5.5 [95% CI 3.5 to 7.6]) and −8.6 [95% CI –9.3 to −7.9]), respectively.

There were substantial differences in mortality trends across countries. Among the 54 countries, the death trends increased in 13 countries, decreased in 16 countries, and remained unchanged in 25 countries. The AAPCs of the mortality trends of each country are listed in Table 1. We further stratified estimates by gender. For males, nine countries showed increasing trends in mortality, with

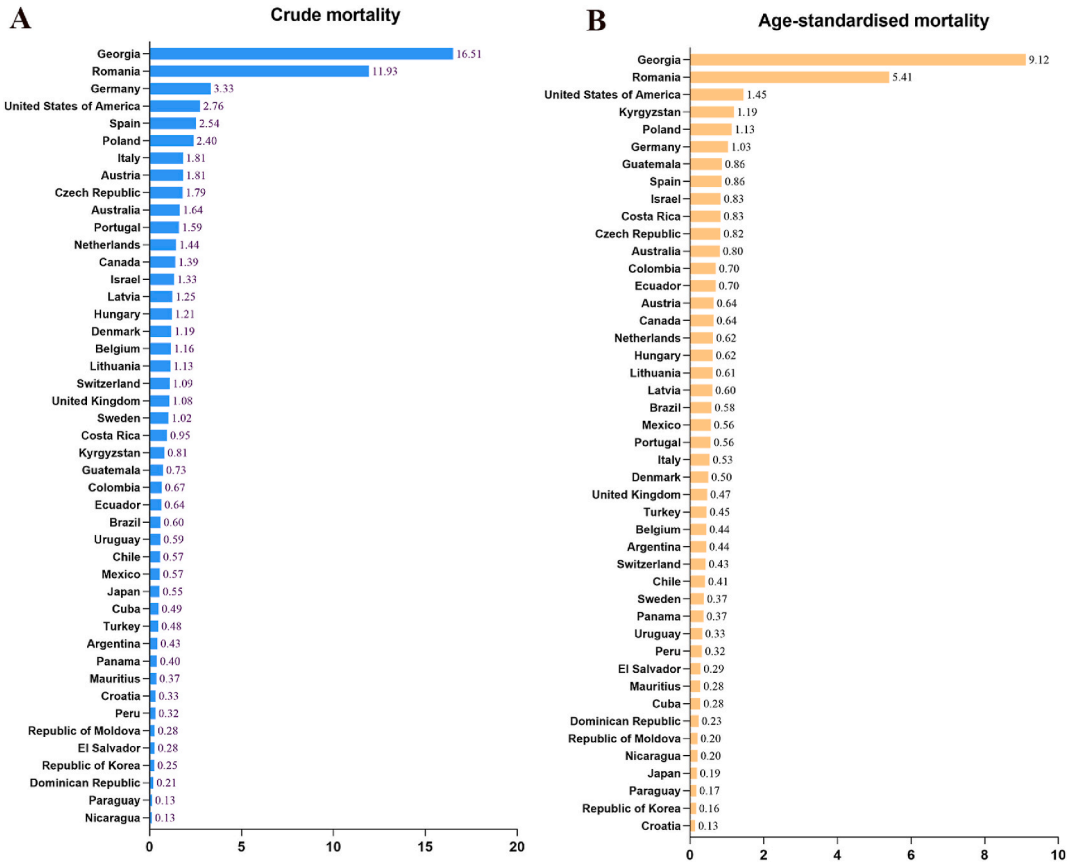

Fig. 1. The 3-year (2017–19) average annual crude mortality (A) and age-standardized mortality (B) per 100,000 from PH.

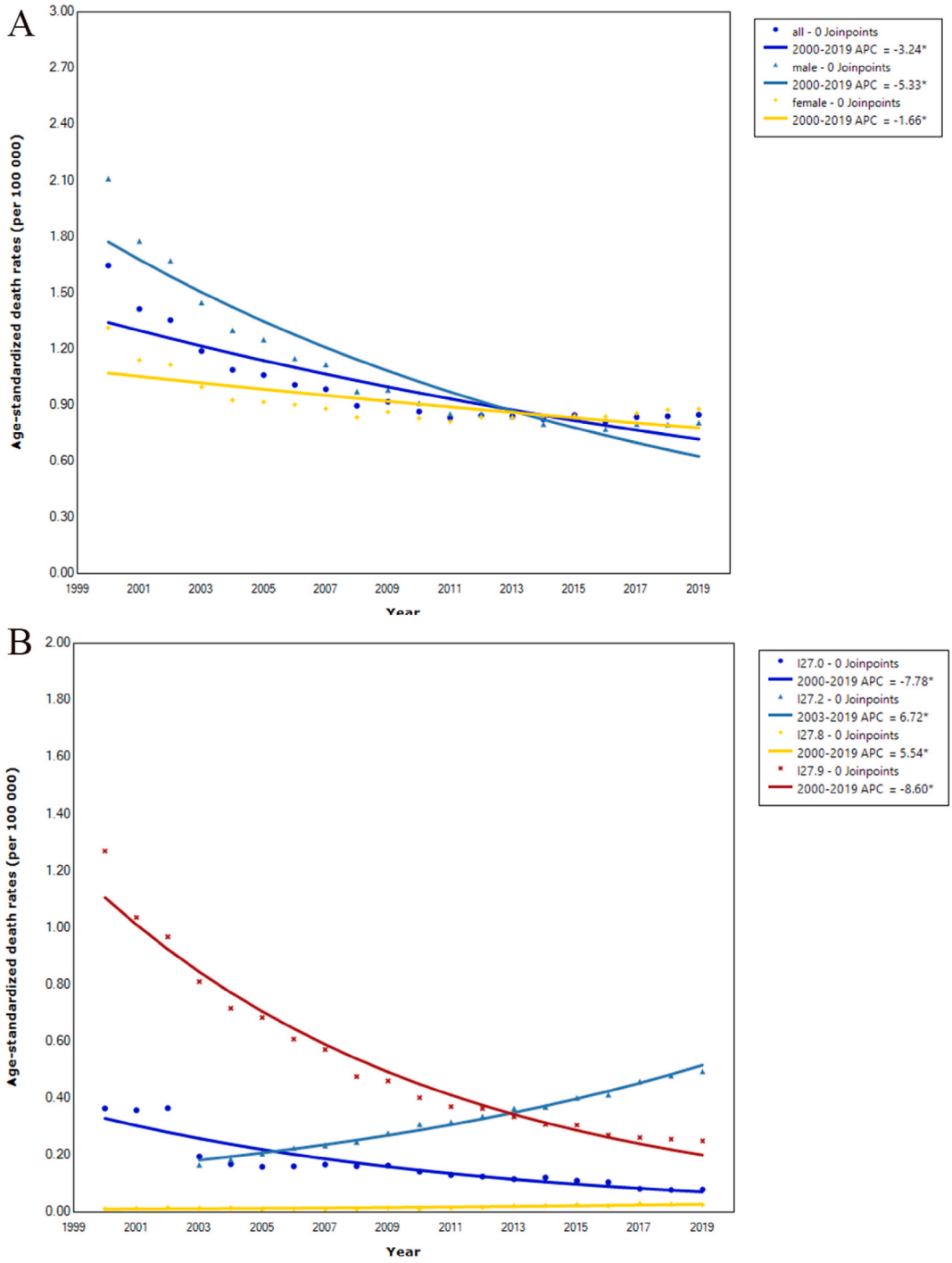

Fig. 2. The joinpoint regression analysis of PH mortality for the overall population (A) and etiologic classifications (B). APC, annual percentage change. *p values less than 0.05.

Guatemala reporting the highest AAPC (7.5, 95% CI [4.1, 11.0], $P < 0.01$), followed by Latvia (AAPC, 7.0, 95% CI [0.5, 13.8], $P = 0.04$), and Sweden (AAPC,6.6, 95% CI [4.9, 8.4], $P = 0.03$). In contrast, eighteen countries had decreasing trends in mortality, with Croatia (AAPC, −14.5, 95% CI [−22.9, −5.2], $P < 0.01$), Mauritius (AAPC, −11.4, 95% CI [−16.7, −5.8], $P < 0.01$), and Poland (AAPC, −9.6, 95% CI [−11.2, −8.0], $P < 0.01$) reporting the largest decreases. Among females, thirteen countries had increasing trends, with Guatemala reporting the highest AAPC (8.0, 95% CI [4.6, 11.5], $P < 0.01$), followed by Sweden (AAPC, 6.8, 95% CI [4,8, 8.9], $P < 0.01$), and Costa Rica (AAPC,4.2, 95% CI [1.7, 6.7], $P < 0.01$). On the contrary, sixteen countries had decreasing trends. Croatia (AAPC,

Table 1
Time trends in age-standardized pulmonary hypertension mortality rates (per 100,000).

Country	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	AAPC (95% CI)
Mauritius						1.23	1.07	0.91	1.18	0.85	0.76	0.78	0.91	0.76	0.78	0.28	0.55	0.19	0.36	0.3	−8.4 (−11.5, −5.3)
Morocco	0.53	0.56	0.55	0.5	0.84			0.63	0.82	0.81	1.1	0.66	0.67	0.69	0.64	0.57	0.28				−1.1 (−5.4, 3.3)
Argentina	0.91	0.94	0.94	1.41	0.8	0.57	0.44	0.65	0.54	0.5	0.58	0.49	0.49	0.48	0.5	0.59	0.48	0.49	0.4	0.42	−3.1 (−7.1, 1.0)
Brazil	2.58	2.33	2.17	1.02	1.04	0.94	1.01	1.07	0.99	0.93	0.92	0.91	0.82	0.77	0.77	0.7	0.72	0.66	0.58	0.51	−7.8 (−9.9, −5.6)
Canada	0.53	0.47	0.51	0.57	0.51	0.57	0.55	0.5	0.51	0.59	0.66	0.63	0.71	0.59	0.64	0.61	0.64	0.6	0.68	0.63	1.4 (0.8, 2.1)
Chile	0.44	0.52	0.36	0.54	0.54	0.48	0.39	0.42	0.33	0.29	0.25	0.25	0.33	0.29	0.36	0.38	0.34	0.41	0.43	0.39	−0.1 (−3.6, 3.6)
Colombia	1.73	2.04	1.98	1.91	1.47	1.48	1.41	1.2	0.86	0.83	0.85	0.72	0.64	0.59	0.78	0.65	0.6	0.55	0.64	0.91	−3.7 (−8.5, 1.4)
Costa Rica	0.38	0.51	0.39	0.15	0.43	0.46	0.3	0.59	0.64	0.56	0.5	0.42	0.55	0.66	0.75	0.75	0.6	0.74	0.99	0.77	4.6 (2.7, 6.4)
Cuba		0.46	0.47	0.62	0.46	0.46	0.4	0.35	0.42	0.47	0.33	0.41	0.28	0.28	0.34	0.41	0.35	0.33	0.25	0.27	−3.2 (−4.6, −1.9)
Dominican Republic	0.3	0.28	0.26	0.25	0.16	0.25	0.26	0.27	0.14	0.14	0.22	0.21	0.22	0.17	0.34	0.18	0.22	0.32	0.37		0.9 (−1.4, 3.2)
Ecuador	3.89	3.15	3.36	2.78	2.78	3.62	3.18	2.22	1.77	2.17	1.54	1.96	2.33	1.49	1.29	0.72	0.61	0.66	0.78	0.64	−8.2 (−10.1, −6.3)
El Salvador	0.25	0.45	0.21	0.44	0.21	0.2	0.31	0.47	0.14	0.26	0.52	0.49	0.24	0.42	0.52	0.41	0.38	0.48	0.37		2.1 (−0.8, 5.1)
Guatemala						0.44	0.46	0.25	0.21	0.36	0.5	0.46	0.36	0.67	0.67	0.72	0.76	0.87	0.87	0.85	7.8 (4.9, 10.8)
Jamaica	0.82	0.8	0.85	0.77	0.66	0.7	0.76			1.74	0.66	0.67	0.97	1.07	1.25						3.1 (−1, 7.4)
Mexico	1.24	1.14	1.07	1.03	0.97	0.98	0.88	1.13	1.07	1.04	1.12	0.91	1.04	1.06	0.67	0.67	0.62	0.57	0.56	0.55	−4.2 (−6, −2.3)
Nicaragua	0.39	0.18	0.2	0.14	0.27	0.62	0.57	0.42	1.04	0.42	0.34	0.47	0.38	0.3	0.47	0.26	0.21	0.26	0.19	0.16	−1.7 (−7.1, 4.1)
Panama	0.51		0.24	0.45	0.21	0.3		0.22		0.2	0.49	0.31	0.31	0.25	0.14	0.19	0.22	0.33	0.32	0.46	−0.8 (−3.8, 2.3)
Paraguay	0.12	0.5	0.28	0.13	0.18	0.14	0.27	0.13	0.41	0.21	0.17	0.22	0.39	0.25	0.3	0.28	0.28	0.18	0.12	0.21	−1.2 (−4.6, 2.3)
Peru	0.31	0.25	0.25	0.33	0.26	0.19	0.29	0.22	0.21	0.28	0.24	0.22	0.23	0.18	0.21	0.24	0.23	0.29	0.35	0.33	1.1 (−1.4, 3.6)
Puerto Rico	0.78	0.75	0.81	0.99	0.51	0.43	0.58	0.62	0.54	0.63	0.65	0.52	1.1	0.73	0.88	1	0.98	0.94			1.7 (−0.6, 4.1)
Trinidad and Tobago	0.58	0.46	0.52	0.86	0.97	1.04	0.68	0.67	1.26	0.82	0.88	0.75	0.78								2.6 (−2.1, 7.5)
United States	1.15	1.15	1.21	1.22	1.14	1.15	1.16	1.12	1.17	1.22	1.24	1.23	1.25	1.32	1.31	1.41	1.42	1.42	1.44	1.5	1.2 (0.8, 1.7)
Uruguay	0.43	0.39	0.61	0.44	0.47	0.41	0.52	0.45	0.53	0.2	0.22		0.42	0.31	0.15	0.31	0.28	0.33	0.36	0.29	−3.0 (−5.0, −0.9)

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Table 1 (*continued*)

Country	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	AAPC (95% CI)
Venezuela	0.25	0.3	0.2	0.16	0.22	0.26	0.16	0.16	0.27	0.21	0.22	0.19	0.25	0.13	0.14	0.17	0.2				−2.0 (−4.2, 0.2)
Israel	0.59	0.44	0.71	0.7	0.65	0.74	0.94	1.28	1.03	1.14	0.92	0.89	0.91	1.01	0.96	0.75	0.76	0.92	0.86	0.72	2.4 (0.3, 4.6)
Japan	0.26	0.28	0.3	0.31	0.28	0.24	0.2	0.19	0.22	0.2	0.19	0.2	0.19	0.18	0.19	0.2	0.21	0.19	0.18	0.19	−1.7 (−3.7, 0.5)
Republic of Korea	0.39	0.21	0.19	0.12	0.14	0.13	0.11	0.12	0.17	0.2	0.19	0.15	0.11	0.17	0.18	0.15	0.16	0.17	0.17	0.15	−3.7 (−7, −0.3)
Turkey										0.56	0.48	0.61	0.52	0.58	0.65	0.6	0.55	0.49	0.48	0.38	−2.7 (−6.7, 1.5)
Austria			0.64	0.73	0.57	0.43	0.32	0.29	0.29	0.45	0.43	0.39	0.42	0.64	0.44	0.54	0.57	0.56	0.78	0.58	−0.3 (−4.1, 3.6)
Belgium	0.41	0.53	0.49	0.46	0.42	0.42	0.51	0.5	0.49	0.49	0.36	0.5	0.51	0.56	0.56	0.46	0.58	0.76	0.57		1.8 (0.6, 3.0)
Croatia	3.82	2.13	1.74	1.8	2.08	2.15	1.72	1.58	0.74	0.68	0.36	0.33	0.27	0.25	0.16	0.24	0.2	0.2		0.21	−14.4 (−20.3, −8.2)
Czech Republic	1.65	1.3	1.31	1.26	1.27	1.2	1.29	1.07	1.44	1.14	1.03	0.99	1.12	1.2	1.01	1.02	0.9	0.93	0.79	0.75	−2.8 (−3.6, −2.0)
Denmark	0.15	0.24	0.55	0.51	0.36	0.45	0.41	0.49	0.43	0.51	0.48	0.38	0.48	0.4	0.46	0.46	0.47	0.49	0.59	0.41	6.4 (0.4, 12.8)
France	0.69	0.65	0.69	0.72	0.6	0.65	0.64	0.63	0.58	0.58	0.56	0.53	0.54	0.51	0.5	0.59	0.5	0.54			−1.8 (−2.4, −1.3)
Georgia					9.83	10.22	11.82	17.44		14.41	4.22	5.82	7.62	5.96	9.91	7.41	6.54	7.18	7.79	12.38	−2.9 (−7, 1.3)
Germany	1	0.9	0.88	0.84	0.78	0.83	0.77	0.85	0.91	0.8	0.83	0.78	0.86	0.91	0.92	0.99	0.96	1.04	1.04	1.01	0.2 (−0.9, 1.3)
Hungary	2.31	2.54	2.18	1.96	1.49	2.65	1.98	1.97	1.86	1.06	1.13	1.09	1.18	0.8	0.76	0.62	0.47	0.55	0.68	0.63	−8.0(-9.8, −6.2)
Ireland								0.35	0.34	0.33	0.51	0.48	0.48	0.57	0.67	0.65			0.58		5.6 (1.3, 10.0)
Italy				0.86	0.82	0.86	0.79	0.72	0.72	0.69	0.67	0.7	0.69	0.63	0.6	0.61	0.53	0.55	0.54	0.51	−3.2 (−3.6, −2.8)
Kyrgyzstan	3.65	4.38	7.13	2.95	1.41	1.32	1.69	5.6	1.84	1.33	1.13	0.6	1.36	1.07	0.89	1.17	1.13	0.85	1.4	1.33	−8.9 (−12.7, −4.9)
Latvia									0.49	0.39	0.23	0.36	0.16	0.23	0.44	0.41	0.56	0.53	0.49	0.79	4.5 (−3.9, 13.6)
Lithuania		0.19	0.35	0.44	0.39	0.21	0.12	0.22	0.2	0.16	0.31	0.38	0.38	0.85	1.05	1.03	0.64	0.54	0.66	0.65	2.2 (−7.3, 12.5)
Netherlands	0.27	0.3	0.29	0.36	0.61	0.41	0.43	0.5	0.58	0.56	0.59	0.53	0.57	0.55	0.57	0.55	0.55	0.64	0.63	0.6	5.1 (2.9, 7.3)
Norway	0.29	0.21	0.23	0.33	0.25	0.55	0.46	0.44	0.25	0.31	0.36	0.39	0.28	0.3	0.29	0.2	0.43				0.3 (−3.0, 3.7)
Poland	6.02	5.36	4.11	3.68	2.63	2.01	1.71	1.28	0.97	1.08	0.84	0.9	0.99	0.9	0.82	1	0.86	1.12	1.07	1.21	−8.9 (−10.2, −7.6)

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Table 1 (*continued*)

Country	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	AAPC (95% CI)
Portugal			0.53	0.48				0.4	0.48	0.44	0.43	0.48	0.56	0.95	0.68	0.63	0.57	0.62	0.54	0.51	−0.2 (−3.8, 3.5)
Republic of Moldova									0.16	0.2		0.14	0.15	0.28	0.53	0.7	0.5	0.24	0.37		11.6 (−2.3, 27.4)
Romania	30.43	25.41	25.04	21.78	18.73	17.09	15.17	13.26	11.51	11.32	9.74	8.78	7.76	7.2	6.52	6.58	5.78	5.66	5.47	5.09	−9.0 (−9.7, −8.2)
Spain	0.75	0.71	0.72	0.74	0.61	0.56	0.57	0.58	0.61	0.54	0.63	0.59	0.64	0.6	0.72	0.93	0.85	0.92	0.84	0.82	0.4 (−2.5, 3.3)
Sweden	0.17	0.21	0.21	0.17	0.29	0.3	0.25	0.3	0.3	0.39	0.35	0.32	0.39	0.5	0.51	0.57	0.56	0.6	0.52		6.9 (5.7, 8.1)
Switzerland	0.57	0.47	0.59	0.62	0.66	0.62	0.59	0.56	0.48	0.59	0.51	0.55	0.58	0.43	0.44	0.42	0.53	0.45	0.38	0.45	−1.8 (−2.7, −0.9)
United Kingdom		0.42	0.38	0.43	0.37	0.37	0.4	0.41	0.44	0.42	0.4	0.4	0.45	0.44	0.45	0.51	0.49	0.47	0.44	0.49	1.2 (0.7, 1.8)
Australia	0.42	0.41	0.44	0.75	0.87		0.6	0.71	0.68	0.65	0.62	0.7	0.77	0.64	0.77	0.8	0.75	0.78	0.84	0.8	4.1 (0.8, 7.5)
New Zealand	0.42	0.19	0.33	0.2	0.29	0.18	0.43	0.21	0.27	0.35	0.41	0.34	0.35	0.39	0.48	0.5	0.5				3.6 (1.0, 6.3)
All population	1.64	1.41	1.35	1.19	1.09	1.06	1.01	0.98	0.90	0.92	0.86	0.83	0.84	0.84	0.82	0.84	0.81	0.84	0.84	0.85	−3.2 (−4.1, −2.4)
Female	1.31	1.14	1.12	1.00	0.93	0.92	0.91	0.88	0.84	0.87	0.83	0.82	0.84	0.83	0.84	0.85	0.84	0.86	0.87	0.89	−1.7 (−2.4, −0.9)
Male	2.11	1.78	1.68	1.45	1.30	1.25	1.15	1.12	0.98	0.98	0.91	0.86	0.85	0.84	0.8	0.84	0.77	0.80	0.80	0.81	−5.3(-6.2, −4.4)

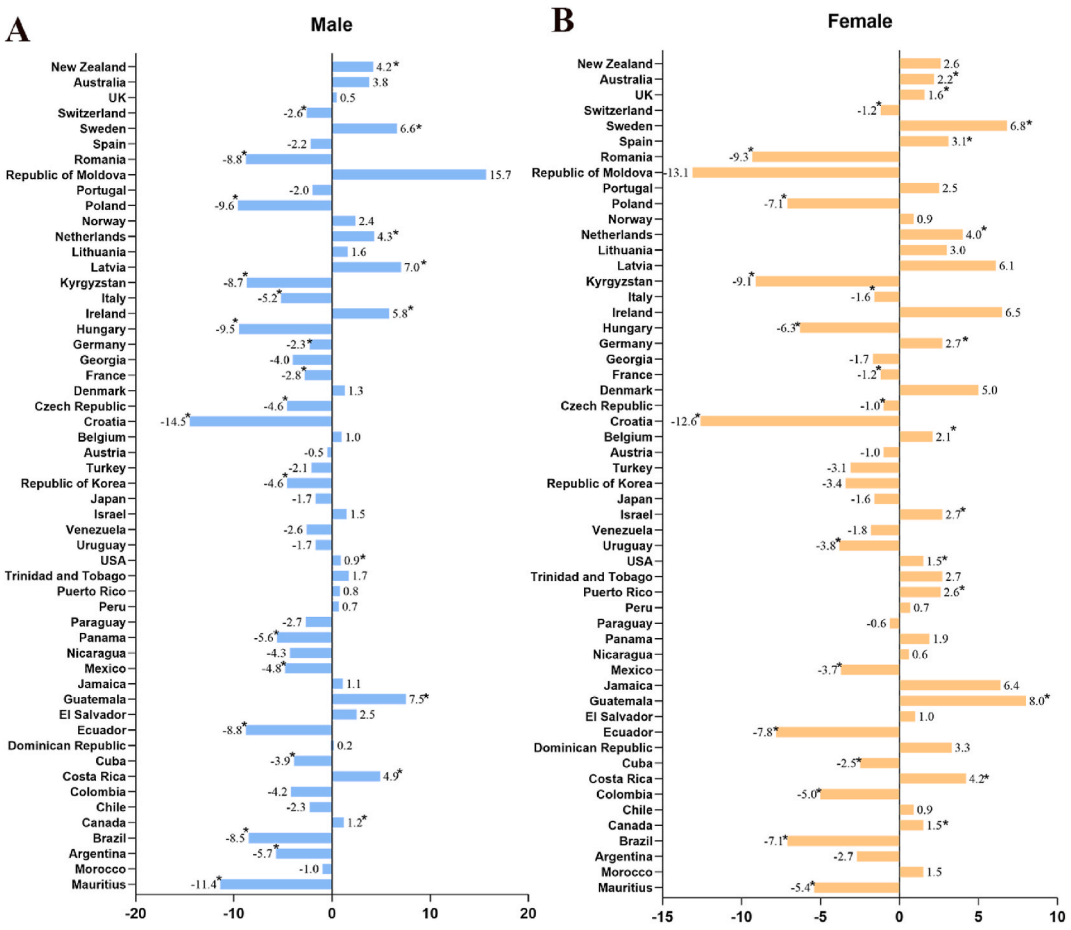

Fig. 3. The AAPCs of PH mortality trends in males (A) and females (B) (*P values less than 0.05).

−12.6, 95% CI [−17.7, −7.0], $P < 0.01$), Romania (AAPC, −9.3, 95% CI [−10.0, −8.6], $P < 0.01$), and Kyrgyzstan (AAPC, −9.1, 95% CI [−12.9, −5.2], $P < 0.01$) had the largest decreases. Overall, Guatemala was the country with the largest increasing trends in both sexes. Conversely, Croatia was the country that had the largest decreasing trends in both sexes. The AAPCs of mortality trends in males and females are presented in Fig. 3 A and B.

3.3. *Age-specific mortality trends*

Fig. 4 displays the LOESS line of best fit for age-specific mortality trends in the last 3 years (2017–19). As expected, PH mortality increased with age in both sexes, especially over 65 years old. Age-specific mortality rates were higher in females than males, and the difference increased with age.

4. Discussion

This comprehensive analysis of international mortality trends across 54 countries revealed an overall decrease in PH mortality trends over the past two decades, which was consistent between sexes. Subgroup analyses found that the mortality rates from primary PH (I27.0) and pulmonary heart disease (unspecified, I27.9) had decreased significantly, while the mortality rate in other secondary PH (I27.2) and other specified pulmonary heart diseases (I27.8) had significantly increased. Although an overall decrease in PH mortality trends, there were substantial differences across countries, with 13 countries experiencing an increase in mortality, 16 countries experiencing a decrease in mortality, and 25 countries experiencing no change in mortality.

PH remains a devastating vascular condition resulting from multiple causes. According to current ESC/ERS guidelines, PH could be divided into 5 clinical subgroups: PAH, PH associated with left heart disease, PH due to chronic lung disease and/or hypoxia, CTEPH, and miscellaneous PH [18]. In the clinic, PH was usually diagnosed at a late stage of the disease, with severe symptoms and poor prognosis [19]. In the REVEAL Registry, 55.6% of patients were New York Heart Association (NYHA) functional class III or IV at the time of enrollment [20]. In the Spanish registry, 69% of patients were in WHO functional class III or IV at diagnosis [21]. In the France registry, 75% of patients at presentation were in NYHA functional class III or IV [22]. Early diagnosis and treatment appeared

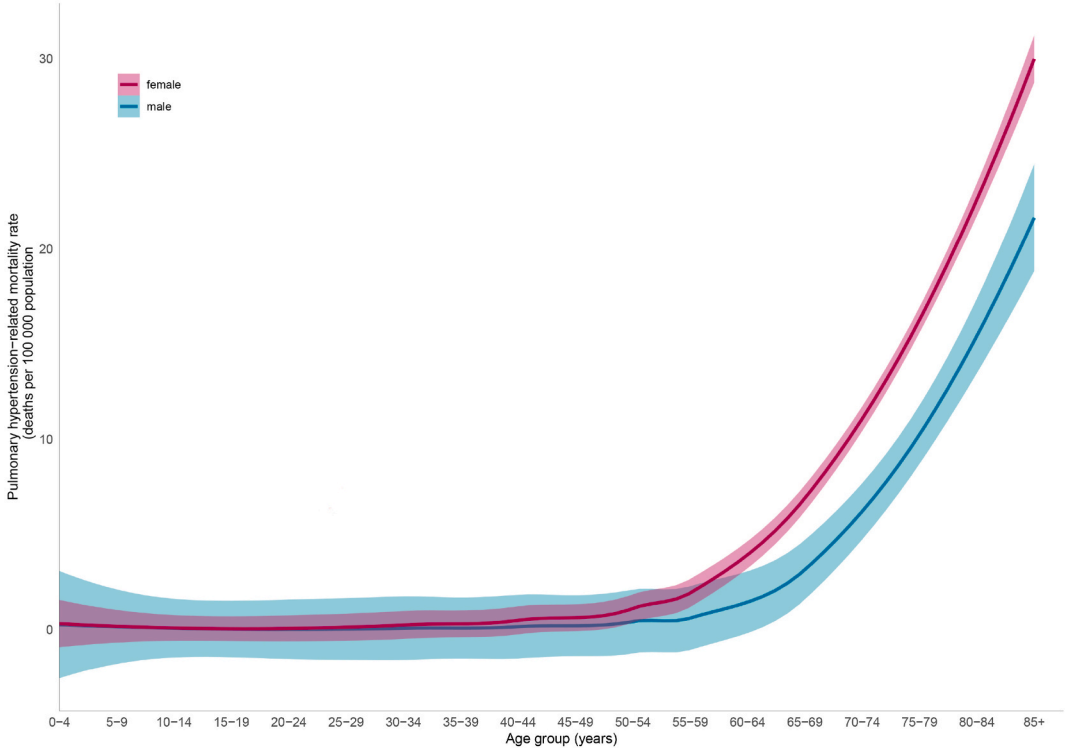

Fig. 4. The LOESS line of best fit for age-specific mortality trends.

increasingly important because it might result in an improvement in long-term prognosis [23].

In this study, we found a significant decrease in the number of deaths coded with PH as the underlying cause of death since the start of the study period in 2000. One possible explanation was decreased case fatality due to dramatic improvements in treatment. PH-targeted therapies, such as prostacyclin analogs, endothelin receptor antagonists, and phosphodiesterase-5 inhibitors, have been widely used in clinical practice over the past 20 years and have been shown to improve hemodynamics and survival in patients with PAH [24,25]. In addition, PEA and Riociguat (a guanylate cyclase stimulator) have also been shown to be beneficial for patients with CTEPH [26,27]. Improvements in clinical management might improve the prognosis of PH, leading to a shift toward PH as a contributing factor to death rather than the underlying cause. However, the WHO mortality database only included deaths coded with PH as an underlying cause of death and did not include deaths caused by PH as a contributing factor. Therefore, a significant decline in PH mortality might be observed in this study. Another possible explanation for decreased mortality was that with the increasing awareness of PH among clinicians, PH could be diagnosed and treated early, which might improve outcomes from advanced PH [28].

In the WHO mortality database, PH was categorized based on ICD-10 codes (I27.0, I27.2, I27.8, and I27.9) instead of clinical phenotypes (e.g., WHO clinical groups). For example, WHO Group 1 PAH could be split into I27.0 (idiopathic PAH), I27.2 (PAH associated with connective tissue disease, HIV, portal hypertension, etc.), and I27.8 (congenital heart disease); WHO Group 3 could be split into I27.2(PH associated with interstitial lung disease, chronic obstructive pulmonary disease, sleep-disordered breathing, etc.) and I27.9(developmental lung diseases); WHO Group 2, Group 4, and Group 5 could be coded as I27.2 [29]. We found that the mortality rates from primary PH (I27.0) and pulmonary heart disease (unspecified, I27.9) had decreased significantly, while the mortality rate in other secondary PH (I27.2) and other specified pulmonary heart diseases (I27.8) had significantly increased, which was consistent with previous reports [12,30]. The specific reasons for the inconsistent mortality trends of PH with different ICD-10 codes were currently unclear. We speculated that the decrease in mortality from primary PH (I27.0) and pulmonary heart disease (unspecified, I27.9) might be due to diagnostic standardization and technological advances that allowed us to accurately identify the etiology of PH and classify them correctly. In addition, there was a change in ICD-10 encoding in 2003, with the addition of I27.2 for secondary PH. This resulted in a shift from coding most cases of PH-related death from primary PH (I27.0) to secondary PH (I27.2), which would also affect the trend of deaths from different ICD-10 codes.

Although an overall decrease in mortality from PH was observed, there were substantial differences in PH mortality and temporal trends across countries. Among the 54 countries, the death trends remained unchanged in 25 countries, decreased in 17 countries, and increased in 13 countries. At the end of the observation period (2017–2019), the highest 3-year mortality was observed in Georgia, Romania, and America. Inconsistent time trends of mortality across countries might be caused by multiple reasons, including different population composition, unequal access to PH care, and different criteria [31]. Currently, early diagnosis and available treatment remain a grand challenge due to limited healthcare resources in some low- and middle-income countries [32]. For those countries with high or rising mortality rates, continuous efforts are needed to reduce mortality risk, such as the establishment of tertiary PH care and

elderly care centers.

This paper was the first study, to our knowledge, to assess international PH mortality trends using national vital registration data from the WHO mortality database. There were several potential limitations. First, the death rate in this study might be lower than that observed in the previous study because the WHO mortality database only contained deaths coded with PH as the underlying cause of death, whereas the previous study included deaths coded with PH as an underlying or contributing cause of death [30,33]. Including only deaths with PH as the underlying cause of death might underestimate the disease burden of PH. Second, in order to improve the reliability of data, we only included countries with a population of over 1 million and with $\geq$10 years of mortality date. This would exclude a lot of countries with small populations and incomplete data, which might limit the generalizability of our findings. Third, since the number of diagnosed cases was not recorded in the WHO mortality database, it was difficult to distinguish if the observed decrease was a result of a reduction in the case-fatality rate or PH incidence. Fourth, the clinical phenotype of PH was very important for clinical guidance. However, the WHO mortality database categorized PH based on ICD-10 codes instead of clinical phenotypes, which might undermine the clinical applications of our findings. Finally, as a secondary analysis of WHO mortality data, the accuracy of our results might be affected by the quality of mortality data from various countries. Therefore, our findings should be interpreted with caution because the reliability of death certification and coding practices might vary between countries.

5. Conclusion

This study found an overall decrease in PH mortality over the past 20 years. However, the mortality rates and temporal trends varied across countries. For countries with high or rising mortality rates, continuous efforts are needed to reduce the mortality.

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Data availability statement

Data used for this study are publicly available on the WHO mortality database website (https://www.who.int/data/data-collection-tools/who-mortality-database

Disclaimer

The original databases are provided by WHO. All analyses, interpretations, and conclusions in this manuscript are responsibility of the authors and not of WHO.

CRediT authorship contribution statement

Ping Lin: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Faming Jiang:** Writing – original draft, Software, Funding acquisition, Formal analysis, Data curation. **Xiaoqian Li:** Validation, Software, Methodology, Investigation, Formal analysis. **Yuean Zhao:**, Validation, Methodology, Investigation, Formal analysis. **Yujun Shi:** Writing – review & editing, Visualization, Validation, Supervision, Resources, Conceptualization. **Zongan Liang:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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