Received: 23 February 2021 | Accepted: 21 March 2021

DOI: 10.1002/rth2.12520

ORIGINAL ARTICLE

Global reporting of pulmonary embolism–related deaths in the World Health Organization mortality database: Vital registration data from 123 countries

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Funding information
Daiichi Sankyo Company, Grant/Award Number: DSE-DE-CV-20001

Handling Editor: Dr Cihan Ay.

Abstract

Introduction: Pulmonary embolism (PE) has not been accounted for as a cause of death contributing to cause-specific mortality in global reports.

Methods: We analyzed global PE-related mortality by focusing on the latest year available for each member state in the World Health Organization (WHO) mortality database, which provides age-sex–specific aggregated mortality data transmitted by national authorities for each underlying cause of death. PE-related deaths were defined by International Classification of Diseases, Tenth Revision codes for acute PE or nonfatal manifestations of venous thromboembolism (VTE). The 2001 WHO standard population served for standardization.

Results: We obtained data from 123 countries covering a total population of 2 602 561 422. Overall, 50 (40.6%) were European, 39 (31.7%) American, 13 (10.6%) Eastern Mediterranean, 13 (10.6%) Western Pacific, 3 (2.4%) Southeast Asian, and 2 (1.6%) African. Of 116 countries classifiable according to population income, 57 (49.1%) were high income, 42 (36.2%) upper-middle income, 14 (12.1%) lower-middle income, and 3 (2.6%) low income. A total of 18 726 382 deaths were recorded, of which 86 930 (0.46%) were attributed to PE. PE-related mortality rate increased with age in most countries. The reporting of PE-related deaths was heterogeneous, with an age-standardized mortality rate ranging from 0 to 24 deaths per 100 000 population-years. Income status only partially explained this heterogeneity.

Conclusions: Reporting of PE-related mortality in official national vital registration was characterized by extreme heterogeneity across countries. These findings mandate enhanced efforts toward systematic and uniform coverage of PE-related mortality and provides a case for full recognition of PE and VTE as a primary cause of death.

KEYWORDS
epidemiology, mortality, pulmonary embolism, venous thromboembolism, World Health Organization

Essentials

- We estimated pulmonary embolism (PE)-related mortality for 123 countries covering a population of 2 602 561 422.
- Reporting of PE-related mortality in official national vital registration was extremely heterogeneous.
- Socioeconomic characteristics and prevalence of risk factors alone cannot explain this heterogeneity.
- As reflected by vital registration data, underrecognition of PE remains a global health care problem.

1 | INTRODUCTION

The incidence of pulmonary embolism (PE) has been steadily increasing over the past 2 decades, at least in high-income countries.[1-5] An improvement in life expectancy, particularly among patients with conditions predisposing to venous thromboembolism (VTE), such as cancer, chronic obstructive pulmonary disease, and autoimmune diseases, may partly explain this finding in most countries. Other factors explaining this trend include the broader adoption of validated diagnostic algorithms, greater awareness, a lower threshold of clinical suspicion, and the standard use of computed tomographic pulmonary angiography.[6,7]

In contrast, both PE-related in-hospital death rate[8-12] and age-standardized mortality from PE[13] have been decreasing or plateauing over the past years, possibly reflecting the greater proportion of "low-risk" cases being diagnosed and an improvement in PE management.[7] This trend parallels the improvements in overall health as measured by age-standardized disability-adjusted life-years from the latest systematic analysis of the Global Burden of Disease Study (2019).[14] Despite these reassuring trends, PE associated with hemodynamic instability portends unacceptably high rates of in-hospital or early death.[15,16] Particularly vulnerable are women during pregnancy and postpartum and obese patients, for whom high-quality evidence supporting clinical decisions is not available.[17-20]

Global awareness campaigns, notably the World Thrombosis Day initiative, alert the general public, physicians, and stakeholders to the burden of thrombosis and promote broad implementation of available management strategies.[21] The gap in global recognition and epidemiologic data quality between PE (and VTE) and conditions such as myocardial infarction and stroke remains substantial. PE is still not listed as a cause of (preventable) death contributing to cause-specific mortality in national reports and global epidemiologic studies.[14,22,23] This gap should be urgently addressed, especially for low- and lower-middle-income countries, for which almost no data are available from epidemiologic analyses and cohort studies.[24-27]

A large and comprehensive overview of global PE-related mortality may help researchers to study differences in reports, identify priorities in VTE management, guide policy makers in designing thromboprophylaxis guidelines, and implement evidence-based patient pathways for VTE diagnosis and treatment. The aim of the present study is to provide a snapshot of current global PE-related mortality in the pre–coronavirus disease 2019 (COVID-19) era based on official national vital registration data from the World Health Organization (WHO) mortality database.

2 | METHODS

The WHO mortality database provides aggregated data grouped by year, country, age, and sex for the underlying (or primary) cause of death listed in death certificates and transmitted annually by deputed national authorities responsible for national vital registration systems to the WHO. Deaths are classified according to standard International Classification of Diseases (ICD) codes. Additionally, the WHO database provides age- and sex-stratified population data taken from the United Nations Population Division. For this analysis, we used the updated version of the WHO database released in 2019.[28]

ICD, Tenth Revision (ICD-10) codes specific for "acute pulmonary embolism with or without acute cor pulmonale" (I26) or codes referring to nonfatal manifestations of VTE (eg, deep vein thrombosis [DVT] or phlebitis/thrombophlebitis) listed as the primary cause of death, namely, "the disease or event that started the chain of events that led to death" were used to define deaths related to PE.[13,29] We have previously shown that death certificates listing DVT as the primary cause of death almost invariably included PE codes as a contributing cause.[30] The present analysis aimed to provide an overview of updated statistics on PE-related mortality. Therefore, we focused on the latest year available in the WHO mortality database for each country or territory after the year 2000.

We categorized states in six regions as indicated by the WHO: African Region, Region of the Americas, Southeast Asia Region, European Region, Eastern Mediterranean Region, and Western Pacific Region. We grouped states into four income groups (low, lower-middle, upper-middle, and high income) based on the World Bank list (2019) of analytical income classification of economies for the fiscal year.[31]

Since age groups were defined differently across states, we created homogeneous 5-year age groups up to 85 years old. Annual mortality data were provided as crude and age-standardized PE-related mortality rates for the latest available year, expressed as the number of PE-related deaths in each age group by the total corresponding 100 000 population of men and women. The updated WHO world standard population (2001) served for standardization.[32] The 95% confidence intervals were calculated based on the Fay's method.[33] We calculated the proportionate mortality in men and women, defined as the proportion of deaths attributed to PE out of total deaths. Three age groups were used (<20, 20–49, ≥50 years) to accommodate the small population size and low number of PE-related deaths in some states. To assess the presence of correlation between income level and age-standardized mortality and proportionate mortality rates, respectively, we used a logistic regression, setting the income level as the independent variable.

We followed the Guidelines for Accurate and Transparent Health Estimates Reporting standards.[34] This study did not need ethics or institutional review board approval because it did not include interventions or data at the individual patient level.

3 | RESULTS

One hundred fifty-nine member states and territories have contributed their vital registration data to the WHO mortality database at least once since the year 2000. Eighteen were excluded because no recent data were provided as ICD-10 or because they no longer exist, whereas 6 states were excluded because of their special coding system, which does not allow identification of the codes for PE-related death in a way comparable to the other states (Table S1). Finally, 12 member states were excluded because their age group definition was not compatible with that of the other states.

Of the 123 member states or territories included in the analysis, 50 (40.6%) were European, 39 (31.7%) American, 13 (10.6%) Eastern Mediterranean, 13 (10.6%) Western Pacific, 3 (2.4%) Southeast Asian, and 2 (1.6%) African. Three (Mayotte, Reunion, and Rodrigues) could not be classified in any WHO region. Data on population size, total annual deaths, and PE-related deaths were collected for the latest year available for each country after 2000. A total of 115 (93.5%) states or territories reported data after the year 2011 (years 2012–2018), and 88 (71.5%) reported data after the year 2015 (years 2016–2018).

Income categorization based on reference tables was possible for 116 states: Of these, 57 (49.1%) were high income, 42 (36.2%) upper-middle income, 14 (12.1%) lower-middle income, and 3 (2.6%) low income. The proportion of states with available mortality data decreased in parallel with the decrease in the states' national income: 57 of 89 (64.0%) high income, 42 of 61 (68.8%), upper-middle income, 14 of 47 (29.8%) lower-middle income, and 3 of 31 (9.7%) low income. Among countries with available data, high-income countries had more recent data: 53 of 57 (92.9%) after the year 2015 among

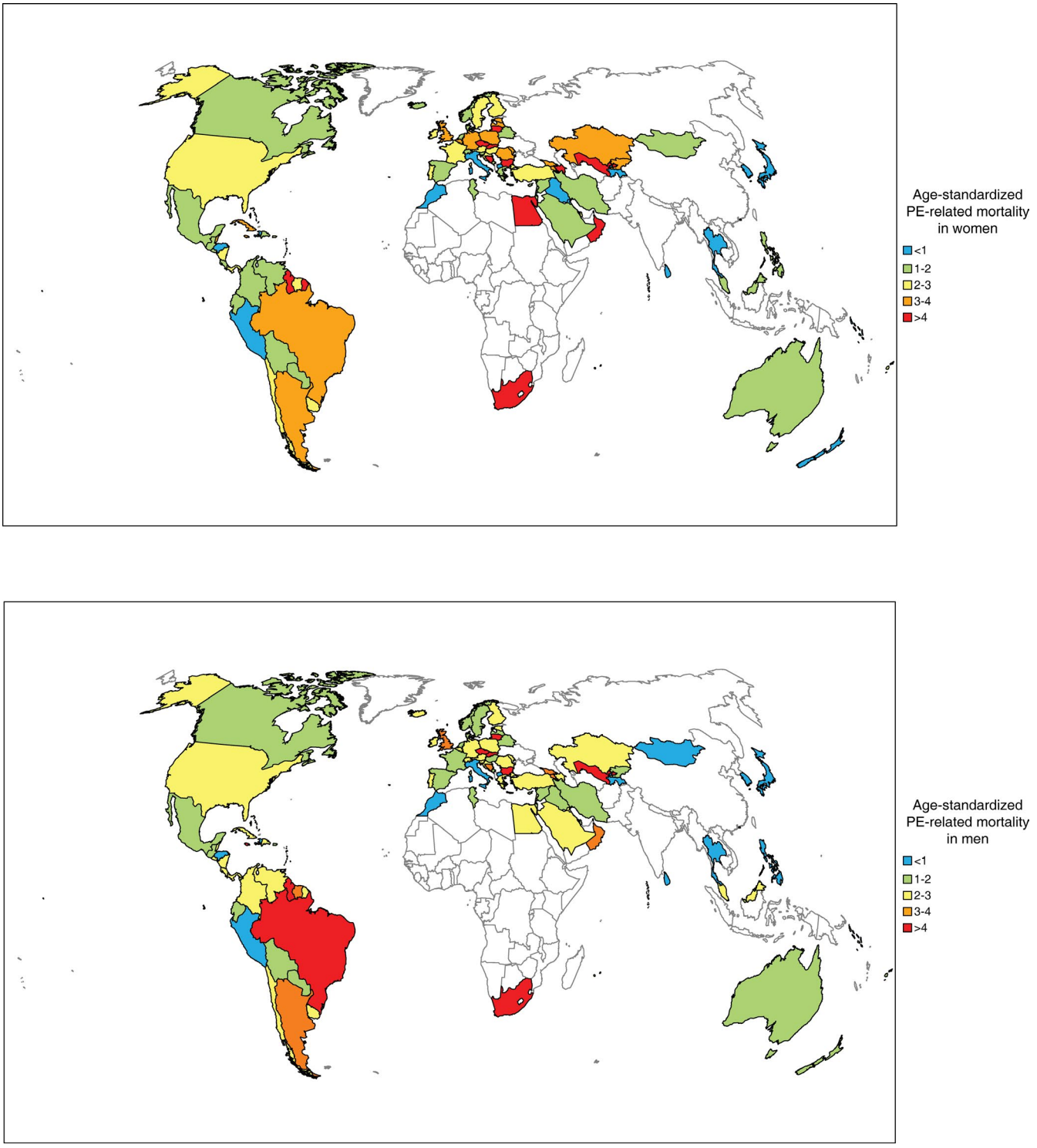

FIGURE 1 Overview of global age-standardized PE-related mortality in women and men. PE, pulmonary embolism

high-income countries, 27 of 42 (64.3%) upper-middle income, 7 of 14 (50.0%) lower-middle income, and 1 of 3 (33.3%) low income.

This analysis covered a total of 2 602 561 422 general population. The total number of deaths recorded was 18 726 382, of which 86 930 (0.46%) had been primarily attributed to PE according to the death certificates. The country with the largest population was the United States, with nearly 160 million men and 164 million women in 2017. The country with the smallest population was Rodrigues with 20 947 men and 21 691 women in 2017.

Tables S2 and S3 show population size, number of PE-related death, crude PE-related mortality by age group and in the entire population, and age-standardized PE-related mortality based on the 2001 world standard population in women and in men, respectively. PE-related mortality rate increased with age with few exceptions,

mostly less populated states with a low absolute number of PE-related deaths. Figure 1 provides a visual overview of the global age-adjusted PE-related mortality in women and men. Figures 2 and 3 show the relationship of country income status with age-standardized mortality rates and proportionate mortality rates, respectively, in both sexes.

In women, an age-standardized PE-related mortality <1.0 death per 100 000 population-years was recorded in Haiti, Honduras, Peru, Morocco, Tajikistan, Former Yugoslav Republic of Macedonia, Thailand, Brunei, Hong Kong, Japan, Kiribati, Mongolia, Philippines, Republic of Korea, Singapore, and Rodrigues. In men, an age-standardized PE-related mortality <1.0 deaths per 100 000 population-years was recorded in Aruba, Haiti, Honduras, Peru, Virgin Islands, Bahrain, Iraq, Lebanon, Morocco, Malta, Tajikistan, Maldives, Sri Lanka, Thailand, Hong Kong, Japan, Kiribati, New Zealand, Republic of Korea, Singapore, and Solomon Islands.

In women, an age-standardized PE-related mortality >10.0 deaths per 100 000 population-years was recorded in Antigua and Barbuda, Bahamas, Barbados, and Saint Vincent and Grenadines. In men, an age-standardized PE-related mortality >10.0 deaths per 100,000 population-years was recorded in Antigua and Barbuda, Bahamas, Saint Vincent and Grenadines, and Bulgaria.

Table S4 shows the population size and the number of PE-related deaths in each state in the latest available year, followed by proportionate PE-related mortality in the entire population of the country and in three age groups, for women and men, respectively.

Excluding member states not reporting any PE-related death, the highest proportionate PE-related mortality rate among women was recorded in Saint Vincent and Grenadines (3.3%) and Bahamas (3.2%), the lowest was in Tajikistan, which reported only one PE-related death. In women, PE was listed as the underlying cause of >1% of overall deaths in Aruba, Bahamas, Barbados, Brazil, Guadeloupe, Jamaica, Martinique, Lithuania, Luxembourg, Slovakia, United Kingdom, Trinidad and Tobago, Saudi Arabia, Tunisia, Bulgaria, Czech Republic, Solomon Islands, and Mayotte.

The highest proportionate PE-related mortality rate among men was recorded in Antigua and Barbuda (3.6%) and the lowest in Sri Lanka (0.1%). In men, PE was listed as the underlying cause of >1% of overall deaths in Antigua and Barbuda, Bahamas, Barbados, Martinique, Saint Vincent and Grenadines, Bulgaria, and Czech Republic. In both sexes, the contribution of PE to total mortality peaked in adults aged 20 to 49 years.

Linear regression modeling showed a positive correlation between the income level and proportionate mortality rate in women ($F = 6.23$; $\beta1 = 1.46$) and men ($F = 4.1$; $\beta1 = 1.01$). There was less clear correlation when the dependent variable was the age-adjusted mortality rate ($F = 2.12$; $\beta1 = 0.49$; $P = .15$ in women; $F = 1.99$; $\beta1 = 0.49$).

4 | DISCUSSION

We provide a comprehensive overview of global PE-related mortality, as reported in national vital registries of 123 states

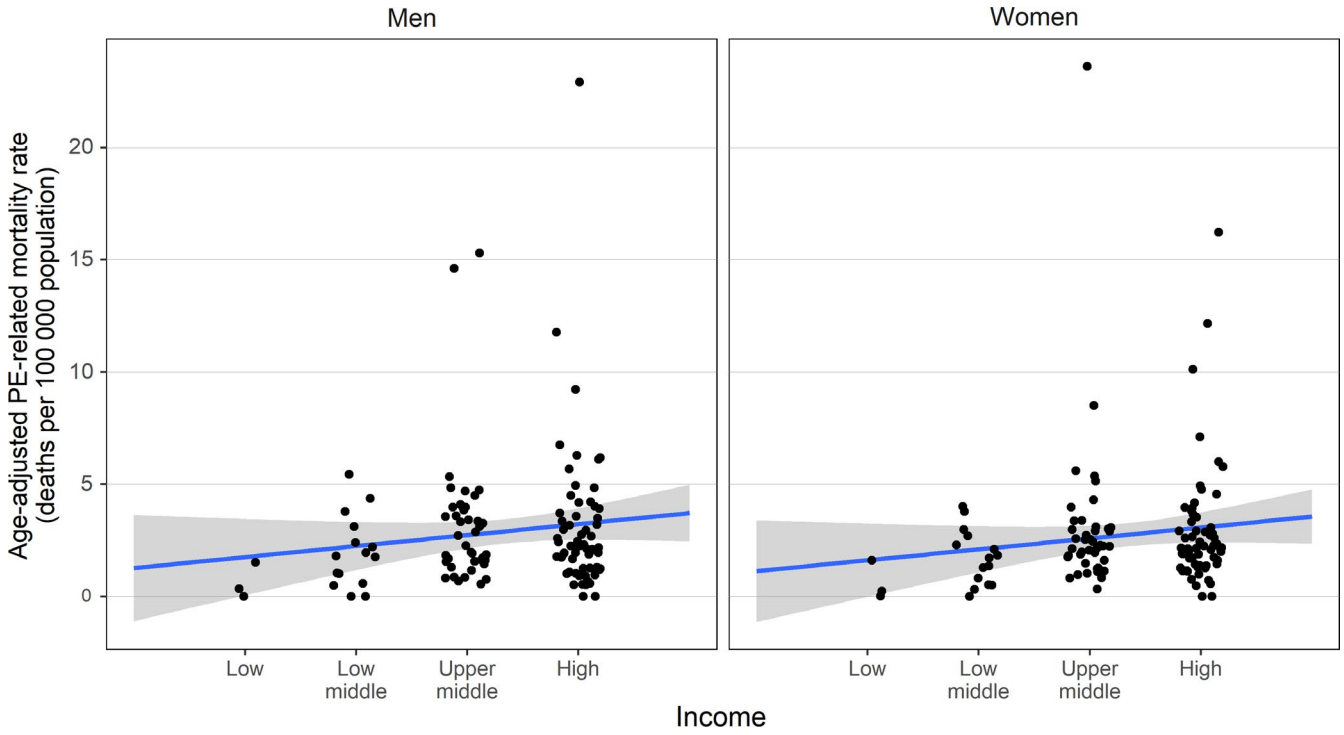

FIGURE 2 Age-standardized mortality rate by country income class in men and women. Jittered plot of the distribution of the age-adjusted pulmonary embolism-related mortality rate by country income class. Each dot represents one country. The fitted regression line (with 95% confidence interval) is shown of the association between income class and mortality rate. PE, pulmonary embolism

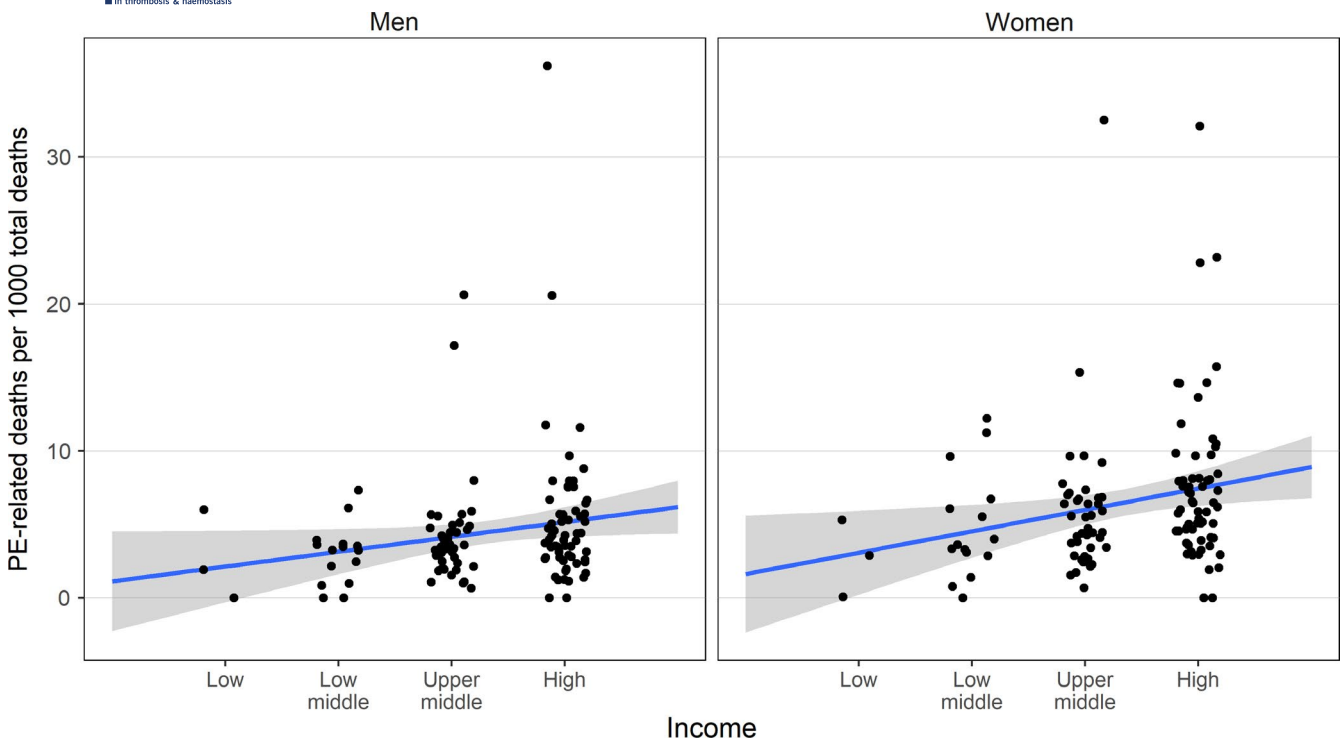

FIGURE 3 Proportionate PE-related mortality by country income class in men and women. Jittered plot of the distribution of PE-related proportionate mortality by country income class. Each dot represents one country. The fitted regression line (with 95% confidence interval) is shown of the association between income class and proportionate mortality. PE, pulmonary embolism

or territories covering >2.6 billion general population in Europe, North and South America, Eastern Mediterranean, Western Pacific, Southeast Asia, and Africa. Several of our findings have the potential to trigger calls for action by health organizations, policy makers, and the thrombosis research community. First, reported deaths were characterized by large heterogeneity across regions and states, which is unlikely to be solely explained by different socioeconomic characteristics, management practices, or prevalence of risk factors. Differences in the accuracy of cause of death reporting are indeed likely and should be taken into account. These differences may originate from local clinical and administrative reporting practices[35,36] or the methods used to diagnose PE in each country.[30,37] Therefore, efforts toward systematic and uniform reporting of VTE-related mortality, for instance, in the context of the Global Burden of Disease (GBD) initiative, are warranted. Second, young women die of PE more frequently than their male peers, not only in Europe and America as we reported in earlier studies,[13,30] but also in other geographic regions. This generalized inequality calls for dedicated studies and tailored recommendations on the appropriate methods and modalities for the prevention, diagnosis, and management of gestational, maternal, and peripartum VTE. A growing proportion of obese patients[38,39] and the broad use of the combined oral contraceptive pill, particularly in high-income countries, may partly explain these results. Third, PE mortality was highest among older adults in both high- and low-income states, which highlights the paucity of higher-quality thrombosis management studies in the elderly. Finally, in addition to abating the burden of VTE-associated death, broad improvements in the management of VTE will also benefit VTE survivors suffering from the long-term limitations and symptoms collectively referred to as "post-VTE syndrome."[40]

Although the GBD 2019 does not report data for VTE as a specific cause of death and disability,[14] VTE is responsible for a substantial burden of disease across the globe. The WHO patient safety program[14] found that VTE accounted for more deaths than any other hospital-acquired disease in low-, middle-, and high-income states. The GBD applies three criteria to include a cause of death: potentially large burden, substantial health policy interest, and feasibility of measurement.[14] Since VTE fulfills all, a strong case can be made that VTE should be reported worldwide as a cause of death.

In the absence of data from national reports and global epidemiologic studies, we performed a cross-sectional study that provides a global overview of the recent PE-related mortality information by systematic analysis of data from the WHO mortality database. Our global approach addressed the lack of data from many non–high-income states, as previously observed by the ISTH Steering Committee for World Thrombosis Day.[14] In regions with a high proportion of low- or lower-middle-income countries, data were consistently fewer or outdated.[41] This problem reflects the scarcity of available resources, not only for scientific projects and data collecting but also for health care governance in low- and middle-income states.

People die of PE at different ages in states of different wealth levels. In high-income states, the contribution of PE to total deaths

is often highest in people aged 20 to 49 years of both sexes. In contrast, in low-income states it tends to be highest in older people, especially in men. A longer life expectancy in high-income states may lead to higher prevalence of comorbidities, such as cancer or cardiovascular disease, which contribute to death more than PE and effectively serve as a competing risk. In low-income states, infectious diseases, maternal and neonatal conditions, and injuries[14] are a leading cause of mortality. Only survivors who reach older age are exposed to noncommunicable diseases such as VTE. This may explain why PE mortality is highest among older adults. However, in recent years, low-income states experienced a transition from infectious diseases to noncommunicable diseases as major causes of death and disability.[14] In several countries, noncommunicable diseases and years lived with disability accounted for more than half of the entire disease burden in 2019.[14] As a result, much more attention to VTE is warranted worldwide.

One consequence of the 2020 coronavirus pandemic was an increase in acute thromboembolic complications.[42,43] Due to its distinctly prothrombotic phenotype,[44] COVID-19 is likely to increase PE-related mortality. This underlines the need for more rapid global implementation of evidence-based preventive and therapeutic measures. Indeed, thrombosis associated with COVID-19 infection may reverse the overall decreasing trend in PE-related mortality observed in the European Region, United States, and Canada over the past 15 to 20 years.[42] VTE is largely preventable, and several randomized controlled trials are currently under way to evaluate thromboprophylaxis in COVID-19 infection, in both ambulatory and hospital settings.[45,46]

Awareness of PE continues to be low: a survey by World Thrombosis Day (WTD) in 2014 showed that 50% of people are not aware of or have never heard the term *pulmonary embolism*.[14] International programs such as the WTD and the WHO's Thirteenth General Program of Work 2019–2023 aim to reduce mortality due to noncommunicable disease by promoting a comprehensive approach that includes timely prevention and diagnosis. Public awareness plays a key role in the implementation of these programs.[14]

Our study has some limits. First, the attribution of deaths to PE as the primary cause is difficult.[47] Deaths primarily related to PE are frequently misclassified as cardiac deaths, and PE as a contributing cause of death may not always be documented (eg, reduction in autopsy/postmortem examination and cancer patients). For these reasons, estimates of the number of deaths due to PE based on death certificates or hospital discharge data may underestimate the real mortality burden. Second, several states do not share data or share data only for specific years, so that cross-country comparison is not possible. This is true especially in low-income states. Therefore, the conclusions drawn from the available data may not be accurate. Third, our study was cross sectional and did not allow for evaluation of trends over time. Fourth, data for two of the world's most populated states, China and India, were not available in the WHO mortality database. However, the availability of data from 123 states and territories on six continents covering more than one-third of the world population supports our findings.

5 | CONCLUSION

In conclusion, the heterogeneity of reporting on PE-related death in the WHO database mandates enhanced efforts toward systematic and uniform coverage of disease-specific mortality. Since VTE fulfills all of the GBD criteria, a strong case can be made that PE should be reported worldwide as a cause of death. Further research, dedicated to implementation of optimized prevention, diagnostic, and treatment strategies for PE, is likely to decrease the global burden of this largely preventable disease.

ACKNOWLEDGMENTS

The work of SB and SVK is supported by the German Federal Ministry of Education and Research (BMBF 01EO1003 and 01EO1503). In addition, the work of SB and SHM has been supported by the University of Mainz in the context of the Inneruniversitäre Forschungsförderung (Stufe I). The work of LV is supported by a grant from Daiichi-Sankyo (DSE-DE-CV-20001). The work of LAC is supported by a Heart & Stroke Foundation of Canada National New Investigator and Ontario Clinician Scientist Award and the University of Ottawa T2 Research Chair in Thrombosis and Anticoagulation Safety. The present work has been endorsed by the WTD Steering Committee of the ISTH.

RELATIONSHIP DISCLOSURE

SB has received congress and travel payments from Daiichi-Sankyo, Boston Scientific, and Bayer HealthCare; institutional grants from Sanofi and Bayer HealthCare; and personal fees and honoraria from Bayer HealthCare, LeoPharma, Boston Scientific, and Daiichi-Sankyo, outside the present work. LV reports payment from Daiichi Sankyo, outside the submitted work. WA reports grants and personal fees from Bayer and personal fees from BMS-Pfizer, Sanofi, and Aspen, outside the submitted work. LAC's institution has received consultancy fees on her behalf from Amag Pharmaceuticals, Bayer, BMS, LEO Pharma, Pfizer, Sanofi, and Servier, outside the submitted work. NK reports grants from Swiss National Science Foundation, Concept Medical, Bard, and Bayer; and personal fees from Bayer, Bard, Medtronic, Boston Scientific, BTG, and Pfizer, outside the submitted work. FNA reports grants from Actelion, Bayer, and Sanofi, outside the submitted work. PS reports personal fees and other payments from WERFEN, and personal fees from CSL BEHRING, UNIQURE, and STAGO, outside the submitted work. DS reports personal fees from Sanofi-Aventis (Suisse) SA, Vernier, Switzerland, outside the submitted work. ACS is a consultant for Janssen, BMS, Portola, Bayer, Boehringer Ingelheim, and the ATLAS Group; and is partially funded from a grant from the Broxmeyer Fund in Clinical Thrombosis.

AUTHOR CONTRIBUTIONS

SB: concept and design, analysis, and/or interpretation of data; critical writing or revising the intellectual content; and final approval of the version to be published. LV and AG: design, analysis and/or interpretation of data; critical writing or revising the intellectual

content; and final approval of the version to be published. SHM and GT: analysis and/or interpretation of data; critical writing or revising the intellectual content; and final approval of the version to be published. WA, LC, GC-M, HD, EVDP, MD, MCGE, FAK, NK, CM, FNÁ, PS, DS, ACS, TU, ZZ, BJH, SVK: interpretation of data, critical writing or revising the intellectual content, and final approval of the version to be published.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

How to cite this article: Barco S, Valerio L, Gallo A, et al. Global reporting of pulmonary embolism–related deaths in the World Health Organization mortality database: Vital registration data from 123 countries. *Res Pract Thromb Haemost*. 2021;5:e12520. https://doi.org/10.1002/rth2.12520