Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

VOL. 80, NO. 16, 2022
ISSN 0735-1097/$36.00

Letters

Annual Mortality Related to Pulmonary Embolism in the U.S. Before and During the COVID-19 Pandemic

Up to 15% excess in all-cause mortality during the pandemic could not be directly attributed to COVID-19 itself or its complications.[1] Increasing pulmonary embolism (PE)-related mortality rates were reported in some European regions in 2020.[2] We sought to investigate the PE-related mortality rate in the United States among patients with or without COVID-19 after the outbreak and compare them with those prior the pandemic.

We accessed the Mortality Multiple Cause of Death database provided by the Centers for Disease Control and Prevention for the years 2018-2019 and 2020. We identified all deaths listing a PE-related (I26.x/I82.x/O88.2) or COVID-19-related (U07.1) International Classification of Diseases-10th Revision code in any position of the death certificate. We used annual national population totals from the U.S. Census Bureau and the 2000 U.S. standard population to calculate PE-related age-adjusted mortality rates in COVID-19 and non-COVID-19 patients for 2020 and the Joinpoint software version 4.9.1.0 (National Institutes of Health) to study changes in trends. We performed subgroup analyses based on age, sex, and race. We calculated the proportionate mortality attributed to PE among COVID-19 deaths.

The study did not require ethics approval, as data were anonymized and publicly available.

Throughout 2020, 49,243 deaths related to PE were recorded in the United States (43,895 without COVID-19 and 5,348 with COVID-19) compared with 39,450 in 2019 and 38,215 in 2018 (**Figure 1A**). The overall age-adjusted PE-related mortality rate was 12.23 (95% CI: 12.12-12.35) per 100,000 population in 2020, 10.92 (95% CI: 10.82-11.03) for PE-related deaths without COVID-19, and 1.31 (95% CI: 1.27-1.35) for PE-related deaths with COVID-19. The corresponding rate was 9.81 (95% CI: 9.71-9.92) in 2018 and 9.95 (95% CI: 9.85-10.05) in 2019. This reflects a 23.8% increase in 2020 compared with 2018-2019; the increase was statistically significant as per Joinpoint analysis.

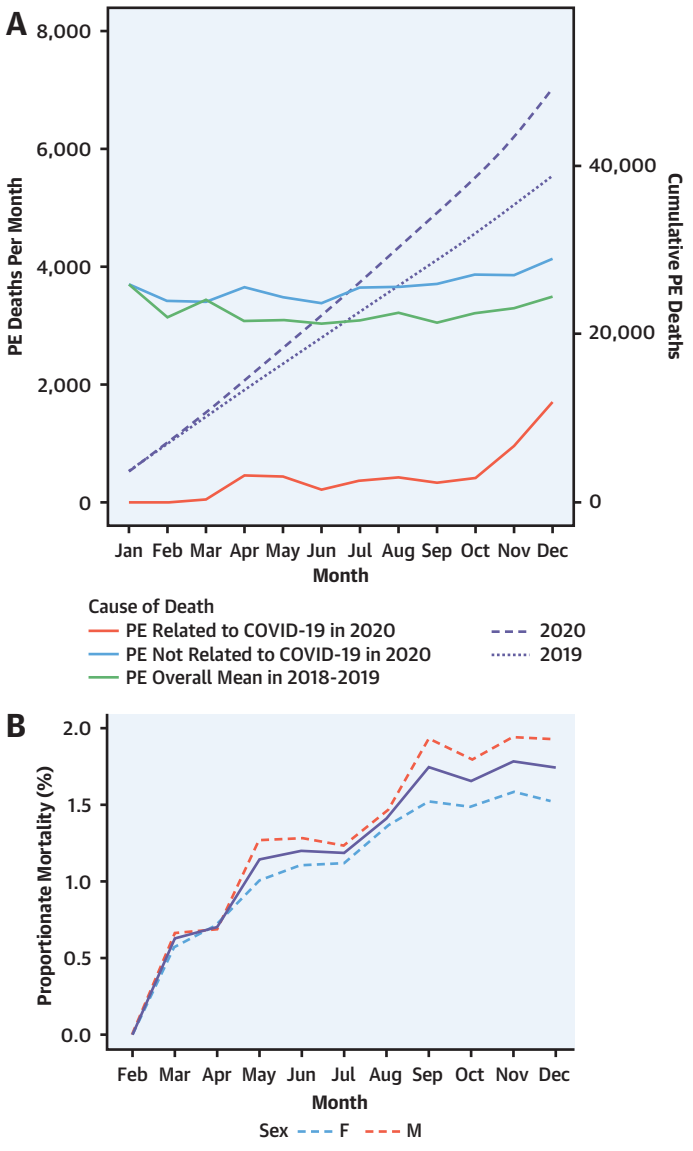
In 2020, the age-adjusted mortality rate of PE-related deaths without COVID-19 was higher for men (11.63 per 100,000; 95% CI: 11.47-11.79) than for women (10.32 per 100,000; 95% CI: 10.18-10.46) (rate ratio: 1.13; 95% CI: 1.10-1.16). This also regarded PE-related deaths with COVID-19 (men: 1.72 per 100,000 [95% CI: 1.65-1.77] vs women: 0.97 per 100,000 [95% CI: 0.93-1.01]), although the difference between sexes appeared even greater (rate ratio: 1.75; 95% CI: 1.63-1.90). PE-related age-adjusted mortality rates were higher among Black people, irrespective of the COVID-19 status. The age-adjusted rate ratio for the Black vs White population with regard to PE-related deaths without COVID-19 was 1.80 (95% CI: 1.74-1.85), rising to 2.14 (95% CI: 1.97-2.35) for PE-related deaths with COVID-19.

Among 385,293 deaths with COVID-19 in 2020, PE was reported in 5,348 (proportionate mortality 1.4%). The proportionate mortality of PE in COVID-19 increased steadily and plateaued in the last months of 2020 (**Figure 1B**). In 2020, 81.5% of PE-related deaths with COVID-19 were reported in a hospital setting, a proportion higher than that of PE-related deaths without COVID-19 (56.2%). The proportionate mortality of PE in deaths with COVID-19 was higher among younger patients (0-44 years of age; 2.7%) than in older adults and elderlies (45-85+ years of age; 1.4%).

In 2020, there was an excess mortality for PE, which appeared synchronously with the COVID-19 pandemic waves. COVID-19 contributed as a cause of death in one-half of the excess PE-related deaths. Nonetheless, a swift increase was observed in PE-related mortality rate without mention of COVID-19 in the death certificates (10.92 in 2020 vs 9.95 in 2019, approximately 10% in 1 year), which diverges form the mild increase observed in the same population between 2009 and 2018 (approximately 2% per year).[3] We hypothesize that possible undiagnosed COVID-19 cases, especially in the early phase of the

JACC VOL. 80, NO. 16, 2022
OCTOBER 18, 2022:1579–1581

FIGURE 1 Mortality Related to PE and COVID-19



(A) Pulmonary embolism–related death count in 2018-2019 and in 2020 depicting a 23.8% increase in 2020. **(B)** Proportionate PE-related mortality in COVID-19 deaths plateauing in the later months of 2020. PE = pulmonary embolism.

pandemic owing to decreased testing capabilities, or the delayed sequelae of COVID-19 left unaccounted for, are mainly responsible for this important leap. Other reasons could include an exaggerated sedentary lifestyle, the avoidance of health care facilities, or health care saturation and poorer management of non-COVID-19-related diseases due to resource shortage.

The proportion of PE-related mortality to COVID-19 total mortality plateaued in the last quarter of 2020, which suggests an increasing accumulation of evidence and awareness of the medical community for the higher incidence of PE in COVID-19 patients throughout the course of the pandemic.[4] In addition, PE during COVID-19 infection was a larger contributor to mortality in younger age.

We observed a substantial increase in the overall PE-related mortality after the pandemic outbreak, which was not limited to deaths with confirmed COVID-19. Whether changes in health care, encompassing preventive, medical, and logistic measures, may have reduced the excess in PE-related mortality concerning the latest waves is being investigated.

Ioannis T. Farmakis, MD, MSc
Luca Valerio, MD
Behnood Bikdeli, MD, MS
Jean M. Connors, MD
George Giannakoulas, MD, PhD
Samuel Z. Goldhaber, MD
Lukas Hobohm, MD, PhD
Beverley J. Hunt, MD, OBE
Karsten Keller, MD, PhD
Alex C. Spyropoulos, MD
***Stefano Barco, MD, PhD**

*Department of Angiology
University Hospital Zurich
Raemistrasse 100, RAE C04
8091 Zurich, Switzerland
E-mail: stefano.barco@usz.ch

https://doi.org/10.1016/j.jacc.2022.08.721

Dr Bikdeli is supported by the IGNITE Award from the Mary Horrigan Connors Center for Women's Health and Gender Biology at Brigham and Women's Hospital and a Career Development Award from the American Heart Association; and has served as a consulting expert, on behalf of the plaintiff, for litigation related to 2 specific brand models of inferior vena cava filters. Dr Connors has received personal fees for scientific advisory boards and consulting from Abbott, Anthos, Alnylam, Bristol Myers Squibb, Five Prime Therapeutics, Pfizer, and Takeda; and has received research funding from CSL Behring. Dr Giannakoulas has received lecture/consultant fees from Bayer HealthCare, Pfizer, and LeoPharma. Dr Hobohm has received lecture/consultant fees from MSD and Actelion, outside the submitted work. Dr Barco has received lecture/consultant fees from Bayer HealthCare, Concept Medical, BTG Pharmaceuticals, INARI, Boston Scientific, and LeoPharma; has received institutional grants from Boston Scientific, Bentley, Bayer HealthCare, INARI, Medtronic, Concept Medical, Bard, and Sanofi; and has received economical support for travel/congress costs from Daiichi-Sankyo, BTG Pharmaceuticals, and Bayer HealthCare, outside the submitted work. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug

Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

REFERENCES

1. Konstantinoudis G, Cameletti M, Gomez-Rubio V, et al. Regional excess mortality during the 2020 COVID-19 pandemic in five European countries. *Nat Commun*. 2022;13:482.

2. Voci D, Fedeli U, Farmakis IT, et al. Deaths related to pulmonary embolism and cardiovascular events before and during the 2020 COVID-19 pandemic: An epidemiological analysis of data from an Italian high-risk area. *Thromb Res*. 2022;212:44–50.

3. Barco S, Valerio L, Ageno W, et al. Age-sex specific pulmonary embolism-related mortality in the USA and Canada, 2000-18: an analysis of the WHO Mortality Database and of the CDC Multiple Cause of Death database. *Lancet Respir Med*. 2021;9:33–42.

4. Jevnikar M, Sanchez O, Chocron R, et al. Prevalence of pulmonary embolism in patients with COVID-19 at the time of hospital admission. *Eur Respir J*. 2021;58:2100116.