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SHORT REPORT
Special populations

Trends and disparities in cardiovascular disease–related mortality among adults with myeloproliferative neoplasms in USA

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Aims We aimed to perform a retrospective cohort study using the Centers for Disease Control and Prevention's (CDC's) Wide-Ranging Online Data for Epidemiologic Research (WONDER) database to analyse the trends in cardiovascular disease (CVD)–related mortality in patients with myeloproliferative neoplasms (MPNs) from 1999 to 2020.

Methods and results We analysed the death certificate data from the CDC WONDER database from 1999 to 2020 for CVD with co-morbid myeloproliferative disorders in the US population. Age-adjusted mortality rates (AAMRs) and 95% confidence intervals (CIs) were computed per 1 million population by standardizing crude mortality rates to the 2000 US census population. To assess annual national mortality trends, we employed the Joinpoint regression model, calculating the annual per cent change in AAMR and corresponding 95% CIs. A total of 15 269 deaths related to CVD occurred in patients with co-morbid MPNs from 1999 to 2020. Overall, there was a decreasing trend in CVD-related AAMRs throughout these years. Males contributed to 51% of total deaths, and their AAMR was persistently higher than women throughout the study. Non-Hispanic (NH) Whites had the highest overall AAMR, followed by NH Blacks, NH American Indians or Alaska Natives, Hispanics or Latinos, and NH Asian or Pacific Islanders.

Conclusion Our findings indicate a significant decline with notable gender, racial/ethnic, and regional differences in CVD-related mortality among patients with MPN over the past two decades. We emphasize the importance of a collaborative approach between oncologists and cardiologists in managing these patients, highlighting the potential benefits of integrating cardio-oncology services to enhance patient outcomes.

Keywords Cardiovascular disease • Ischaemic heart disease • Myeloproliferative neoplasms • Mortality • Disparities • Outcome

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Myeloproliferative neoplasms (MPNs), including polycythaemia vera (PV), essential thrombocytosis, myelofibrosis (MF), and chronic myelogenous leukaemia are clonal stem cell neoplasms that may be associated with an increased risk of developing cardiovascular disease (CVD).[1] The burden of CVD-related mortality has not been thoroughly investigated in patients with MPNs. Therefore, we performed a retrospective cohort study using the Centers for Disease Control and Prevention's (CDC's) Wide-Ranging Online Data for Epidemiologic Research (WONDER) database to analyse the trends in CVD-related mortality in patients with MPN from 1999 to 2020.

This study utilized completely de-identified publicly available data from the multiple cause death files obtained from the CDC's WONDER database.[2] The CDC has been collecting mortality data through standardized death certificates across all US states for the past many decades, providing a consistent and comprehensive record of deaths across the country. We analysed the death certificate data from 1999 to 2020 for CVD with co-morbid MPNs in the US population aged ≥25 years using codes from the International Classification of Diseases, Tenth Revision (ICD-10). Cardiovascular death related to myeloproliferative disorders was ascertained with CVDs (ICD-10 codes: I00–I78) listed as the underlying or primary cause of death and MPNs (ICD-10 codes: C92.1, D45, D47.1, and D47.3) listed as a contributing cause of death in the multiple cause death files.[2] We further stratified CVDs into ischaemic heart diseases (IHDs, including angina pectoris, myocardial infarction, and other forms of acute and chronic IHD), hypertensive diseases (including essential hypertension, hypertensive heart disease with and without heart failure, hypertensive renal disease with and without renal failure, combined hypertensive heart and renal disease, and secondary hypertension), and cerebrovascular diseases (including subarachnoid, intracerebral and other intracranial haemorrhages, cerebral infarction, unspecified stroke, and miscellaneous forms of cerebrovascular diseases). Age-adjusted mortality rates (AAMRs) and 95% confidence intervals (CIs) were computed per 1 million population by standardizing crude mortality rates to the 2000 US census population. To assess annual national mortality trends, we employed the Joinpoint Regression Program (Joinpoint V 4.9.0.0, National Cancer Institute), which is a statistical method used to identify points where significant changes in trends occur, allowing us to calculate the annual per cent change (APC) in mortality rates and pinpoint periods of increase or decrease in our data. Given the de-identified and publicly available nature of the database, institutional review board approval was not required.

A total of 15 269 deaths related to CVD occurred in patients with co-morbid MPNs from 1999 to 2020. Overall, there was a decreasing trend in CVD-related AAMRs throughout these years. The AAMR from CVD decreased from 5.56/1 million population in 1999 to 2.92/1 million population by 2020 (APC −3.81; 95% CI −4.57 to −3.05; $P < 0.05$). On further stratification based on the type of CVD,IHDs contributed to the largest proportion of CVD-related deaths accounting for 48% of all CVD-related deaths. The AAMR from IHD decreased from 2.87/1 million population in 1999 to 1.3/1 million population by 2020 (APC −4.8; 95% CI: −5.5 to −4.1; $P < 0.05$). Cerebrovascular diseases were the second major cause of death accounting for 14% of all CVD-related deaths, and their AAMR decreased from 0.84/1 million population in 1999 to 0.45/1 million population by 2020 (APC −4.1; 95% CI −5.5 to −2.7; $P < 0.05$). Age-adjusted mortality rate from hypertensive diseases, which contributed to 8% of total CVD-related deaths, had a non-significant increase from 0.3/1 million population in 1999 to 0.4/1 million population by 2020 (APC 0.94; 95% CI: −0.17 to 2.08; $P = 0.09$; *Table 1*).

Males contributed to 51% of total deaths, and their AAMR was persistently higher than women throughout the years (overall AAMR: 4.7/1 million population vs. 2.59/1 million population, respectively). Both the males (APC −3.70; 95% CI −4.51 to −2.88; $P < 0.05$) and females (APC −4.22; 95% CI −5.01 to −3.42; $P < 0.05$) had an overall decreasing trend in AAMRs throughout the years (*Figure 1*). On a race-stratified analysis, non-Hispanic (NH) Whites had the highest overall AAMR (3.51/1 million population), followed by NH Blacks (2.2/1 million population), NH American Indians or Alaska Natives (1.88/1 million population), Hispanic or Latinos (1.59/1 million population), and NH Asian or Pacific Islanders (1.51/1 million population). On stratification by age, older adults (65 years and above) had a numerically higher overall AAMR (15.13/1 million population) than younger adults aged 25–64 years (0.34/1 million population). A stratified analysis based on urbanization revealed a higher overall AAMR in rural areas (3.52/1 million population) when compared with urban areas (3.15/1 million population). Age-adjusted mortality rate varied significantly across states, with an AAMR of 7.27/1 million population in North Dakota to 1.39/1 million population in Louisiana (*Figure 1*). On a stratified analysis based on region, the West region had the highest overall AAMR (3.75/1 million population), followed by the Midwest (3.64/1 million population), Northeast (3.39/1 million population), and South regions (2.52/1 million population).

There are limited data on the trends in CVD-related mortality in patients with MPNs, and our study provides important insights using a large national database. The significant findings of our study include the following:

(1) Overall, there was a decreasing trend in CVD-related AAMRs in patients with co-morbid MPNs from 1999 to 2020.
(2) Males contributed to 51% of total deaths, and their AAMR was persistently higher than women throughout the study.
(3) NH Whites had the highest overall AAMR, followed by NH Blacks, NH American Indians or Alaska Natives, Hispanics or Latinos, and NH Asian or Pacific Islanders.

Myeloproliferative neoplasm are situated on the continuum of clonal haematopoietic processes ranging from clonal haematopoiesis of indeterminate potential (CHIP) to diseases such as essential thrombocythaemia, PV, and MF or post-MPN acute leukaemia.[1] Although people with CHIP may not develop overt MPNs, studies have demonstrated a link between CHIP and CVD.[3] Clonal haematopoiesis of indeterminate potential due to mutations in *JAK2* has been associated with the highest risk for myocardial infarction and accounts for up to 19% of all MPN-inducing mutations in patients with myocardial infarction and CHIP, thereby, suggesting shared pathogenesis that connects disorders of clonal haematopoiesis, including MPNs, to atherosclerosis and CVD.[3] Our study demonstrated an overall decrease in CVD-related mortality in patients with MPN in USA over the last two decades. Similar findings have been demonstrated for patients with other cancers including non-Hodgkin lymphoma and breast cancer survivors.[4,5] Several factors have been suggested for the decline in CVD mortality in these studies, such as increased recognition of cardiotoxicity, better cardioprotection strategies during radiotherapy treatment, more frequent cardiac monitoring, and the use of dexrazoxane to mitigate anthracycline toxicity. Multiple other studies have also shown decreasing overall CVD mortality in USA and CVD mortality among cancer patients at large over the last few decades.[6,7] The decrease in CVD mortality observed in our study could likely be due to the increased recognition of adverse cardiac events in patients with cancer and more comprehensive screening for CVDs in cancer patients, overall increased utilization of cardioprotective medications such as statins, and increased recognition and utilization of therapies such as aspirin, cytoreduction using hydroxyurea, and phlebotomy, which have shown to prevent thrombotic events and therefore reduce morbidity and mortality in patients with MPNs.[8–10] In our analysis, we have also observed an upward spike in mortality in 2020, which is probably driven by COVID-19 pandemic-driven excess mortality worldwide.[11]

This study has some limitations, and it is important to exercise caution when interpreting the results of our study. Owing to the nature of

Table 1 Age-adjusted mortality rates (95% confidence intervals) from cardiovascular disease in patients with co-morbid myeloproliferative neoplasms from 1999 to 2020, stratified by the type of cardiovascular disease

Year	Cardiovascular disease	IHD	Cerebrovascular disease	Hypertensive disease
1999	5.6 (5.21–5.91)	2.87 (2.62–3.12)	0.84 (0.71–0.98)	0.3 (0.23–0.40)
2000	5.17 (4.83–5.50)	2.71 (2.47–2.95)	0.77 (0.64–0.90)	0.22 (0.16–0.31)
2001	4.77 (4.45–5.09)	2.46 (2.23–2.69)	0.74 (0.61–0.87)	0.25 (0.18–0.34)
2002	4.6 (4.29–4.92)	2.35 (2.12–2.57)	0.6 (0.49–0.71)	0.27 (0.20–0.37)
2003	4.3 (4.01–4.60)	2.2 (1.99–2.41)	0.61 (0.50–0.73)	0.28 (0.20–0.36)
2004	4.11 (3.82–4.40)	2.05 (1.85–2.26)	0.6 (0.49–0.71)	0.27 (0.20–0.35)
2005	3.67 (3.40–3.94)	1.79 (1.60–1.98)	0.58 (0.47–0.69)	0.22 (0.16–0.29)
2006	3.39 (3.13–3.64)	1.64 (1.46–1.82)	0.44 (0.35–0.54)	0.24 (0.18–0.32)
2007	3.09 (2.85–3.33)	1.65 (1.47–1.83)	0.31 (0.24–0.40)	0.24 (0.18–0.32)
2008	3.11 (2.86–3.35)	1.56 (1.38–1.73)	0.38 (0.30–0.48)	0.26 (0.19–0.34)
2009	2.87 (2.64–3.10)	1.42 (1.26–1.58)	0.36 (0.28–0.46)	0.2 (0.14–0.27)
2010	2.87 (2.64–3.10)	1.3 (1.15–1.46)	0.32 (0.25–0.41)	0.26 (0.20–0.34)
2011	2.69 (2.47–2.91)	1.33 (1.18–1.49)	0.35 (0.28–0.44)	0.26 (0.20–0.34)
2012	2.63 (2.42–2.85)	1.21 (1.06–1.35)	0.29 (0.23–0.38)	0.25 (0.19–0.32)
2013	2.59 (2.38–2.80)	1.25 (1.10–1.39)	0.34 (0.27–0.43)	0.23 (0.17–0.30)
2014	2.57 (2.37–2.78)	1.09 (0.96–1.23)	0.37 (0.30–0.46)	0.19 (0.14–0.25)
2015	2.43 (2.23–2.63)	1.14 (1.01–1.28)	0.29 (0.23–0.37)	0.24 (0.18–0.31)
2016	2.46 (2.27–2.66)	1.07 (0.94–1.20)	0.31 (0.24–0.39)	0.26 (0.20–0.34)
2017	2.37 (2.18–2.56)	1.06 (0.93–1.18)	0.3 (0.24–0.38)	0.25 (0.19–0.32)
2018	2.4 (2.21–2.59)	1.02 (0.90–1.15)	0.32 (0.26–0.40)	0.26 (0.20–0.33)
2019	2.49 (2.30–2.69)	1.03 (0.91–1.15)	0.38 (0.31–0.46)	0.32 (0.25–0.40)
2020	2.92 (2.72–3.13)	1.3 (1.16–1.44)	0.45 (0.37–0.53)	0.4 (0.32–0.48)
Total	**3.23 (3.18–3.28)**	**1.56 (1.52–1.59)**	**0.46 (0.44–0.48)**	**0.24 (0.23–0.26)**

death certificate data, an accurate assessment of the cause of death cannot be determined. The identification of decedents' race and ethnicity was based on information extracted from death certificates, which may occasionally be inaccurate, leading to potential misclassification. Additionally, the database lacks information at individual levels, such as socio-economic factors, co-morbidity status, duration of disease,

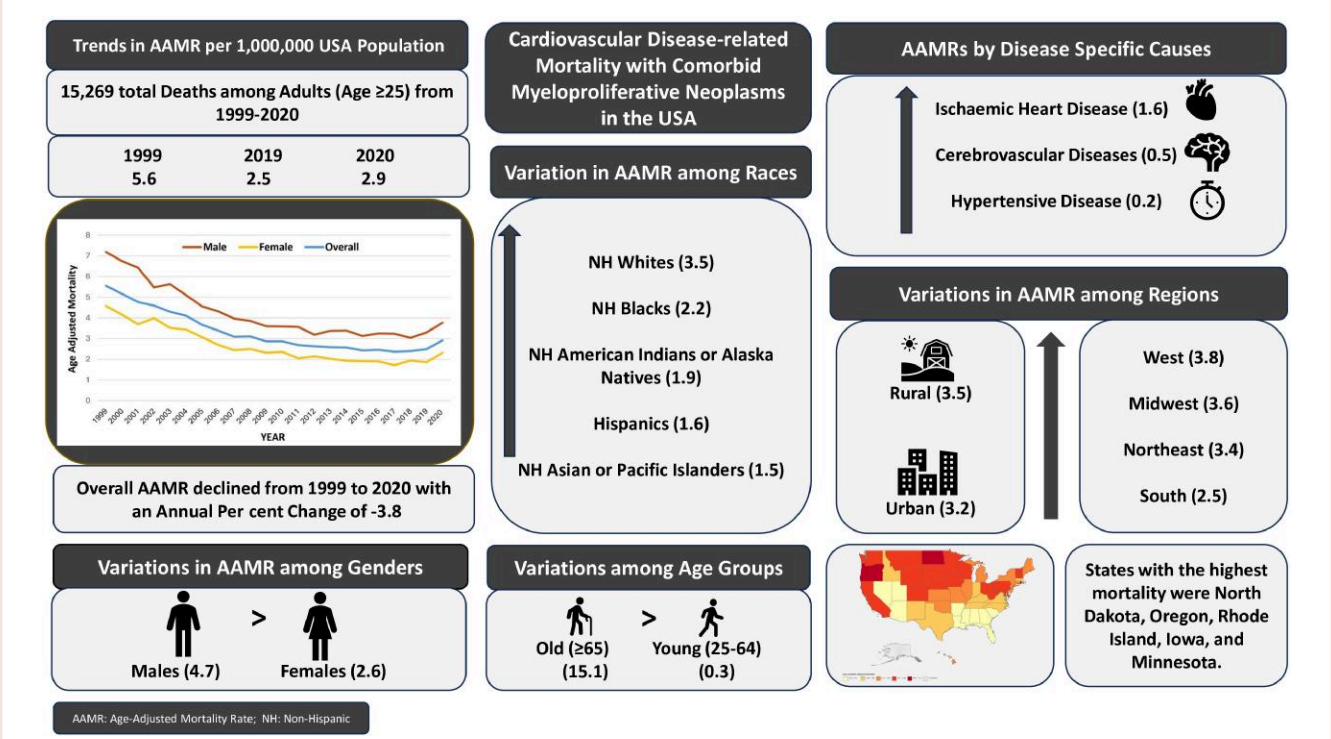

Figure 1 Cardiovascular disease–related mortality in adult patients with co-morbid myeloproliferative neoplasms in the USA from 1999 to 2020.

and medical treatments, which are essential confounders for mortality and can influence access to healthcare.

In conclusion, our study demonstrates a significant decrease in CVD-related mortality in patients with MPN over the last two decades. Notable gender, racial/ethnic, and regional differences exist in the rates of CVD-related mortality in patients with MPNs. These findings underscore the importance of a multi-disciplinary approach to the care of these patients, particularly between oncologists and cardiologists, and suggest the widespread adoption of cardio-oncology services to improve the outcomes of patients with MPNs.

Lead author biography

Dr Siddharth Agarwal is an Assistant Professor of Medicine and a Cardiology fellow at Mayo Clinic in Rochester. He earned his medical degree from Vardhman Mahavir Medical College and Safdarjung Hospital in India and completed his Internal Medicine residency at the University of Oklahoma. His research focus centres on managing cardiovascular disease in specialized patient populations, particularly individuals undergoing cancer treatment.

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical approval

Due to the de-identified nature of the dataset, the need for informed consent and Institutional Review Board approval are waived.

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