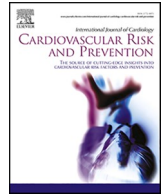




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## Patterns in mortality associated with heart failure and lung cancer among older adults in the United States: An analysis of 20 years

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### ABSTRACT

**Background:** Despite an established association between heart failure (HF) and lung cancer (LC), there is limited evidence available regarding mortality patterns among the older ( $\geq 65$  years) population in the United States.

**Methods:** The mortality data, spanning 1999 to 2019, was surveyed using the Centers for Disease Control and Prevention's Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database with HF and LC identified as underlying or contributing causes of death. Crude and age-adjusted mortality rates (AAMR) were calculated per 100,000 individuals. Joinpoint regression was applied to establish annual percent changes (APCs) for the trends in years, demographics (sex, race), and geographical regions.

**Results:** Between 1999 and 2019, the overall AAMR slightly decreased from 13.0 to 11.4. However, the AAMRs significantly increased (APC: 6.37; 95 % CI: 3.39 to 8.23) from 2017 to 2019. Males had double the AAMRs compared to females (overall AAMR: 15.7 vs. 8.0), yet both sexes experienced a final incline in death rates. Among the distinct racial and ethnic groups, non-Hispanic (NH) Whites (11.9) and NH Black/African Americans (10.9) portrayed the highest AAMRs. Patients most commonly died in medical facilities (41.03 %). Geographical disparities were evident with higher AAMRs in non-metropolitan areas (14.3) and the Midwest (12.7). States with the highest fatality involved West Virginia, Oklahoma, Kentucky, Mississippi, and Arkansas.

**Conclusion:** The abrupt rise in overall mortality rates for HF and LC from 2017 to 2019 is noteworthy. A focused analysis of demographic and geographic disparities is warranted to address this emerging trend.

### 1. Introduction

In the United States (US), cancer and cardiovascular diseases (CVD) account for nearly half of all deaths and have been ranked consistently as the leading causes of mortality over the past century [1,2]. A recent projection estimates that in 2024 alone, more than 600,000 deaths will be attributed to cancer, with lung cancer (LC) being the predominant

contributor. Despite being the third most commonly diagnosed cancer, LC tops the list in terms of cancer-related fatalities [3]. It is also worthwhile to mention that approximately 80 percent of the deaths due to LC in the US are due to direct smoking [4].

CVDs are suggested to be the second most frequent cause of death among cancer patients [5]. These patients face more than twofold higher risk of dying from CVD compared to the general population [6]. Shared

**Abbreviations:** US, United States; CVD, cardiovascular disease; LC, lung cancer; HF, heart failure; CDC WONDER, centers for disease control and prevention's wide-ranging online data for epidemiologic research; ICD, international classification of diseases; STROBE, strengthening the reporting of observational studies in epidemiology; NH, non-Hispanic; AAMR, age-adjusted mortality rate; APC, annual percent change; CI, confidence interval.

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risk factors, such as obesity and smoking, as well as common symptoms like dyspnea, fatigue, edema, and weight loss, link heart failure (HF) and cancer [7]. Importantly, cardiotoxicity, a frequent adverse effect of chemotherapy and anticancer medications, can contribute to HF development in cancer patients, and such patients face a 3.5-fold higher risk of fatality in comparison to those with idiopathic cardiomyopathy [8,9].

Regrettably, recommendations for preventing heart disease in cancer patients remain scarce. Currently, no formal guidelines exist to aid healthcare professionals in identifying cancer patients at the highest risk of fatal heart disease [6]. Given the rapid introduction of novel therapies for both CVDs and LC, it is imperative to assess demographic and temporal trends in HF and LC-associated deaths. In this study, we analyzed these trends stratified by year, gender, and demographic subgroups from 1999 to 2019 within the US.

## 2. Material and methods

### 2.1. Study design and Cohort

The data for mortality was retrieved using the Centers for Disease Control and Prevention's Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database [10], which comprises extensive epidemiological data. Our evaluation targeted mortality trends among the older population with concomitant diagnoses of HF and LC over a period spanning 1999 and 2019. We employed the International Statistical Classification of Diseases and Related Health Problems (ICD) codes, 10th Revision, to identify HF and malignant neoplasm of bronchus and lung on death certificates by using the codes I50 and C34, respectively. Similar codes have been used in previous studies to represent the assigned diseases [11]. This investigation centered on certificates of death within the Multiple Cause of Death Public Use dataset, enabling us to inspect fatality among patients ( $\geq 65$  years) with a concomitant diagnosis of HF and LC. Prior research studies have employed a similar age cutoff for characterizing individuals as older adults [11]. The investigation was restricted until the year 2019 to avoid COVID-19 as a confounding factor that resulted in a substantial amount of deaths in the year 2020. The overall fatalities for the year 2020 were reported separately. This approach follows a previously published research study of a similar nature and design [12]. We regarded an institutional review board permission to be unnecessary for this research study as the dataset, issued by the government, is non-identifiable and is available publicly. To ensure quality reporting, the criteria outlined in Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were implemented in this observational research [13].

### 2.2. Data acquisition

To conduct our research, demographic characteristics (encompassing population size, gender, racial and ethnic identity, geographical location, urbanization status, and location where death was documented) were analyzed. The definitions for racial and ethnic categories encompassed non-Hispanic (NH) American Indian or Alaska Native, NH Black or African American, NH White, NH Asian or Pacific Islander, and Hispanic or Latino populations. Alaskan Natives were excluded from race-wise analysis due to unreliable data. The locations where deaths were documented involved medical facilities, residences, hospice facilities, nursing homes/long-term care facilities, and instances where the location remained unspecified.

The study population was geographically divided, taking into account the National Center for Health Statistics Urban-Rural Classification Scheme. Urban areas housed populations of 50,000 or more, while Rural areas included locales with fewer than 50,000 residents. Furthermore, in accordance with the US Census Bureau's classification, the whole United States was divided into four separate regions:

Northeast, Midwest, South, and West, respectively [14].

### 2.3. Statistical analysis

We methodically evaluated overall, gender, race, urbanization, and geography-related fatality patterns by computing both crude and age-adjusted mortality rates (AAMR) per 100,000 individuals. AAMRs were standardized as per the 2000 US population.

The Joinpoint Regression Program (Version 5.0.2, National Cancer Institute) was implemented as a statistical software for examining temporal shifts in mortality rates [15]. This analytical approach involved fitting log-linear regression models to the raw data trends, allowing us to calculate the annual percent change (APC) in AAMR and its 95 % confidence interval (CI). We analyzed whether APCs indicated increasing or decreasing trends by assessing their statistical deviation from the null hypothesis of zero change. A two-tailed *t*-test, with a threshold of  $P < 0.05$ , was used to determine statistical significance. Similar statistical methods have been used before to analyze the data [16,17].

## 3. Results

A cumulative of 95,543 older patients with concurrent HF and LC died between 1999 and 2019 (Supplemental Table A1). We were able to access information related to death location for 91,548 fatalities. Within this group, 41.03 % of deaths were documented at medical facilities, 33.56 % at residences, 20.11 % at nursing homes, and 5.28 % at hospice facilities (Supplemental Table A2).

The overall AAMR experienced a slight decline during our study period (1999: 13.0 vs 2019: 11.4). The mortality rate initially remained stable from 1999 to 2004, which was pursued by a substantial depreciation until 2013 (APC: -2.71; 95% CI: -4.58 to -2.29). Following a period of stable rise till 2017, the trend reverted with a profound rise in AAMRs until 2019 (APC: 6.37; 95 % CI: 3.39 to 8.23) (Fig. 1, Supplemental Tables A3 and A.9).

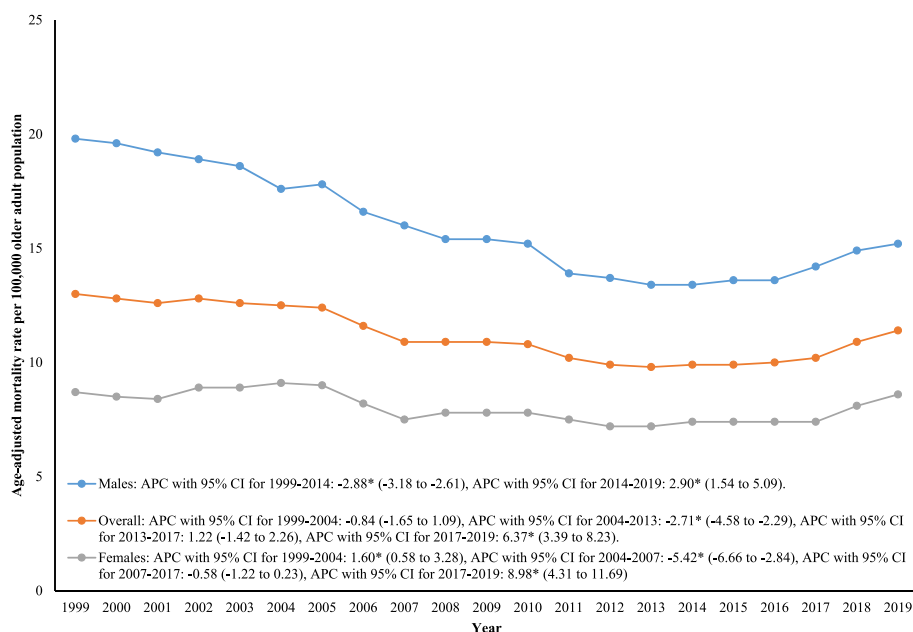
### 3.1. Variations in mortality trends within demographic subgroups associated with HF and LC

#### 3.1.1. Sex

Throughout our study period, males had almost double the AAMRs (Overall AAMR: 15.7) compared to females (Overall AAMR: 8.0). For males, the death rates declined significantly during the initial segment spanning from 1999 to 2014 (APC: -2.88; 95% CI: -3.18 to -2.61), which was trailed by a notable increase in AAMRs until 2019 (APC: 2.90; 95 % CI: 1.54 to 5.09). Females, however, exhibited a more fluctuating trend with the mortality rates initially rising from 1999 to 2004 (APC: 1.60; 95 % CI: 0.58 to 3.28) and then declining abruptly until 2007 (APC: -5.42; 95% CI: -6.66 to -2.84). Following this, AAMRs stabilized until 2017, however, the mortality rate inclined in the following years (APC: 8.98; 95 % CI: 4.31 to 11.69) (Fig. 1, Supplemental Tables A3 and A.9).

#### 3.1.2. Race

The overall AAMR was detected to be the highest among NH White populations (11.9), immediately trailed by NH Black or African American populations (10.9). Conversely, the lowest overall death rates were detected among Hispanic or Latino populations (4.6) and NH Asian or Pacific Islander populations (4.4). Concerning the NH White populations, after an initial period of stability, the AAMRs considerably dropped from 2003 to 2014 (APC: -2.32; 95% CI: -3.70 to -1.97), succeeded by a noteworthy surge in AAMRs until 2019 (APC: 4.04; 95 % CI: 2.73 to 6.02). Similarly, the AAMRs dropped considerably from 1999 to 2017 for NH Black and African American populations (APC: -1.70; 95 % CI: -3.71 to -1.02) and until 2014 in the case of Hispanic or Latino communities (APC: -3.63; 95% CI: -7.54 to -2.62). A reversal of trend occurred with both races subsequently experiencing an ascend



**Fig. 1.** Patterns related to overall and sex-associated age-adjusted death rates per 100,000, among older ( $\geq 65$ ) adults with heart failure and lung cancer in the United States, 1999 to 2019.

\*Demonstrates that the annual percent change (APC) is significantly different from zero at  $\alpha = 0.05$ .

in AAMRs until 2019; however, the trend appeared to be non-significant (APC for NH Black or African American: 8.03; 95% CI: -1.27 to 13.01; APC for Hispanic or Latino: 1.82; 95% CI: -1.99 to 11.89). Regarding the NH Asian or Pacific Islander subgroup, a constant drop in mortality was noted over the 20-year period (APC: -2.67; 95% CI: -3.64 to -1.55) (Fig. 2, Supplemental Tables A4 and A.9).

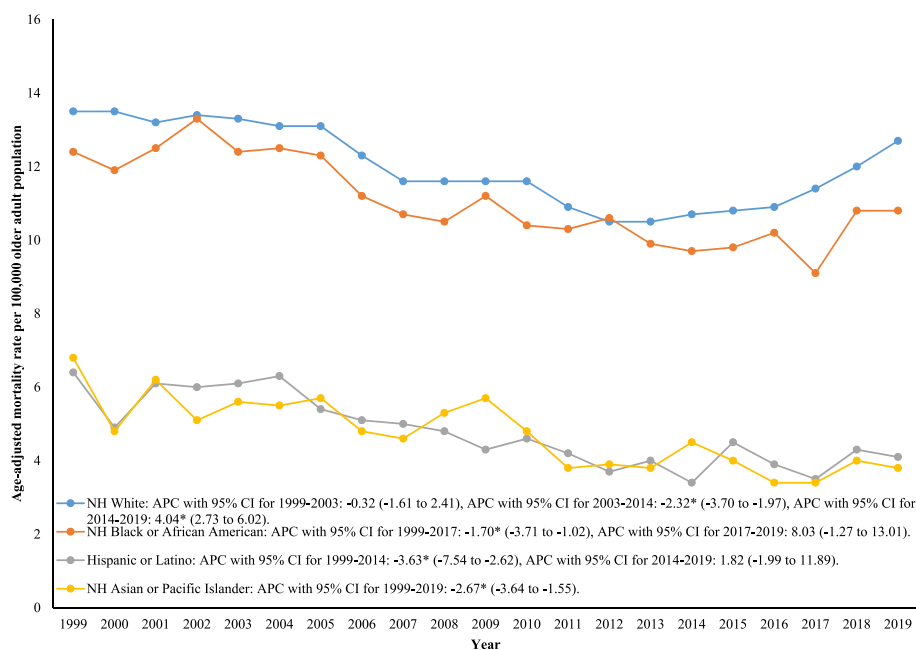
### 3.1.3. Geographic variations

Stratification by states revealed notable disparities in fatality, with death rates varying from 5.0 in Utah to 18.9 in Arkansas. States with AAMRs in the upper 90th percentile (West Virginia, Oklahoma,

Kentucky, Mississippi, Arkansas) had mortality rates as high as threefold compared to the states falling into the lower 10th percentile (Utah, Arizona, Nevada, District of Columbia, and Hawaii) (Fig. 3, Supplemental Table A5).

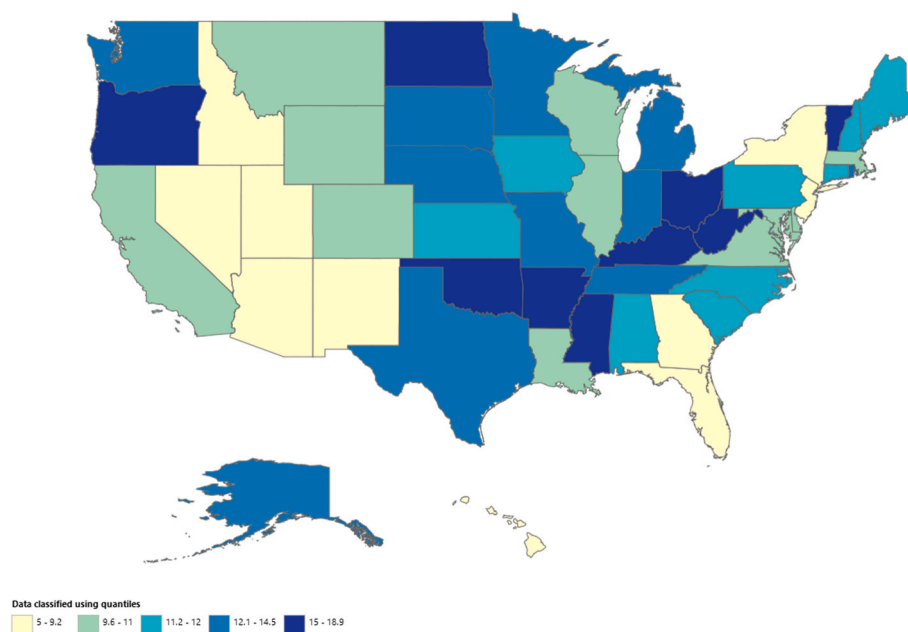
Among all the regions in the US, the Midwestern region was noticed with the highest overall fatality (AAMR: 12.7). The Southern region followed (AAMR: 11.3), while the West (AAMR: 10.1) and Northeast (AAMR: 10.1) were observed to be the regions depicting the lowest overall mortality (Supplemental table A6).

Higher age-adjusted death rates were noted in non-metropolitan areas (14.3) as compared to metropolitan areas (10.4). In non-



**Fig. 2.** Patterns in age-adjusted death rates per 100,000, among older ( $\geq 65$ ) adults with heart failure and lung cancer categorized by race/ethnicity in the United States, 1999 to 2019.

\*Demonstrates that the annual percent change (APC) is significantly different from zero at  $\alpha = 0.05$ .



**Fig. 3.** Heart failure and lung cancer-associated age-adjusted death rates per 100,000, among older ( $\geq 65$ ) adults categorized by states in the United States, 1999 to 2019.

\*Map lines delineate study areas and do not necessarily depict accepted national boundaries.

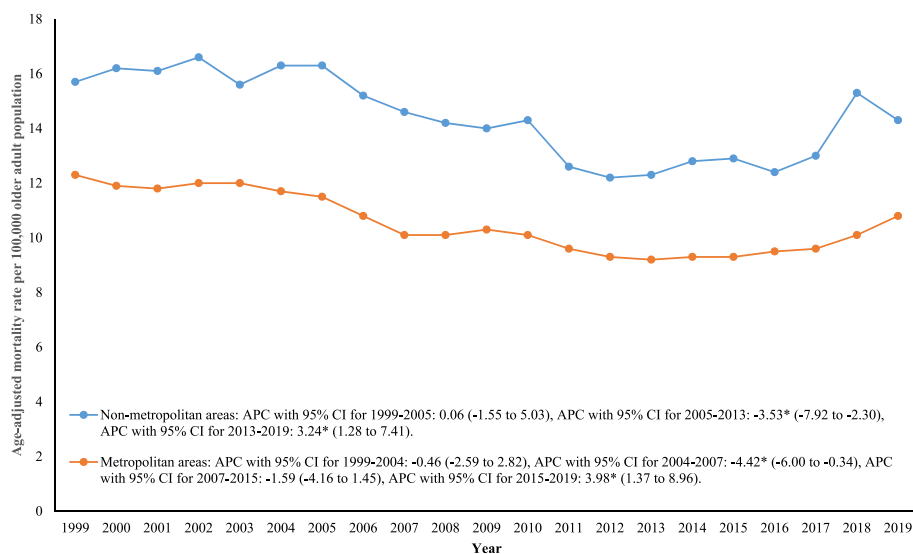
metropolitan areas, AAMRs were noted to be stagnant between 1999 and 2005, succeeded by a noteworthy fall in mortality until 2013 (APC: -3.53; 95% CI: -7.92 to -2.30), and eventually trailed by a prominent incline until 2019 (APC: 3.24; 95% CI: 1.28 to 7.41). Similarly, metropolitan areas, after an initial period of stability, experienced a substantial decrease in AAMRs between 2004 and 2007 (APC: -4.42; 95% CI: -6.00 to -0.34), with a phase of relative stability thereafter until 2015. A prominent uptrend in AAMRs was then noted until 2019 (APC: 3.98; 95% CI: 1.37 to 8.96) (Fig. 4, Supplemental Tables A7 and A.9).

### 3.2. Overall fatality patterns related to HF alone and LC alone between 1999 and 2019

Concerning HF alone, the overall AAMR was noted to be 659.2,

ranging between 769.4 in 1999 and 653.8 in 2019. The fatality rate dropped notably until 2005 (APC: -1.66; 95% CI: -2.77 to -0.49) which then further dropped sharply until 2009 (APC: -3.37; 95% CI: -4.54 to -0.89). The trend then underwent a period of relative stability until 2012 after which the fatality rates inclined for the remaining years (APC: 1.48; 95% CI: 0.75 to 2.62) (Supplemental Tables A8 and A.9).

About LC, an overall AAMR of 291.0 was noted, ranging between 335.8 in 1999 to 220.4 in 2019. The mortality trend remained stable initially until 2001; however, it was observed to drop after that for the remaining years (APC for year interval 2001 to 2005: -0.81; 95% CI: -1.86 to -0.45; APC for year interval 2005 to 2010: -1.64; 95% CI: -2.97 to -1.17; APC for year interval 2010 to 2014: -2.98; 95% CI: -4.43 to -2.47; APC for year interval 2014 to 2019: -3.95; 95% CI: -4.93 to -3.18) (Supplemental Tables A8 and A.9).



**Fig. 4.** Patterns in age-adjusted death rates per 100,000, among older ( $\geq 65$ ) adults with heart failure and lung cancer categorized by urban-rural classification in the United States, 1999 to 2019.

\*Demonstrates that the annual percent change (APC) is significantly different from zero at  $\alpha = 0.05$ .

### 3.3. HF and LC combined, HF alone and LC alone associated AAMRs in the year 2020

The AAMR regarding HF and LC combined was noted to be at 11.9 for 2020. Similarly, in the same year, HF alone and LC alone were noted with an AAMR of 698.6 and 214.3 respectively.

## 4. Discussion

Our study reveals significant findings obtained from analyzing a 20-year timeframe of HF and LC-related mortality among older adults in the United States. Although the overall mortality rate slightly declined between 1999 and 2019, the increase in trend from 2017 to 2019 is noteworthy. During the study period, males had nearly double the mortality rate as females. Among the racial groups, NH Whites reported the highest death rates, while the Hispanic or Latinos and NH Asian or Pacific Islanders had the lowest. Significant geographic and regional variations in the trends were also observed, with the highest death rate noted in the Midwest region and the rural localities. West Virginia, Oklahoma, Kentucky, Mississippi, and Arkansas had nearly three folds the AAMRs in comparison to the states on the lower end of the spectrum, which included Utah, Arizona, Nevada, the District of Columbia, and Hawaii.

Both cancer and HF are a major cause of mortality and morbidity worldwide [18,19]. It is hypothesized that chronic non-communicable diseases – namely CVDs, diabetes mellitus, and cancers – are inter-linked and share common comorbidities, collectively referred to as “CVD-DM-cancer strips” (CDC strips). The CDC strips consist of three pairs of branches, one of which represents the Cancer-CVD or CVD-Cancer relationship [20]. There have been reports of a frequent occurrence of HF and cancer, with emerging evidence suggesting a direct relationship between the two diseases [21]. Additionally, lung cancer, one of the most frequently occurring cancers, is a multifaceted disease with various histological variants. Individuals diagnosed with LC frequently exhibit concurrent cardiovascular conditions and may encounter diverse cardiovascular complications, such as HF, during their antineoplastic therapy [22]. The oncology domain has witnessed an increasing utilization of recently discovered targeted medicines [23]. While there have been significant advancements in survival rates, certain treatments for LC, such as high-dose chemotherapy, anthracyclines, and tyrosine kinase inhibitors, have been known to produce cardiotoxic events, including HF [20,23,24]. Despite contributing substantially to morbidity, mortality, and both direct and indirect healthcare costs, these disease clusters may be mitigated through the management of modifiable risk factors including behavior, environment, diet, and exercise [20].

Although the results of our study demonstrate only a slight decrease in overall mortality due to HF and LC in the older population from 1999 to 2019, a rising trend was seen from 2017 onwards. This can be attributed to the fact that the likelihood of mortality due to heart disease and cancer often rises in correlation with advancing age [25]. Consequently, the incidence of deaths caused by heart disease and cancer escalates as the population of the US expands and ages [19,25]. Additionally, the increase in LC survival and shared risk factors such as hypertension, obesity, diabetes, smoking, and genetics could be the reason for these trends [21]. Nevertheless, this data should be used to guide the efforts to treat and prevent cardiovascular complications in LC patients, especially older adults, since older individuals face the greatest susceptibility to both the occurrence and death rates associated with LC [26].

Furthermore, our data revealed that older males exhibited a consistent pattern of higher mortality rates than females throughout the study period. One possible explanation for these results is that both mortality rates for HF and LC, when observed separately, are higher in males than in females [17,27]. Additionally, as stated earlier, smoking is a significant risk factor for LC and HF [21,27]. Smoking is responsible for 80 %

of the cases of LC [27] and has a substantial impact on the globally increased rates of death from LC. The possible explanation for higher mortality rates in males could be the greater prevalence of smoking in males as compared to females [28]. Sex differences in body composition can also affect pharmacokinetic and pharmacodynamic variations, leading to different responses to guideline-directed medical therapy for HF [29]. It is important to conduct comprehensive research on sex-based differences to develop sex-sensitive strategies and guidelines for the prevention, diagnosis, treatment, and management of LC and HF.

Our findings also reveal substantial disparities among racial and ethnic groups, with older NH-White and African American adults demonstrating the highest while Hispanic or Latino and NH-Asian individuals exhibiting the lowest mortality rates in HF and LC patients. These variations might also be attributed to the prevalence [30], and according to one study, Hispanic populations had the lowest prevalence of LC [31]. Moreover, different patterns of behavioral risk factors in different racial groups could be a cause of disparities in mortality rates among them. For instance, NH Black or African American and NH White individuals have the highest rates of smoking, while Hispanic and NH Asian or Pacific Islander individuals demonstrate the lowest rates [30]. Considering that race is a concept created by society, and various factors can lead to mortality before the age of 75, this could indicate disparities connected to the influence of survival bias [17]. Additionally, the relationship between social determinants of health is complicated and diversified [30]. However, geographical residence, along with environmental factors, including smoking, radon, pollution, and other unidentified elements, can potentially contribute to racial and ethnic differences [31]. Over the past decade, African Americans experienced the most significant increase in death rates compared to other racial groups [32]. This phenomenon can also be ascribed to socioeconomic obstacles and the expenses associated with insurance, resulting in situations such as insufficient utilization of healthcare services [33] and a lack of or minimal health insurance coverage [34].

We also studied the significant geographical variations in the mortality trends. The Midwestern region was recorded with the highest fatality while the West and Northeast were identified as regions depicting the lowest death rates. A study that explored the mortality trends due to HF suggested that the significant regional disparity may be attributed to inconsistencies in outpatient cardiology practice, including variations in the extent to which guideline-directed therapy is implemented, the impact of state regulations on Medicaid, limited availability of high-quality healthcare, a higher prevalence of comorbidities, and a sedentary lifestyle [17]. The Midwest and South have the greatest smoking prevalence rates, while the Northeast and West have the lowest rates. This disparity may account for variations in death rates across different regions in the US [30]. Additionally, trends in LC incidence are also changing based on the residential location [31]. Our findings also revealed that non-metropolitan areas had significantly higher mortality rates than metropolitan areas which can be supported by the differences in environmental and behavioral risk factors. A recent investigation revealed that the rate of death caused by smoking has decreased most rapidly in major cities and coastal regions. In contrast, it has decreased at a slower pace in rural areas of the US [30,35]. Furthermore, there is a lesser supply of primary care physicians in rural locations, contributing to greater mortality rates [36]. This is because the primary care physician density had the most significant impact on reducing cause-specific mortality rates for cardiovascular disease and cancer. These conditions have been proven to be highly responsive to primary care management or early screening through primary care, resulting in delayed mortality [36].

The Centers for Disease Control and Prevention (CDC) estimates that there are roughly 91,000 premature deaths and 84,000 early deaths caused by heart disease and cancer each year respectively, which have the potential to be avoided [37]. Targeted interventions, such as the use of telemedicine platforms, equitable access to healthcare, tailored smoking cessation, and screening programs, can provide benefits to



vulnerable subgroups throughout cancer and cardiovascular care. This also warrants a more proactive approach involving optimal care coordination between oncologists and cardiologists. Moreover, future investigations should explore the possible risk factors responsible for the racial and regional disparities.

Our study has certain limitations that should be addressed. First, the dependence on certificates of death and utilization of ICD codes augment the potential for a misleading diagnosis, misinterpretation, omission, and/or transcription errors of data, accounting for marginal unreliability. Secondly, the lack of laboratory data, lifestyle information including socioeconomic status and smoking habits, air quality index of different geographical regions, the echocardiographic results, the histologic subtypes of LC, and other HF and LC-related specifications severely limit the extent of our analysis. Third, we had to exclude the data of Alaskan natives from our race-wise analysis since most of the data was unreliable.

## 5. Conclusion

In conclusion, in the US, older adults have shown an overall slight declining trend of mortality associated with HF and LC, however, the rise in fatality in the final years of the study duration is alarming. Disparities in mortality were also evident, which was more widespread among males, NH White and NH Black or African American individuals, and those living in rural regions. LC and HF are both alarming public health concerns. Future research studies are crucial to further investigate the underlying mechanisms and to develop optimal management strategies.

## CRediT authorship contribution statement

**Abdul Ahad:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Project administration, Investigation, Formal analysis, Conceptualization. **Eeshal Fatima:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Wania Sultan:** Writing – review & editing, Writing – original draft, Formal analysis. **Muhammad Haleem Nasar:** Writing – review & editing, Writing – original draft, Formal analysis. **Adeena Jamil:** Writing – review & editing, Writing – original draft, Validation, Supervision, Formal analysis. **Muteia Shakoor:** Writing – review & editing, Writing – original draft, Formal analysis. **Irfan Ullah:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology. **M Chadi Alraies:** Writing – review & editing, Visualization, Validation, Supervision. **Naeif Almagal:** Writing – review & editing, Visualization, Validation, Supervision.

## Declaration

This manuscript represents original research with every author's contribution. It is not currently under review or previously published elsewhere and will not be published anywhere in any form after its acceptance. We have thoroughly reviewed the instructions for authors and confirm that no funding sources are associated with this work. All authors declare no conflicts of interest. We agree to all conditions and grant publication rights. The manuscript has been approved by all authors for submission to the journal.

## Research data

All the data used in this research has been obtained from the CDC WONDER database, the link to which is provided in the materials and methods section of the manuscript. It is government-issued data that is freely accessible from the internet.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcrp.2024.200353>.

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