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ARTICLE

Demographic and regional trends of heart failure and cachexia-related mortality among older adults in the United States, from 1999 to 2020

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Abstract

Cachexia is a debilitating yet under-recognized condition, particularly among the elderly population. It has been shown that patients with heart failure (HF) often have cachexia, leading to worsening mortality rates. There is limited research on mortality trends and demographic disparities in terms of cachexia. CDC WONDER (Centers for Disease Control and Prevention Wide-Ranging ONline Data for Epidemiologic Research) database was used, where HF and cachexia were listed as either contributory or underlying causes of death in adults >65 years from 1999-2020. Age-adjusted mortality rates (AAMRs) and annual percent changes (APC) were calculated and stratified by year, sex, race/ethnicity, and region. No change in mortality was seen due to HF + cachexia from 2004-2020 (APC -2.1%; 95% CI, -3.2 to 0.6). Almost half of the deaths (47%) occurred within nursing homes. Notably, White adults had a higher mortality than Black/ African American adults (23.8; 95% CI, 23.4 to 24.1 vs 18.4; 95% CI, 17.4 to 19.4). Mortality rates were also higher in rural areas than urban areas (27.9; 95% CI, 27.1 to 28.7 vs 22.1; 95% CI, 21.8 to 22.4). States in the top 90th percentile, including Idaho, Utah, Vermont, South Carolina, Alaska and New Hampshire, had 5-fold higher mortality than states in the lower 10th percentile. No change in mortality was seen due to HF and cachexia-related mortality in the last decade, with substantial racial and regional disparities. Targeted interventions are needed to curb these mortality trends.

Key words: chronic heart failure; CVD in elderly; cachexia.

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Introduction

Heart failure (HF) affects 64 million individuals worldwide and around 7 million individuals in the United States, which is expected to double in 2050.[1] Patients with HF often have multiple co-morbidities which affect their prognosis and quality of life. Another important factor in elderly patients with HF is cachexia, which often remains under-recognized. Cachexia in HF patients is a multifactorial condition characterized by involuntary non-edematous weight loss of more than 6% within 12 months or less, loss of skeletal muscle (with or without fat loss), decreased appetite, systemic inflammation, and a catabolic state unresponsive to nutritional support. It leads to reduced physical function and increased mortality.[2] It is an intense catabolic state involving muscle loss or wasting at multiorgan levels, which cannot be reversed by nutritional intake alone. Cachexia not only affects quality of life, but is also an important risk factor for mortality, regardless of age, and ejection fraction (EF).[3] Currently, it affects approximately 10-15% of patients with chronic HF, which can reach as high as 39% depending on the diagnostic criteria employed for cachexia.[4]

Knowledge gaps persist in understanding the interplay between HF and cachexia, as each condition can trigger and exacerbate the other. Chronic HF triggers systemic inflammation, marked by elevated circulating cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and C-reactive protein (CRP) which activate proteolytic systems, contributing to profound

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skeletal and cardiac muscle degradation.[3-5] Importantly, when HF leads to cachexia, a condition commonly referred as cardiac cachexia, it carries a significant annual mortality risk of approximately 50%.[5] Despite its significant impact on mortality and morbidity, existing studies often focused on HF outcomes and mortality without stratifying for the presence of cachexia. Therefore, in this study, we aimed to investigate the demographic and regional disparities due to HF + cachexia-related mortality among older adults in the US from 1999 to 2020.

Materials and Methods

Study setting and population

The Centers for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database was utilized to access data on deaths related to cardiovascular diseases in the United States.[6] The Multiple Cause-of-Death (MCOD) Public use death certificates were used to identify cases where both HF and cachexia were listed as either contributory or underlying causes of death on death-certificates. This database has previously been utilized to analyze mortality patterns related to HF.[7] Cachexia was identified using the International Classification of Diseases 10th Revision Clinical Modification (ICD-10-CM) codes R64, while HF was identified using ICD-10-CM codes I11.0, I13.0, I13.2, I50, I25.5, I42, O90.3, focusing on individuals ≥65 years.[7] This study was not subject to local Institutional Review Board approval as it utilized deidentified government-issued publicly available data and adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for reporting.

Data extraction

Data on HF and cachexia-related deaths, population size, year, location of death, demographics, urban-rural classification, census regions and states, were extracted. The location of death was categorized into medical facilities (outpatient or emergency room, inpatient, death on arrival, or unknown status), home, hospice, and nursing home/long-term care facility. Demographic information (sex, race/ethnicity) and regional details (urban-rural classification, census region and state) were extracted for the period spanning 1999 to 2020. To assess the population by urban-rural classification, the National Center for Health Statistics Urban-Rural Classification Scheme was employed, dividing counties into metropolitan (large central metropolitan, large fringe metropolitan, medium metropolitan, and small metropolitan) and non-metropolitan (micropolitan and noncore) categories following the 2013 US census classification.[8] Race and ethnicity were classified into Black or African American and White based on data reported on death certificates, which has been used in previous analyses of the WONDER database. The regions were classified into Northeast, Midwest, South, and West based on Census Bureau definitions.

Statistical analysis

To analyze national trends in HF + cachexia-related mortality, we calculated both crude and age-adjusted mortality rates (AAMRs) per 1,000,000 population from 1999 to 2020. AAMRs were stratified by year, sex, race and ethnicity, census region, state, and urban-rural status, along with 95% confidence intervals (CIs). Crude mortality rates (CMRs) were obtained by dividing the number of HF and cachexia-related deaths by the corresponding U.S. population for each year. AAMRs were calculated by standardizing HF + cachexia-related deaths to the year 2000 U.S. standard population.

To determine the national annual trends in heart failure and cachexia-related mortality, the Joinpoint Regression Program (Joinpoint V 5.2.0, National Cancer Institute) was used to identify the annual percent change (APC) with a 95% CI in AAMRs from 1999 to 2020.[9] By fitting log-linear regression models to the data, this method identifies variations in AAMR over time, indicating increasing or decreasing trends in HF + cachexia-related mortality. APCs and 95% CI for age-adjusted mortality rates were computed for the identified line segments connecting joinpoints. We used 2-tailed t-testing to determine if the slope of annual percent change describing the change in mortality was significantly different from zero. Statistical significance was set at $p<0.05$.

Results

Overall

A total of 21,650 deaths related to HF + cachexia occurred between 1999 and 2020 among adults in the US aged ≥65 (*Supplementary Table 1*). Information for the location of death was available for 21,572 deaths. Of these deaths, 47% (n= 10,191) occurred in nursing homes/long term care, 24% (n= 5277) occurred at patients' homes, 19% (n= 4155) occurred in medical facilities, and 3% (n= 651) in hospice facilities (*Supplementary Table 2*). Over this period, AAMR initially declined by 4.3% (95% CI, -8.7 to -2.3) from 1999 to 2004, after which no change in mortality was apparent until 2020 (Figure 1a).

Heart failure + cachexia-related mortality stratified by gender

Males and females had similar AAMR throughout the study period (overall AAMR females: 20.3 [95% CI, 18.6 to 21.9]; males: 21.3 [95% CI, 19.2 to 23.4]). Over the two decades, the AAMR for adult females decreased consistently by 2.6% (95% CI, -3.0 to -2.2), annually. Conversely, the AAMR for adult males initially declined by 7.2% (95% CI: -13.4% to -2.3%) from 1999 to 2002, after which no decline in mortality was apparent until 2020 (*Supplementary Table 3*, Figure 1a).

Heart failure + cachexia-related mortality stratified by race

Over the study period, White adults had a higher overall mortality rate than Black/African America adults (overall AAMR White: 23.8 [95% CI, 23.4 to 24.1]; Black/African American: 18.4 [95% CI, 17.4 to 19.4]) (Figure 1b). Notably, Black adults had a consistent decline in mortality from 1999-2020 with APC of -2.3% (95% CI, -3.3 to -1.3). In contrast, AAMR of White adults decreased from 1999 to 2003 by 4.8% (95% CI, -9.0 to -2.4), after which there was no significant change in mortality was apparent until 2020 (*Supplementary Table 3*, Figure 1b).

Heart failure + cachexia-related mortality stratified by region

Overall HF + cachexia related mortality decreased consistently in both rural and urban areas, with rural areas having higher mortality than urban areas (rural overall AAMR: 27.9 [95% CI, 27.1 to 28.7]; urban overall AAMR: 22.1 [95% CI, 21.8-22.4]) (*Supplementary Table 4*, Figure 2a).

AAMR varied widely in different states, ranging from 6.2 (95% CI, 4.9 to 7.8) in Louisiana to 107 (95% CI, 97.1 to 116.9) in New Hampshire. States that fell in the top 90th percentile were Idaho, Utah, Vermont, South Carolina, Alaska and New Hampshire which had approximately five times the AAMR of the states that fell into the lower 10th percentile, namely Louisiana, Mississippi, Florida, New York, Kentucky and Maryland (*Supplementary Table 5*; Figure 2b).

When stratified by regions, West had the highest overall AAMR, followed by Midwest, Northeast, and South (Overall AAMR, West: 34.1 [95% CI 33.2 to 34.9]; Midwest: 22.8 [95% CI, 22.2 to 23.5]; Northeast: 18.7 [95% CI, 18.1 to 19.3]; South: 19.4 [95% CI 18.9 to 19.8]). Notably, North, South, and Midwest regions had a steady decline in AAMR from 1999 to 2020. In contrast, West had no decline in mortality from 2004 to 2018 (APC -0.5%, [95% CI: -1.0 to 6.1]) (*Supplementary Table 6*; Figure 2c).

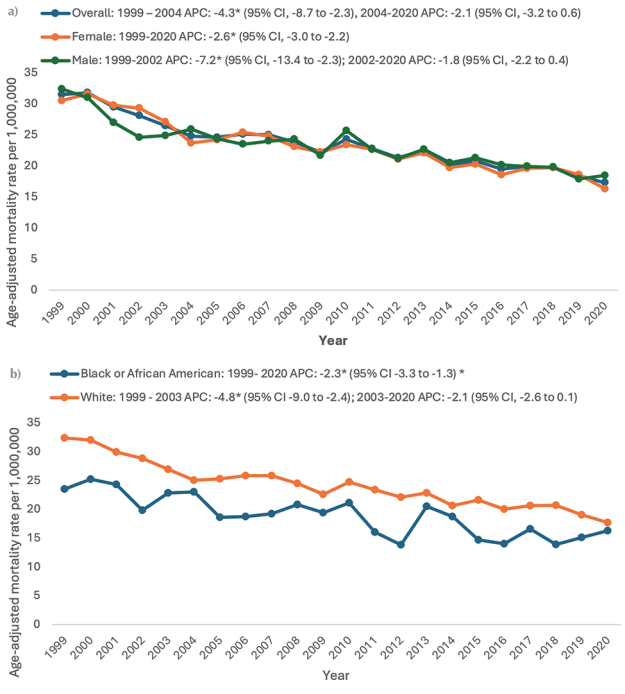

Figure 1. Heart failure and cachexia related age adjusted mortality rates per 1,000,000 stratified by gender (a) and by race (b) among the population aged ≥65, in the United States, 1999-2020.

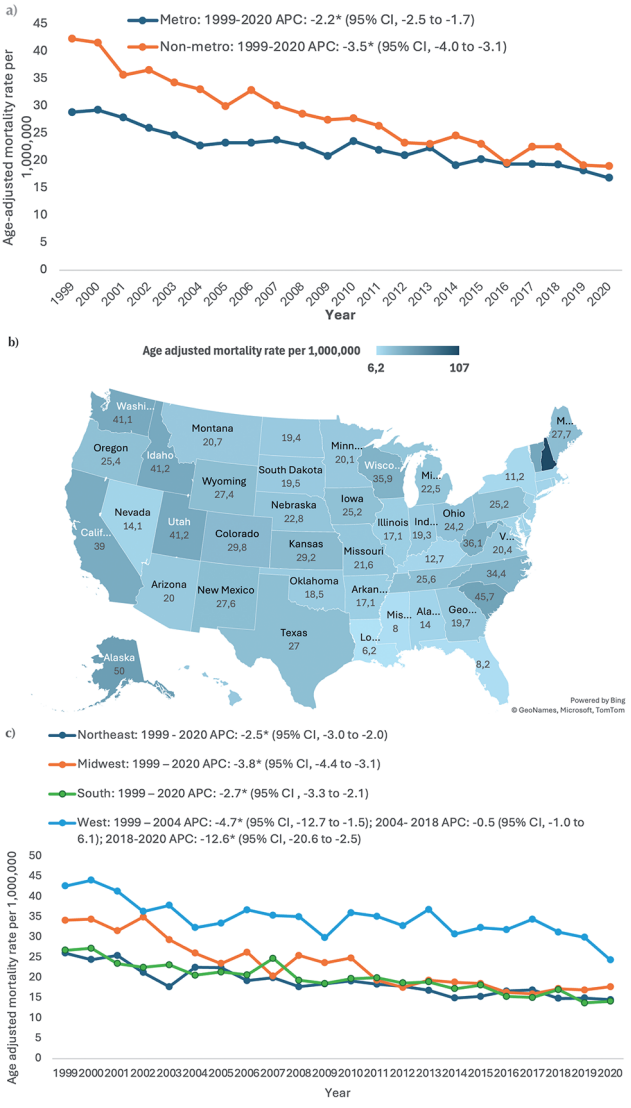

Figure 2. Heart failure and cachexia related age adjusted mortality rates per 1,000,000 stratified by urbanization (a), by state (b), and by census region (c) among the population aged ≥65, in the United States, 1999-2020.

Mortality rates for HF and cachexia individually

Overall, AAMR for HF decreased from 8730.6 (95% CI, 8699.3 to 8761.9) in 1999 to 7705.9 (95% CI, 76821.1 to 7729.7) in 2020 (*Supplementary Table 7*, Figure 3a). Similarly, overall AAMR for cachexia, irrespective of HF decreased from 305.8 (95% CI, 299.9 to 311.6) in 1999 to 181.4 (95% CI, 177.7 to 185) in 2020 (*Supplementary Table 7*, Figure 3b).

Discussion

In this 20-year analysis of 21,650 deaths among adults aged ≥65 years, we observed several key findings (Figure 4). First, after an initial decline in AAMRs from 1999 to 2004, no change in mortality was apparent until 2020. Second, males and females had similar overall AAMR, with females having a consistent decline in mortality while males had no change in mortality from 2002 onwards. Third, Whites had higher mortality than Blacks/African Americans. Lastly, significant regional variability existed, with states in the top 90th percentile (Idaho, Utah, Vermont, South Carolina, Alaska and New Hampshire) had approximately five times the AAMR of the states that fell into the lower 10th percentile (Louisiana, Mississippi, Florida, New York, Kentucky and Maryland).

The two distinct phases of HF and cachexia-related mortality in our study, i.e. initial decline in AAMR from 1999-2004 followed by no change until 2020, reflects both advancements in HF management and the persistent challenges posed by cachexia. Adoption of guideline-directed medical therapy (GDMT) and device therapy significantly reduced mortality and hospitalizations in HF by targeting neurohormonal pathways which are central to disease progression,[10-12] as evidenced by Siddiqi *et al*. who showed consistent decline in overall mortality for HF from 1999 to 2012.[7] On the contrary, our findings of plateaued HF and cachexia-related mortality from 2004 onwards suggest that therapeutic advancements in HF may not sufficiently address the unique challenges of systemic inflammation and metabolic imbalance posed by cachexia.[13] Pro-inflammatory cytokines such as TNF-α and IL-6 drive the pathophysiology of cachexia, leading to activation of the ubiquitin-proteasome pathway, exacerbating muscle loss, anorexia, and metabolic exhaustion.[5] Cardiac atrophy and reduced left ventricular (LV) mass associated with cachexia have also been identified as predictors of decreased overall survival; however, these effects were particularly pronounced in cancer patients undergoing chemotherapy and radiation therapy.[14] Conventional HF therapies do not adequately address or target these processes, necessitating novel approaches that specifically target cachexia's underlying mechanisms.

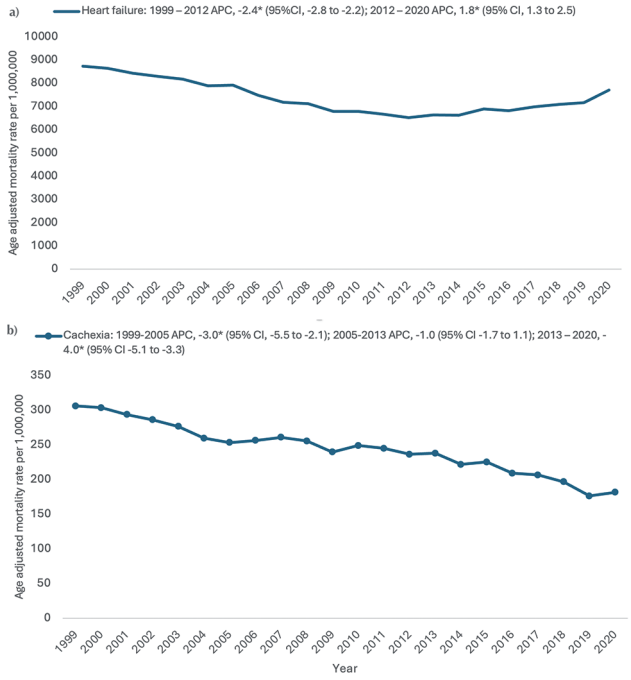

Figure 3. Heart failure (a) and cachexia (b) related age adjusted mortality rates per 1,000,000 among the population aged ≥65, in the United States, 1999-2020.

Our results indicate a consistent decrease in mortality rates among women with HF and cachexia, contrasted with stagnation in men. Women with HF often present with HF with preserved ejection fraction (HFpEF), which carries a different pathophysiological trajectory and is associated with a relatively better prognosis, compared to HF with reduced ejection fraction (HFrEF), more common in men.[15-17] Bekfani *et al.*[18] demonstrated that the prevalence of sarcopenia is lower among patients with left ventricular ejection fraction (LVEF) >40% compared to those with reduced ejection fraction. Furthermore, men typically have lower levels of estrogen, which has been shown to reduce muscle stem cell apoptosis and suppress mediators of muscle atrophy.[19] The absence of these protective effects in men may lead to more severe cardiac remodeling and dysfunction. These findings underscore the importance of gender-specific strategies in HF-cachexia management, including early screening and tailored therapeutic approaches.

The higher mortality rates in White adults compared to Black adults with HF and cachexia during the earlier years as observed in our study, can partly be attributed to survival bias and competing risks. Black adults with HF are disproportionately burdened by earlier onset of cardiovascular disease, often linked to social determinants of health, and may face premature mortality due to other comorbidities such as hypertension or diabetes, limiting their progression to advanced cachexia.[20] However, the narrowing racial gap in mortality observed toward the end of the study period aligns with improved access to GDMT and community-level interventions targeting cardiovascular health disparities.[21] Black adults with HF frequently present with increased LV mass, a characteristic associated with heightened HF severity.[22] However, the combination of a higher baseline LV mass and potential genetic variations in muscle composition may confer a relative resistance to the progression

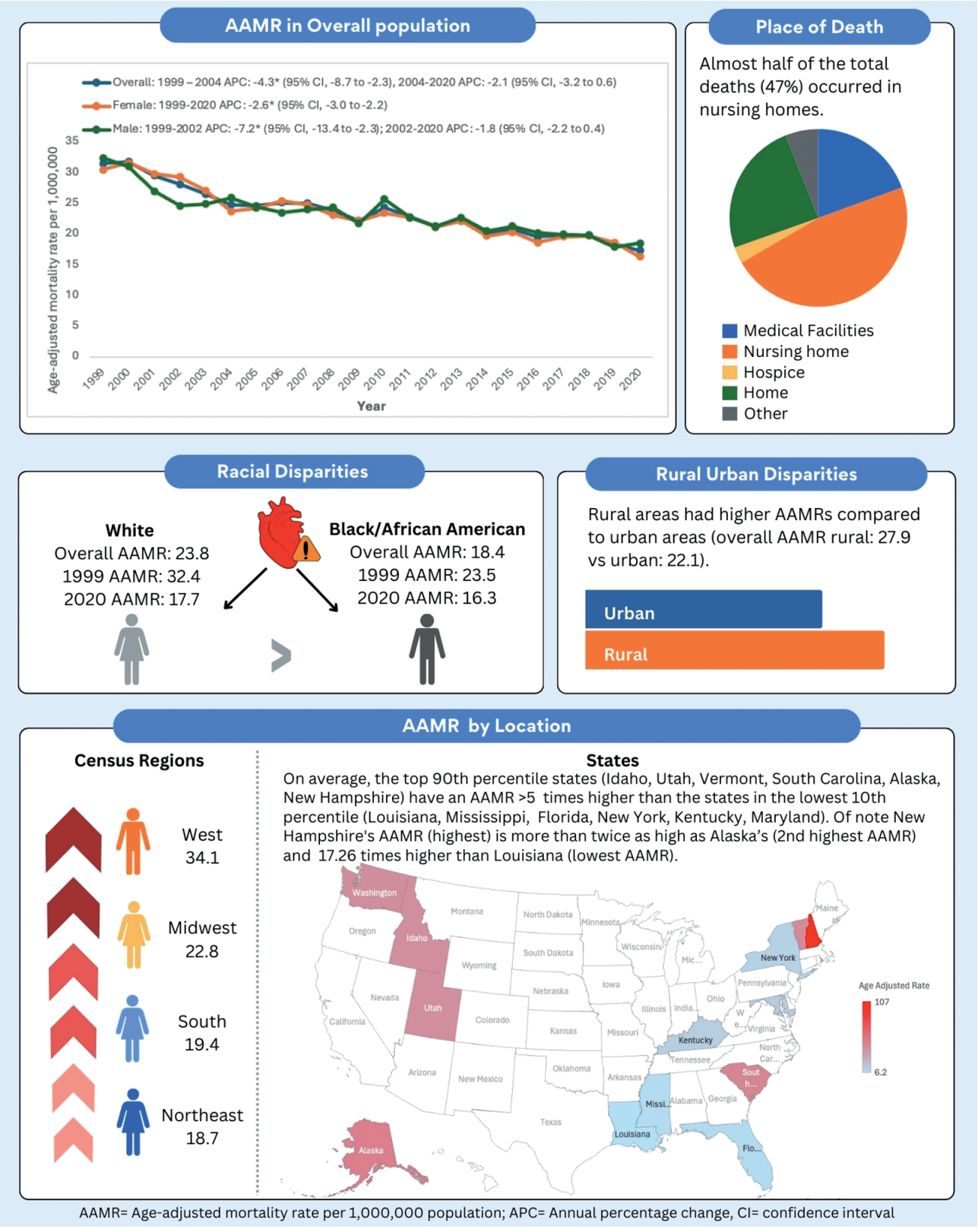

Figure 4. Demographic and regional trends of heart failure and cachexia-related mortality among older adults in the United States, from 1999 to 2020.

of cachexia in this population over time. Studies in cancer patients have demonstrated that reduced LV mass, particularly in those with cachexia, is linked to diminished physical function and independently predicts increased all-cause mortality.[14] Nevertheless, systemic inequities in healthcare access, delayed diagnoses, and underutilization of advanced HF therapies also remain significant barriers to achieving equitable outcomes. To address these disparities, efforts should focus on expanding access to preventive care, providing targeted education on HF management, and tackling systemic barriers such as implicit bias in healthcare delivery.

The higher mortality rates observed in rural areas compared to urban settings in our study reflect critical disparities in healthcare access, resource availability, and socioeconomic conditions. Rural populations often face limited access to specialists, including cardiologists, and fewer healthcare facilities capable of providing advanced HF and cachexia care.[23] Siddiqi *et al*. highlighted similarly high mortality in rural populations with HF.[7] This disparity is further exacerbated by the closure of rural hospitals in recent decades. The higher prevalence of comorbidities such as obesity, diabetes, and chronic kidney disease in rural areas also exacerbates mortality risks, increasing the progression of cachexia with further inflammation.[24] While the steeper decline in rural AAMRs compared to urban areas suggests progress in addressing these inequities, the persistent disparity highlights the need for sustained interventions. Telemedicine has shown promise in bridging these gaps, enabling earlier detection and management of cachexia.[25] Significant state-wide variations were also noted in our study, with states in the top 90th percentile showing five times the mortality rates of states in the lower 10th percentile. This could be attributed to variations in local health infrastructure, access to Medicaid and disparities in the burden of cardiovascular comorbidities. Our findings highlight the need for extensive population-based studies in these regions to delineate factors causing these disparities.

Future directions and challenges

A major challenge in HF-associated cachexia is the ongoing debate regarding its uniform definition. Initially, Anker *et al*. proposed a criterion of 7.5% unintentional weight loss, which was subsequently revised to 6%.[3,26] The lack of a standardized definition for cachexia has led to significant inconsistencies in prevalence estimates reported across studies. For instance, the FRAGILE-HF study identified a prevalence of 35.5%, while Morishita *et al*. reported a lower prevalence of 23.8% in HF populations.[27,28] Notably, these discrepancies may partly stem from differences in study populations, as the median age of participants varied significantly between the two investigations. Nonetheless, these findings highlight the need for consensus definitions and uniform methodologies to improve comparability and reliability in cachexia research within HF.

Early detection of cachexia also continues to be a challenge. Screening questionnaires have been developed; however, they have not been tested in the context of HF. Panoramic ultrasound to monitor quadriceps atrophy and C-terminal agrin fragment (CAF), which reflects the degradation of neuromuscular junction, have shown promise in early detection of cachexia. Reduced hand grip strength (HGS) has been shown to be associated with higher mortality and decreased functional reserve, however this was demonstrated in cancer cachexia.[29] Currently, dual-energy X-ray absorptiometry (DEXA), CT and MRI continue to be the gold standard for assessment of muscle wasting , however DEXA is unreliable in fluid overload states.[30] This underscores the need to formulate a screening tool using questionnaires to assess functional capacity, biochemical markers, and imaging modalities to help with earlier detection of cachexia in HF.

Therapeutic approaches are still inadequately studied. The COPERNICUS trial showed that BB use prevented 33% of the patients from developing significant weight loss.[31] Another study showed that Angiotensin II caused marked diaphragmatic muscle atrophy.[32] There appears to be hesitation among providers with prescribing these medications to patients falling in the spectrum of wasting syndrome;[33] however, optimal GDMT should still be the backbone of HF therapy even in patients with cachexia.[12]

Exercise training and high-caloric protein rich supplementation has shown benefit in improving quality of life (QoL) and reducing inflammatory markers which are central to pathophysiology of cachexia.[4] Beyond its anti-inflammatory effects, exercise improves oxidative capacity and enhances muscle function, potentially slowing the progression of muscle wasting in these patients.[30]

Pharmacological interventions further bolster these strategies. Testosterone's anabolic effects counteract muscle atrophy, making it a vital component of a multimodal therapeutic strategy.[4] Furthermore, branched-chain amino acid (BCAA) supplementation and ghrelin lead to improvement in muscle mass and functional capacity.[30] Anti-inflammatory agents, including TNF-α inhibitors and IL-6 receptor antagonists have been theorized to be beneficial, however trials using TNF-α including etanercept and infliximab have not shown much benefit.[30]

Currently, most studies focus on how treatment modalities lead to improvement in prognosis, however functional capacity assessments using either a maximal oxygen consumption test or a 6-minute walking test (6MWT) serve as a more reliable endpoint than subjective assessment.[34] Future trials should focus on diagnostics utilizing artificial intelligence and interdisciplinary therapeutic strategies to mitigate the devastating impacts of cachexia on morbidity, mortality, and QoL in HF patients.

Limitations

This study has several limitations that should be considered. Dependence on death certificates and ICD coding might lead to underreporting or misclassification of cachexia, as its features often overlap with other chronic conditions like frailty and sarcopenia. Furthermore, the CDC WONDER database does not provide detailed clinical information, such as the severity of HF, cachexia staging, or treatment histories, which limits the ability

to comprehensively interpret the observed patterns. The study's observational design restricts the ability to draw causal conclusions, and its findings may not be fully applicable to younger populations or settings outside the United States.

Conclusions

In conclusion, this study highlights no change in mortality due to HF + cachexia from 2004 to 2020 with persistent disparities across race, and geography. White adults had higher mortality than Black/African American adults. The West region had the highest mortality rates across all regions. These findings emphasize the need for a multidisciplinary approach and focus on cardio-nutritional approaches to deal with the HF-cachexia syndemic. Moreover, there is a need for consensus on definitions of cachexia in HF and uniform methodologies and therapies to improve morbidity and mortality in patients with HF and cachexia.

Contributions

All authors made a substantive intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest

The authors declare no competing interests, and all authors confirm accuracy.

Ethics approval

Institutional review board approval was not required for this study as only aggregated deidentified data were used in the analysis.

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Online supplementary material:
Supplementary Table 1. Cachexia and HF-related deaths, stratified by gender and race.
Supplementary Table 2. Cachexia and HF-related deaths, stratified by place of death.
Supplementary Table 3. HF and cachexia-related age adjusted mortality rates, stratified by gender and race.
Supplementary Table 4. HF and cachexia-related age adjusted mortality rates, stratified by urbanization.
Supplementary Table 5. HF and cachexia-related age adjusted mortality rates, stratified by state.
Supplementary Table 6. HF and cachexia-related age adjusted mortality rates, stratified by census region.
Supplementary Table 7. HF and cachexia-related age adjusted mortality rates per 1,000,000.