Sex-Based Differences in Hematologic Malignancy Mortality Across Therapeutic Eras in the United States: A CDC WONDER Analysis (1990-2020)

S. CHANIYARA[1], T. MEHTA[1], N. VAVALIYA[2], K. PATIDAR[3]

1.GCS Medcal collage, Hospital and Research Center, Ahmedabad, India. 2. Northwest Health Porter Hospital, Indiana, United states of America. 3. Jinan University School of Medicine, Guangzhou, China.

INTRODUCTION AND AIM

- Men consistently show higher incidence and mortality across hematological malignancies. [1,2,3]
- Although advances in diagnosis and treatment have substantially improved survival, whether the benefits are equally distributed between sexes remain uncertain.[5,6]
- A U.S. analysis confirmed that cancer incidence and overall survival were generally lower in males than females across cancer types.[4]
- Female CML patients achieve 23% higher Imatinib exposure and higher major molecular response rates (80% vs 45%; p=0.018) despite greater treatment intolerance along with more chemotherapy related adverse reactions likely related to- - genetic variation and sex hormone effects on drug metabolism. [2,7,8]
- Despite these documented differences, only 0.5% of cancer clinical trials in the Trialtrove database included curated sex-based comparisons. As of 2025, practical management of hematological malignancies remains effectively sex-blind. [2,9]

METHODOLOGY

- Retrospective population-based analysis using the CDC WONDER bridged-race database, 1999-2020 database to evaluate age-adjusted mortality rates (AAMRs) for hematological malignancies (ICD-10 C81–C96). US 2000 population used for standardization.
- Data were stratified by sex and divided into three therapeutic eras to evaluate if the shift from cytotoxic chemotherapy (pre-novel agent era, 1999–2005) to first-generation biologics (early targeted therapy era, 2005–2012) and modern immunotherapies (modern era, 2013–2020) mitigated or exacerbated the sex-based mortality gap.
- Trends were assessed using linear regression slopes (β), percent change across eras, and male-to-female mortality ratios with Pearson correlation (r).

CONCLUSIONS

- Although mortality has declined in both sex, but the male-to-female mortality gap has widened which is consistent with global data for leukemia, myeloma, NHL, and Hodgkin lymphoma from 1990 to 2019.[3]
- The steeper decline in female mortality (13.8% vs. 10.5% in this study; AAPC −1.63%) suggesting novel agents may disproportionately benefit women, potentially through pharmacokinetic advantage. [2,7,10]
- The persistent disparities show the need for sex-stratified reporting, clinical trials, investigations and treatment strategies.[7,8,9]
- Without sex-stratified analysis and reporting, precision medicine may continue to widen rather than reduce the sex-based mortality gap in hematologic malignancies. [7,9]

RESULTS

Overall trends (1999–2020).

- Mean AAMR fell from the pre-novel era to the modern era by 13.8% in females (13.23 → 11.40) and by 10.5% in males (22.63 → 20.25).
- Linear regression across the full study period: steeper annual decline in males (β = −0.156/year, r = −0.93) than in females (β = −0.122/year, r = −0.93).
- Relative reduction was smaller in males than females when comparing the beginning and end of the study period (8.97% vs. 15.31%, respectively).

Era-stratified trends

- ***Pre-novel agent era (1999–2005):*** steepest declines of the three eras (females β = −0.233/year, r = −0.96; males β = −0.209/year, r = −0.84).
- ***Early targeted therapy era (2005–2012):*** The rate of decline slowed in females (β = −0.081/year, r = −0.74) compared to males (β = −0.152/year, r = −0.96).
- ***Modern era (2013–2020):*** Declines flattened for both sexes. Female mortality showing a weak downward trend (β = −0.046/year, r = −0.45) and male mortality essentially plateauing (β = −0.009/year, r = −0.05).

Male-to-female mortality ratio

- The M:F AAMR ratio rose from 1.68 in 1999 to 1.81 in 2020, and increased progressively across eras: 1.71 in the pre-novel agent era, 1.77 in the early targeted therapy era, and 1.78 in the modern era.

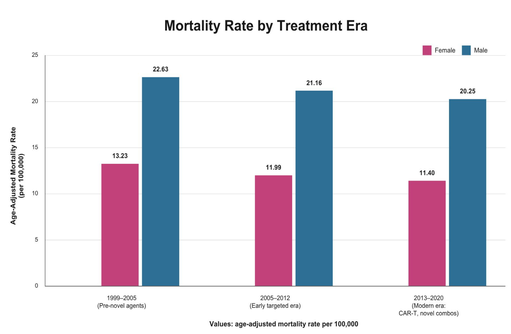

Figure 1

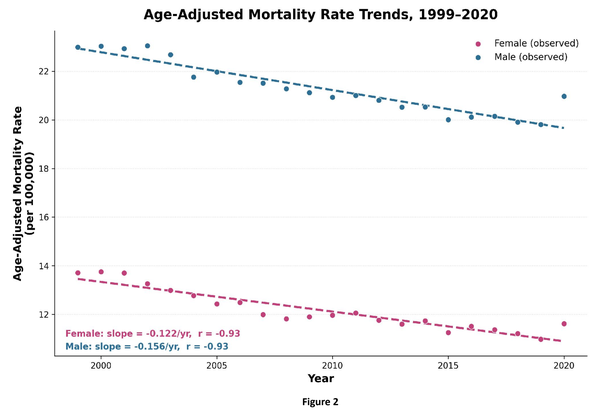

Figure 2

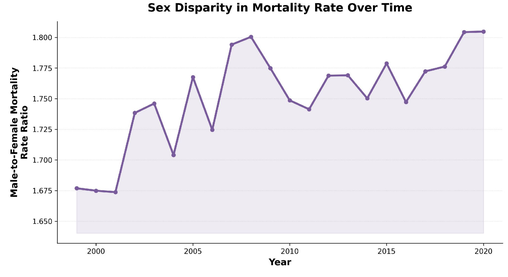

Figure 3

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CONTACT INFORMATION

Presenter : Dr. Nihar Vavaliya
Email : nihar.vavaliya@nwhealthin.com

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