



Seasonal variations of arrhythmias and their impact on mortality in cancer patients with health disparities: A propensity score adjusted machine learning analysis of over 100 million hospitalizations across 3 years

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Abstract

Title: Seasonal Variations of Arrhythmias and Their Impact on Mortality in Cancer Patients with Health Disparities: A Propensity Score Adjusted Machine Learning Analysis of over 100 Million Hospitalizations Across 3 Years

Background: Arrhythmias are observed to increase during high influenza activity seasons (HIA, December to February) with significant clinical impact among high-risk patients, so their outcomes may be optimized through closer monitoring of these populations. It is unknown if cancer is such a risk factor.

Methods: This is a retrospective analysis of arrhythmia-related mortality and the effect of health disparities in patients with cancer during HIA and non-HIA seasons in a nationally representative database. Machine learning-augmented propensity score adjusted multivariable regression (ML-PSr) was performed using the 2016-2018 National Inpatient Sample (NIS), the United States' largest all-payer hospitalized dataset.

Results: A number of 16,795,379 (18.48%) patients presented with arrhythmia of whom 3,214,914 (19.14%) were during HIA. In ML-PSr, HIA did not significantly increase the odds of arrhythmia for cancer patients (OR 1.01, 95%CI 0.99-1.03, $p=0.37$), but the odds of arrhythmia-related mortality were higher during HIA seasons (OR 1.19, 95%CI 1.12-1.27, $p<0.001$) compared to non-HIA seasons (OR 1.17, 95%CI 1.13-1.22, $p<0.001$). Primary malignancies with the highest prevalence of arrhythmias during HIA were that of the lung (19.60%), leukemia (11.49%), non-Hodgkin lymphoma (NHL) (8.24%), prostate (8.15%), and multiple myeloma (MM) (6.21%) ($p<0.001$). HIA increased arrhythmia-related mortality most for the following primary malignancies by year: gastrointestinal in 2016 (OR 1.15, 95%CI 1.01-1.32, $p=0.039$), leukemia in 2017 (OR 1.31, 95%CI 1.10-1.54, $p=0.002$), GI in 2018 (OR 1.14, 95%CI 1.01-1.29, $p=0.029$), and renal in 2018 (OR 1.54, 95%CI 1.06-2.23, $p=0.025$). Among patients with active cancer and arrhythmia, African Americans had significantly greater mortality than Caucasians (OR 1.13, 95%CI 1.03-1.23, $p=0.013$), independent of socioeconomic and clinical confounders.

Conclusion: This study suggests arrhythmia-related mortality was higher during HIA seasons compared to non-HIA seasons in cancer patients and showed notable disparities by race and worse outcomes by primary malignancy.

Keywords

arrhythmia, respiratory illness season, disparities, machine learning, cardio-oncology, cancer

Introduction

Various cardiovascular diseases and arrhythmias undergo seasonal variations and are known to increase during high influenza activity season (HIA), ^[1] which is defined as December through

February. Within these periods of increased prevalence of cardiac arrhythmias, there is a direct correlation to the number of related hospitalizations, morbidity, and mortality. ^[2] Although several studies have demonstrated this association between seasonal variation and cardiac disorders, ^[3] there are few studies evaluating these outcomes in cancer patients. Cancer patients are at increased risk for arrhythmias in the setting of unique electrophysiologic issues and treatment therapies, ^[4] such that their outcomes may be optimized through closer monitoring, prevention strategies, and vaccination during HIA. Arrhythmia-related morbidities and mortalities in cancer patients may also vary based on race, income, geography, and even primary malignancy for which our study aimed to analyze and better quantify. Our goal is to better understand the impact of socioeconomic disparities and seasonal variations on arrhythmia prevalence and arrhythmia-related mortality in cancer patients.

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Methods

1. Data Source

The National Inpatient Sample (NIS) is the largest publicly available U.S. all-payer inpatient healthcare administrative dataset spanning approximately 4,500 hospitals in 50 states, and it was the data source for this study. The dataset includes demographic, comorbidity, procedural, complication, mortality, length of stay, total cost, and hospital characteristics for each hospitalization. The 2016, 2017, and 2018 NIS datasets were selected for this study as they are among the latest available datasets and the first to use International Classification of Disease-10 (ICD-10) coding and as such better reflect current clinical trends in diagnoses, treatments, and outcomes compared to prior years. Study inclusion criteria included all NIS hospitalizations for adults aged 18 years or older during the above index time periods. Per the US Department of Health and Human Services (DHHS) and National Bureau of Economic Research, no review by an Institutional Review Board (IRB) is required for the NIS under the HIPPA Privacy Rule since the NIS is a limited data set (in which 16 direct identified specified by the Privacy Rule have been removed).^[5, 6] This study used de-identified data and was conducted according to the ethical principles in the Declaration of Helsinki.

2. Study Design

To conduct a more comprehensive analysis more broadly and practically applicable within current healthcare systems, the primary analysis consisted of AI-driven Computational Ethics and policy analysis (AiCE) according to its first empirical (clinical then economic) step then the second ethical-policy step.^[7-9] The first empirical step featured a nationally representative retrospective longitudinal multicenter cohort analysis of inpatient mortality and total cost among all hospitalized adults including by active cancer, arrhythmia, and season (by High Influenza Activity Season [HIA] defined by the US Centers for Disease Control as December to February).^[10] It additionally utilized ML-PSr and deep learning (DL) artificial neural network to assess inpatient mortality and cost. A cost analysis was then conducted using the above clinical results. This empirical step was followed by the final ethical-policy step in which the above AI-augmented empirical results informed a pluralistic-based global bioethical analysis to optimize equitable care for the above patient populations.

3. Descriptive and Bivariable Statistical Analysis

Descriptive statistics were performed for the full sample to define the arrhythmia among all adult hospitalizations. Bivariable analysis was then performed according to active cancer (yes/no) and HIA (yes/no) across the full 2016-2018 duration and within each year separately (2016, 2017, and 2018). For continuous variables, independent sample t-tests were performed to compare means, and Wilcoxon rank sum tests were performed for medians. For categorical variables, Pearson Chi-square tests or Fisher exact tests were performed to compare proportions as applicable.

Demographics included age, sex, race, income, insurance, urban density, and region. Comorbidities were selected for analysis (and identified in the dataset by their ICD-10 codes) based on their clinical and/or statistical significance identified in prior published studies and current clinical practice. They included cancer status (active, prior, and metastatic), hypertension, diabetes, coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, cirrhosis, and chronic kidney disease. The 26 primary malignancies investigated included the brain and nervous system, head or neck, thyroid, breast, lung, esophagus, stomach, pancreas, liver or bile system, rectum or anus, colon, peritoneum, bone or connective tissue system, hematological malignancies (including Hodgkin lymphoma, non-Hodgkin lymphoma, leukemia, and multiple myeloma), melanoma, non-melanoma skin, uterus, cervix, ovarian, prostate, testes, bladder, and renal.

4. Regression Statistical Analysis, Machine Learning Analysis, and Model Optimization Overview

The primary outcome was inpatient mortality (yes/no), and the secondary outcomes were arrhythmia (yes/no; defined as non-sinus rhythm and non-eucardia) and total hospitalization cost (in U.S. dollars [\$]). The regression statistical analysis, machine learning analysis, and model optimization methods have been explained in our previously published study.^[11]

5. Bayesian Machine Learning-Augmented Propensity Score Translational (BAM-PS) Statistics

Regression analysis featured the particular technique within BAM-PSr performed for the above NIS dataset.^[10, 12-14] This technique integrates ML-PSr, in which the traditional statistical methodology of causal inference-based propensity score analysis is augmented (a) by machine learning capable of handling higher dimensional, more complex, and faster data streams, and then translates its results as informative priors for (b) Bayesian regression. Regression was conducted on the above outcomes and stratified by active cancer and HIA (and additionally included sub-group analysis by primary malignancy among patients with active cancer). The propensity score (modified as a disease risk score) for the likelihood of presenting during HIA was first created (utilizing the same above variables used in the final regression model given the double propensity score adjustment method), a balance was confirmed among blocks, and then the propensity score was included in the final regression models as an adjusted variable.^[15, 16]

6. Health Disparity Analysis

Mortality disparity analysis was conducted using ML-PSr to assess possible significant disparities independent of clinical confounding.

7. Cost-Effectiveness and Cost Benefit Analysis

Cost analysis was conducted by calculating the significant and independent mortality disparities (if any) from ML-PSr multiplied by the 2022 inflation adjusted statistical value of a human life as utilized by the US federal government for health and public policy.^[17]

8. Computational Ethical and Policy Analysis

The second or ethical-policy step within AiCE was then conducted by integrating the above quantitative analyses with ethical analysis using the pluralistic global bioethical framework of the Personalist Social Contract (PSC).^[18-20] The PSC is a novel integration of modern ethics (principally utilitarianism-informed Rawlsian social contract of political liberalism, bounded by Kantian deontology and informed by feminist, Marxist, deconstructionist, and ecological ethics) and classical ethics (principally Thomistic-Aristotelian virtue ethics, articulated by William Carlo's esse/essence revision of Norris Clarke's Strong Thomistic Personalism, a derivative formulation of Thomism as a development of classical Aristotelianism metaphysics).^[21-27] It uniquely articulates the philosophical foundation and framework of the United Nation's 1948 Universal Declaration of Human Rights, founded on the primary metaphysical principle of human dignity and resultant rights and duties, which has since united the world's diverse belief systems and 193 nations in what has become the dominant modern ethical framework and foundation of international law.

9. Quality Control, Result Reporting, and Analytic Software

An academic physician-data scientist, biostatistician, and ethicist (DJM) confirmed that the final analytic models were sufficiently supported by the existing literature and related theories. Mean values are reported with standard deviation (SDs). Fully adjusted regression results were reported with 95% confidence intervals (CIs) with statistical significance set at a 2-tailed p-value of <0.05. Statistical analysis was performed with STATA 17.0 MP edition (STATACorp, College Station, TX, USA), and ML and DL analyses were performed with Java 9 (Oracle, Redwood Chores, CA, USA).

Results

1. Descriptive Statistics for Study Sample and Sub-Group Analysis in Cancer

Among 90,869,382 adult hospitalizations, 16,795,379 (18.48%) presented with arrhythmia of whom 3,214,914 (19.14%) were during HIA. Among patients with arrhythmia during HIA, there was a longitudinal increase among those with active cancer from 1.95% (2016) to 7.41% (2017) to 7.54% (2018).

2. Bivariable Analysis of Arrhythmia by Cancer and HIA

Arrhythmia was more prevalent among adults during HIA compared to non-HIA in 2016 (18.32% versus 17.43%), in 2017 (16.52% versus 15.70%), and 2018 (17.41% versus 16.44%) (all $p<0.001$) (Table 1; Figure 1). Arrhythmia was less likely for those with active cancer versus those without in 2016 during HIA (19.02% versus 26.36%) and non-HIA (19.44% versus 27.32%), more likely in 2017 during HIA (19.65% versus 16.32%) and non-HIA (19.50% versus 15.44%), and more likely in 2018 during HIA (20.92% versus 17.17%) and non-HIA (20.36% versus 16.17%) (all $p<0.001$). From 2016-2018, the primary malignancies with the highest prevalence of arrhythmias during HIA were lung (19.60%), leukemia (11.49%), NHL (8.24%), prostate (8.15%), and MM (6.21%) ($p<0.001$).

3. ML-PS multivariable regression of arrhythmia, mortality, and cost stratified by cancer

In ML-PSr, HIA did not significantly increase the odds of arrhythmia for patients with active cancer (OR 1.01, 95%CI 0.99-1.03, $p=0.37$), but it did for those without it (OR 1.01, 95%CI 1.01-1.02, $p=0.003$) (Table 1). Among patients with active cancer, arrhythmia increased mortality odds during HIA (OR 1.19, 95%CI 1.12-1.27, $p<0.001$) greater than non-arrhythmia during non-HIA (OR 1.17, 95%CI 1.13-1.22, $p<0.001$). Arrhythmia-related total hospitalization cost was not significantly different during HIA (\$2,312.96, $p=0.003$) and non-HIA seasons (\$3,474.68, $p<0.001$).

4. ML-PS multivariable regression by sub-group analysis among primary malignancies

Among patients with arrhythmia and active cancer during HIA, the mortality rate increased the most in different primary malignancies in different years as follows: GI in 2016 (OR 1.15, 95%CI 1.01-1.32, $p=0.039$), leukemia in 2017 (OR 1.31, 95%CI 1.10-1.54, $p=0.002$), GI in 2018 (OR 1.14, 95%CI 1.01-1.29, $p=0.029$), and renal in 2018 (OR 1.54, 95%CI 1.06-2.23, $p=0.025$).

5. ML-PS multivariable regression of mortality disparities

In ML-PSr, among patients with active cancer and arrhythmia, the only significant mortality disparities across all 3 years were for African Americans who had significantly greater mortality rates than Caucasians (OR 1.13, 95%CI 1.03-1.23, $p=0.013$), independent of the above socio-economic and clinical confounders otherwise. Based on the related population averaged (predictive margins) increased mortality likelihood multiplied by the number of African Americans and Caucasians with cancer and arrhythmia and the 2022 inflation adjusted statistical value of a human life, this translates into an excess annual mortality of 406 African Americans and \$5.16 billion among adult patients with cancer and arrhythmia.

6. Computational ethical and policy analysis

The above health and economic results then informed the final or focused computational ethical-policy analysis step of AiCE. The primary material object of this ethical analysis was arrhythmia, the primary context was inpatient healthcare delivery to patients with active cancer and arrhythmia, and the primary formal object or ethical analytic framework is the PSC. Applied to this concrete ethical situation, the formal PSC argument is as follows. (Premise 1) Arrhythmia in active cancer diagnosed inpatient carries a high mortality risk, which may be significantly increased during HIA. (Premise 2) Among this patient population, there appears to be significant disparities for African Americans who are more likely to die inpatient than their Caucasian counterparts, even when adjusting for clinical severity and other such relevant factors. (Premise 3) Life and equal societal protection are fundamental individual and state rights logically derivative from the human person's dignity and are politically enshrined across the United Nations, multiple other international institutions, and the majority of nations' constitutions and legal statutes. (Premise 4) Respect for dignity at the individual level requires respecting the person's rights to goods (beginning with the primary good of life) necessary

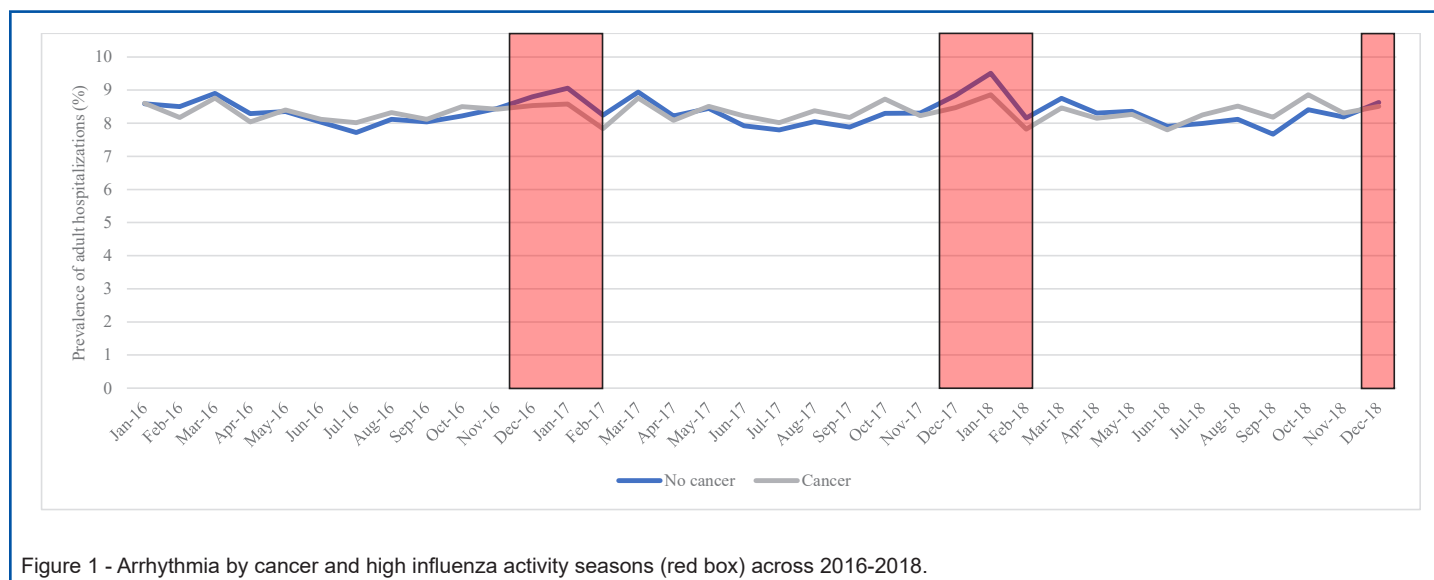


Table 1 - ML-PS multivariable regression of arrhythmia, mortality, and cost by cancer and HIA*

Outcome	Predictor	2016-2018	2016	2017	2018
Arrhythmia					
Without active cancer	HIA	1.01 (1.01-1.02, p=0.003)	1.02 (1.01-1.04, p=0.009)	1.01 (1.00-1.01, p=0.001)	1.01 (1.01-1.02, p<0.001)
With active cancer	HIA	1.01 (0.99-1.03, p=0.367)	1.02 (1.00-1.04, p=0.031)	1.00 (0.98-1.02, p=0.939)	1.01 (1.00-1.03, p=0.132)
Mortality with cancer					
Non-HIA	Arrhythmia	1.17 (1.13-1.22, p<0.001)	1.18 (1.14-1.23, p<0.001)	1.15 (1.11-1.20, p<0.001)	1.17 (1.13-1.22, p<0.001)
HIA	Arrhythmia	1.19 (1.12-1.27, p<0.001)	1.20 (1.12-1.28, p<0.001)	1.15 (1.08-1.23, p<0.001)	1.23 (1.16-1.31, p<0.001)
Cost with cancer (US\$)					
Non-HIA	Arrhythmia	3474.68 (2988.81-4240.62, p<0.001)	3690.58 (2972.38-4408.78, p<0.001)	3371.19 (2631.76-4110.62, p<0.001)	3362.28 (2522.10-4202.45, p<0.001)
HIA	Arrhythmia	2312.96 (981.69-3644.23, p=0.003)	3516.63 (2309.55-4723.71, p<0.001)	1771.52 (426.56-3116.48, p=0.010)	1650.72 (208.96-3092.49, p=0.025)

*Fully adjusted for age, sex, race, insurance, income, urban density, region, congestive heart failure, metastases, mortality risk, and the likelihood of presenting during HIA

for the person to develop through just and stable commitment to the common good and thus the community in reciprocal care for the individual. (Premise 5) Respect for dignity at the communal level requires respecting other cultures as the communal manifestations of their constitutive individuals seeking through justice the common good (as the objective good of the community, entailing the objective good of individual flourishing, and subjectively experienced as the ultimate individual good of self-actualization through justice). (Premise 6) Racial disparities in hospitalization outcomes for patients with arrhythmia and cancer can produce disproportionate morbidity and even related mortality in those clinical and social sub-communities, resulting in a disproportionate threat to the preservation of those persons and related cultures, leading to the global human community's impoverishment with the loss or diminishment of those individuals and cultures. (Premise 7) The reduction of such disparities may result in over hundreds of additional patients living and \$5 billion

saved annually. (Premise 8) Disparities in the effective and equitable chronic and acute treatment of patients with arrhythmia and cancer undermines respect for the rights of patients and respect for their cultures, which is critical to the wellbeing of societies that encompass all peoples and cultures. (Premise 9) (Conclusion) Therefore, clinical, economic, and ethical justifications support greater healthcare policy and healthcare system investment reducing disparities in the health and cost burden of arrhythmia, particularly in those with active cancer to ensure equitable, value-based healthcare for all peoples regardless of socio-demographics.

Discussion

Our study found that cancer patients experienced increased arrhythmia-related mortality during HIA, with notable difference

by primary malignancy. Our findings are consistent with prior studies describing worsening mortality rates and the occurrence of arrhythmia-related hospitalizations during winter months.^[28-35] Lower temperatures and viral illnesses are considered the driving mechanisms for higher rates of mortality related to arrhythmias during HIA. Cooler, drier weather has been linked with exacerbations in atrial and ventricular arrhythmias.^[36, 37] It is believed that as temperatures fall, heat loss is minimized through peripheral vasoconstriction and redistribution of blood to the core which results in increased cardiac output.^[38] Related elevations in metabolic production can also be quantified by higher rates of norepinephrine and epinephrine measured in the plasma and urine during wintertime.^[39] For cancer patients who undergo radiation, chemotherapy, immunotherapy and may be more sensitive to fluctuations in temperature, these processes can become more pronounced. Through rises in sympathetic drive, central blood volume, and left ventricular end diastolic pressure, increases in atrial distension can incline the atria to fibrillate.^[38, 40]

Viral illness is often accompanied by fluid loss, fever, elevated heart rate and hypoxia which are known to worsen arrhythmias. We must promote the administration of the influenza vaccines as a routine public health measure during HIA for cancer patients. Such preventative measures hope to reduce the rates of HIA arrhythmia mortality seen in this analysis.

As the field of cardio-oncology grows, the socioeconomic disparities in care are being further recognized. Amongst patients with arrhythmia and active cancer in HIA, African Americans had significantly greater mortality than Caucasians independent of socioeconomic and clinical confounders which translated to more than \$5.16 billion dollars in cost. Disparities in care are multifactorial and have been speculated to stem from a combination of structural racism, higher prevalence of cardiovascular risk factors, and reduced access to specialty care.^[41] The American Heart Association (AHA) Council on Epidemiology and Prevention notes that African Americans have worse cardiovascular health and significantly higher rates of fatal coronary artery disease compared to their non-Hispanic White counterparts with increased prevalence of hypertension, diabetes, and obesity. A cross-sectional analysis of the Multi-Ethnic Study of Atherosclerosis (MESA) performed by Heckbert et al.^[42] detailed the differences by race/ethnicity in the prevalence of clinically detected and monitor-detected atrial fibrillation and found that the prevalence of clinically detected atrial fibrillation was substantially lower in African Americans than in White participants. The lower rates of detection of arrhythmia may reflect differences in symptom perception, clinical atrial fibrillation recognition, or health care access. These data in conjunction with our findings may even represent an underrepresentation of the morbidity and mortality burden that arrhythmias may have in the African American patient population. In addition to the cardiovascular disparities experienced by African Americans, there has been a disproportionate cancer burden, including the highest mortality and the lowest survival of any racial/ethnic group for most cancers reported by the American Cancer Society.^[43] African American/Black people have higher mortality rates than any other broadly defined racial/ethnic group

for most cancers and other leading causes of death, including heart disease, stroke, and diabetes with these disparities being driven by lower socioeconomic status.^[44] We hope that our findings will enable the cardio-oncologic community to recognize existing racial healthcare imbalances and encourage collective steps towards providing equitable care.

Analysis of the data comparing various geographic regions (New England, Mid-Atlantic, East-North-Central, West-North-Central, South-Atlantic, East-South-Central, West-South-Central, Mountain, Pacific) and population sizes was tested utilizing multiple variables and permutations until an optimal model performance was confirmed. Urban density was chosen as a five-level categorical variable (central metropolitan region of at least one million people, 250,000 – 999,999, 50,000 – 249,999, micro, and less than micro) rather than a two-level variable (urban versus non-urban) and the regional analysis was kept at the original NIS-supplied nine level categorical variable. Individual comparisons were not made because of the large scope of the study and given the complexity of clinical trends and capacities that limit the ability to meaningfully compare one region versus another region, aside from how the variable was used in the study as per the NIS convention, which uses the New England region as the base comparison group given it consistently ranks amid the best performing healthcare regions nationally. Also, changing the region variable to have a different base comparison group (i.e., setting the Mountain region as the base comparison instead of New England) did not significantly change the main findings from the study.

The most common cancers with increased mortality and prevalence of arrhythmias during HIA were gastrointestinal (GI), leukemia, and lung cancers. These cancers have been previously linked to arrhythmias in the literature,^[45] connections which can be attributed to overlapping risk factors, symptomology, chemotherapy, and post-surgical complications. In GI cancers, patients frequently experience anemia and electrolyte abnormalities from malabsorption (vomiting, diarrhea, bowel resection). The presence of common cancer risk factors such as obesity, smoking and alcohol can further worsen arrhythmia outcomes. Amongst hematologic cancers, acute leukemia is shown to predispose patients to cardiac disease even before initiation of chemotherapy.^[46] Leukemia chemotherapy regimens involve alkylating agents, anthracyclines, tyrosine kinase inhibitors and arsenic trioxide; medications all regularly associated with sinus bradycardia, AV block, atrial fibrillation, ventricular tachycardia/fibrillation, and QT interval prolongation.^[47-49] The increased risk of arrhythmias from leukemia chemotherapy regimens in conjunction with our findings of worsened mortality in HIA-associated arrhythmias for leukemia is concerning.

Finally, lung cancer is often accompanied by hypoxia, demand ischemia, and is more common in smokers, all clinical factors that exacerbate arrhythmias. Patients who undergo lung resection may experience arrhythmias from direct myopericardial irritation or as a post-operative complication of intra-thoracic surgery.^[50-52] The same can be said for any other major surgeries such as colectomy or esophageal surgery in GI cancers.^[53] With respect to all cancers,

our study found increased prevalence of arrhythmias during HIA for cancer patients for 2017, 2018, but not 2016. The de-identified NIS data are not tracked to the individual level, which prevents a more granular analysis of the discrepancy of patients with active cancer and arrhythmia during HIA in 2016 compared with 2017 and 2018. It is possible that there was a national trend from 2016-2018 of improved diagnosis rates of arrhythmia in active cancer during the HIA season as clinicians have improved the understanding of the association of the above risk factors. Additionally, this patient group of arrhythmias in cancer patients appears to begin to better approximate the general population in 2017-2018, further suggesting the above improved rates of clinician diagnosis and documentation over time. The ML-PS analysis did not find significantly increased odds for arrhythmia during HIA for cancer patients using these findings, but inclusion of additional years in the 2019-2020 dataset may reveal more precise results and possibly confirm the above trend. The current literature supports that a diagnosis of cancer and even a history of cancer after active treatment predisposes patients to increased arrhythmias.^[54-57] Our findings of worsening mortality rates with HIA-associated arrhythmias in cancer patients should prompt physicians to practice caution in this vulnerable population.

Conclusion

In conclusion, our nationally representative study shows that there is increased arrhythmia-related mortality during high influenza activity season in patients with cancer. Cancer presents a unique challenge to the management of cardiac arrhythmias and through investigations of these disparities, we hope to more appropriately address these barriers to treatment and better establish standards of cardiac care in the cardio-oncology patient population.

Clinical Perspectives

According to our findings, physicians should educate and encourage cancer patients to adopt greater preventative measures during HIA to avoid arrhythmias-related mortality. These include emphasizing the importance of regular influenza in the vulnerable cancer population. Closer monitoring is recommended in the outpatient and inpatient setting, specifically for patients with lung, GI, and hematologic malignancies who were found to experience higher mortality and prevalence of arrhythmias during HIA. Lastly, recognizing racial disparities within medical outcomes is crucial for taking incremental steps towards equitable patient care.

Limitations

Firstly, we conducted a large population case-control study for which a definitive case-effect conclusion may not be established. A consequence of using the NIS database is the lack of a comparative matched control group, but this was mitigated through our propensity score adjustment and machine learning statistical approach.

Secondly, our findings pertain mainly to the inpatient setting with a lack of long-term follow-up. However, our results lay the groundwork for further outpatient studies to investigate similar themes for HIA associated arrhythmias in cancer. Lastly, we were not able to confirm the increased odds of arrhythmias occurring during HIA seen in the general population, for cancer patients. Inclusion of additional NIS data beyond 2018 may reveal more precise results.

Ethical Approval

The NIS is classified as a limited data set by the United States' Agency for Healthcare Research and Quality under the Department of Health and Human Services. As a Healthcare Cost and Utilization Project limited data set, the NIS does not require the institutional review board (IRB) approval under HIPAA. The study was performed under the ethical principles in the 1975 Declaration of Helsinki and related global bioethical standards.

List of Abbreviations

AHA	American Heart Association
AI	Artificial Intelligence
AiCE	Artificial Intelligence Driven Computational Ethics
BAM-PS	Bayesian Machine Learning-Augmented Propensity Score
DL	Deep Learning
GI	Gastrointestinal
HIA	High Influenza Activity
IRB	Institutional Review Board
MESA	Multi-Ethnic Study of Atherosclerosis
ML-PSr	Machine Learning-Augmented Propensity Score
MM	Multiple Myeloma
NHL	Non-Hodgkin Lymphoma
NIS	National Inpatient Sample
PSC	Personalist Social Contract

Declarations

Ethics Approval and Consent to Participate

The NIS is classified as a limited data set by the United States' Agency for Healthcare Research and Quality under the Department of Health and Human Services. As an HCUP limited data set, the NIS does not require IRB approval under HIPAA. The study was performed under the ethical principles in the 1975 Declaration of Helsinki and related global bioethical standards.

Consent for Publication

Not Applicable.

Availability of Data and Materials

The data generated or analyzed during this study are available from the corresponding author on reasonable request.

Competing Interests

The authors declare that they have no competing interests.

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Not Applicable.

REFERENCES

1. Loomba RS. Seasonal variation in paroxysmal atrial fibrillation: A systematic review. *J Atr Fibrillation*. 2015;7(5):1201. Epub 20150228. doi: 10.4022/jafib.1201. PubMed PMID: 27957153; PubMed Central PMCID: PMC5135221.
2. Wattigney WA, Mensah GA, Croft JB. Increasing trends in hospitalization for atrial fibrillation in the United States, 1985 through 1999: implications for primary prevention. *Circulation*. 2003;108(6):711-6. Epub 20030728. doi: 10.1161/01.CIR.0000083722.42033.0A. PubMed PMID: 12885749.
3. Fares A. Winter cardiovascular diseases phenomenon. *N Am J Med Sci*. 2013;5(4):266-79. doi: 10.4103/1947-2714.110430. PubMed PMID: 23724401; PubMed Central PMCID: PMC3662093.
4. Viganego F, Singh R, Fradley MG. Arrhythmias and other electrophysiology issues in cancer patients receiving chemotherapy or radiation. *Curr Cardiol Rep*. 2016;18(6):52. doi: 10.1007/s11886-016-0730-0. PubMed PMID: 27108362.
5. Agency for Healthcare Research and Quality. Healthcare cost and utilization project data use agreement course: Agency for Healthcare Research and Quality [Internet]. 2021 [2023 March 25]. Available from: https://hcup-us.ahrq.gov/DUA/dua_508/DUA508version.jsp.
6. National Bureau of Economic Research. Guidance: Data sets not requiring IRB review: National Bureau of Economic Research [Internet]. 2023 [2023 March 25]. Available from: <https://www.nber.org/programs-projects/projects-and-centers/human-subjects-protection-and-institutional-review-board-irb/guidance-data-sets-not-requiring-irb-review>.
7. Monlezun DJ, Sinyavskiy O, Peters N, Steigner L, Aksamit T, Girault MI, et al. Artificial intelligence-augmented propensity score, cost effectiveness and computational ethical analysis of cardiac arrest and active cancer with novel mortality predictive score. *Medicina (Kaunas)*. 2022;58(8):Epub 20220803. doi: 10.3390/medicina58081039. PubMed PMID: 36013506; PubMed Central PMCID: PMC9412828.
8. Razavi AC, Sapin A, Monlezun DJ, McCormack IG, Latoff A, Pedroza K, et al. Effect of culinary education curriculum on Mediterranean diet adherence and food cost savings in families: a randomised controlled trial. *Public Health Nutr*. 2021;24(8):2297-303. Epub 20200803. doi: 10.1017/S1368980020002256. PubMed PMID: 32744215.
9. Razavi AC, Monlezun DJ, Sapin A, Stauber Z, Schradle K, Schlag E, et al. Multisite culinary medicine curriculum is associated with cardioprotective dietary patterns and lifestyle medicine competencies among medical trainees. *Am J Lifestyle Med*. 2020;14(2):225-33. Epub 20200124. doi: 10.1177/1559827619901104. PubMed PMID: 32231488; PubMed Central PMCID: PMC7092396.
10. Centers for Disease Control and Prevention. Flu season: Center for Disease Control and Prevention [Internet]. 2022 [2023 March 205]. Available from: <https://www.cdc.gov/flu/about/season/flu-season.htm>.
11. Monlezun DJ, Badalamenti A, Javaid A, Marmagkiolis K, Honan K, Kim JW, et al. Artificial intelligence-augmented analysis of contemporary procedural, mortality, and cost trends in carcinoid heart disease in a large national cohort with a focus on the "forgotten pulmonic valve". *Front Cardiovasc Med*. 2022;9:1071138. Epub 20230208. doi: 10.3389/fcvm.2022.1071138. PubMed PMID: 36843627; PubMed Central PMCID: PMC9945326.
12. Monlezun DJ, Lawless S, Palaskas N, Peerlbhai S, Charitakis K, Marmagkiolis K, et al. Machine learning-augmented propensity score analysis of percutaneous coronary intervention in over 30 million cancer and non-cancer patients. *Front Cardiovasc Med*. 2021;8:620857. Epub 20210406. doi: 10.3389/fcvm.2021.620857. PubMed PMID: 33889598; PubMed Central PMCID: PMC8055825.
13. Monlezun DJ, Carr C, Niu T, Nordio F, DeValle N, Sarris L, et al. Meta-analysis and machine learning-augmented mixed effects cohort analysis of improved diets among 5847 medical trainees, providers and patients. *Public Health Nutr*. 2022;25(2):281-9. Epub 20210628. doi: 10.1017/s1368980021002809. PubMed PMID: 34176552; PubMed Central PMCID: PMC8883775.
14. Khadra H, Kholmatov R, Monlezun D, Kandil E. Do anticoagulation medications increase the risk of haematoma in ultrasound-guided fine needle aspiration of thyroid lesions? *Cytopathology*. 2018;29(6):565-8. Epub 20180803. doi: 10.1111/cyt.12608. PubMed PMID: 29969159.
15. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17(19):2265-81. doi: 10.1002/(sici)1097-0258(19981015)17:19<2265::aid-sim918>3.0.co;2-b. PubMed PMID: 9802183.
16. Elze MC, Gregson J, Baber U, Williamson E, Sartori S, Mehran R, et al. Comparison of propensity score methods and covariate adjustment: evaluation in 4 cardiovascular studies. *J Am Coll Cardiol*. 2017;69(3):345-57. doi: 10.1016/j.jacc.2016.10.060. PubMed PMID: 28104076.
17. US Department of Transportation. Departmental guidance on valuation of a statistical life in economic analysis: U.S. Department of Transportation [Internet]. 2022 [2023 March 25]. Available from: <https://www.transportation.gov/office-policy/transportation-policy/revised-departmental-guidance-on-valuation-of-a-statistical-life-in-economic-analysis>.
18. Monlezun DJ. The global bioethics of artificial intelligence and human rights. Cambridge: Cambridge Scholars Press; 2020.
19. Garcia A, Monlezun D. Ethical challenges in COVID-19 biomedical research, vaccination, and therapy. *Bioethics during COVID-19*. Cambridge: Cambridge Scholars Press; 2022.
20. Monlezun D, Sotomayor C, Peters N, Steigner L, Gallagher C, García A. The global AI ethics of COVID-19 recovery: Narrative review and personalist social contract ethical analysis of AI-driven optimization of public health effectiveness and social equities. *Medicine and ethics*. 2022;33(2). doi: <http://dx.doi.org/10.36105/mye.2022v33n2.02>.
21. Schaeffer MD. Thomistic personalism: clarifying and advancing the project. 2016.
22. Carlo WE. The ultimate reducibility of essence to existence in existential metaphysics: M. Nijhoff. 1966.
23. Clarke WN. Explorations in metaphysics: Being--God--person. 1994.
24. Aristotle A. Aristotle metaphysics. Cambridge, MA: Harvard University Press; 1933.
25. Clarke WN. Person and being. 1993.
26. Clarke WN. The creative retrieval of Saint Thomas Aquinas: essays in Thomistic philosophy, new and old. New York: Fordham Univ Press; 2009.
27. Aquinas T. Summa theologiae: Guerin; 1869.
28. Gluszek A, Kocon S, Zuk K, Aljabali P, Gluza A, Siwek K. Episodes of atrial fibrillation and meteorological conditions. *Kardiol Pol*. 2008;66(9):958-63; discussion 64-5. PubMed PMID: 18924023.
29. Fustinoni O, Saposnik G, Esnaola y Rojas MM, Lakkis SG, Sposato LA, Re NI. Higher frequency of atrial fibrillation linked to colder seasons

and air temperature on the day of ischemic stroke onset. *J Stroke Cerebrovasc Dis.* 2013;22(4):476-81. Epub 20130404. doi: 10.1016/j.jstrokecerebrovasdis.2013.03.009. PubMed PMID: 23562211.

30. Deshmukh AJ, Pant S, Kumar G, Hayes K, Badheka AO, Dabhadkar KC, et al. Seasonal variations in atrial fibrillation related hospitalizations. *Int J Cardiol.* 2013;168(2):1555-6. Epub 20130307. doi: 10.1016/j.ijcard.2012.12.104. PubMed PMID: 23465251.

31. Upshur RE, Moineddin R, Crighton EJ, Mamdani M. Is there a clinically significant seasonal component to hospital admissions for atrial fibrillation? *BMC Health Serv Res.* 2004;4(1):5. Epub 20040319. doi: 10.1186/1472-6963-4-5. PubMed PMID: 15033001; PubMed Central PMCID: PMC400747.

32. Watanabe E, Kuno Y, Takasuga H, Tong M, Sobue Y, Uchiyama T, et al. Seasonal variation in paroxysmal atrial fibrillation documented by 24-hour Holter electrocardiogram. *Heart Rhythm.* 2007;4(1):27-31. Epub 20060928. doi: 10.1016/j.hrthm.2006.09.030. PubMed PMID: 17198985.

33. Murphy NF, Stewart S, MacIntyre K, Capewell S, McMurray JJ. Seasonal variation in morbidity and mortality related to atrial fibrillation. *Int J Cardiol.* 2004;97(2):283-8. doi: 10.1016/j.ijcard.2004.03.041. PubMed PMID: 15458696.

34. Frost L, Johnsen SP, Pedersen L, Husted S, Engholm G, Sorensen HT, et al. Seasonal variation in hospital discharge diagnosis of atrial fibrillation: a population-based study. *Epidemiology.* 2002;13(2):211-5. doi: 10.1097/00001648-200203000-00017. PubMed PMID: 11880763.

35. Frost L, Vukelic Andersen L, Mortensen LS, Dethlefsen C. Seasonal variation in stroke and stroke-associated mortality in patients with a hospital diagnosis of nonvalvular atrial fibrillation or flutter. A population-based study in Denmark. *Neuroepidemiology.* 2006;26(4):220-5. Epub 20060425. doi: 10.1159/000092796. PubMed PMID: 16645321.

36. Nguyen JL, Link MS, Luttmann-Gibson H, Laden F, Schwartz J, Wessler BS, et al. Drier air, lower temperatures, and triggering of paroxysmal atrial fibrillation. *Epidemiology.* 2015;26(3):374-80. doi: 10.1097/EDE.0000000000000284. PubMed PMID: 25756220; PubMed Central PMCID: PMC4502955.

37. Nguyen JL, Laden F, Link MS, Schwartz J, Luttmann-Gibson H, Dockery DW. Weather and triggering of ventricular arrhythmias in patients with implantable cardioverter-defibrillators. *J Expo Sci Environ Epidemiol.* 2015;25(2):175-81. Epub 20131030. doi: 10.1038/jes.2013.72. PubMed PMID: 24169878; PubMed Central PMCID: PMC4503240.

38. Cagle A, Hubbard R. Cold-related cardiac mortality in King County, Washington, USA 1980-2001. *Ann Hum Biol.* 2005;32(4):525-37. doi: 10.1080/03014460500153758. PubMed PMID: 16147400.

39. Schneider A, Schuh A, Maetzel FK, Ruckerl R, Breitner S, Peters A. Weather-induced ischemia and arrhythmia in patients undergoing cardiac rehabilitation: another difference between men and women. *Int J Biometeorol.* 2008;52(6):535-47. Epub 20080129. doi: 10.1007/s00484-008-0144-9. PubMed PMID: 18228048.

40. Kupari M, Koskinen P. Seasonal variation in occurrence of acute atrial fibrillation and relation to air temperature and sale of alcohol. *Am J Cardiol.* 1990;66(20):1519-20. doi: 10.1016/0002-9149(90)90549-g. PubMed PMID: 2252006.

41. Fazal M, Malisa J, Rhee JW, Witteles RM, Rodriguez F. Racial and ethnic disparities in cardio-oncology: a call to action. *JACC CardioOncol.* 2021;3(2):201-4. Epub 20210615. doi: 10.1016/j.jacc.2021.05.001. PubMed PMID: 34308372; PubMed Central PMCID: PMC8301207.

42. Heckbert SR, Austin TR, Jensen PN, Chen LY, Post WS, Floyd JS, et al. Differences by Race/Ethnicity in the Prevalence of Clinically Detected and Monitor-Detected Atrial Fibrillation: MESA. *Circ Arrhythm Electrophysiol.* 2020;13(1):e007698. Epub 20200114. doi: 10.1161/CIRCEP.119.007698. PubMed PMID: 31934795; PubMed Central PMCID: PMC7204495.

43. Giaquinto AN, Miller KD, Tossas KY, Winn RA, Jemal A, Siegel RL. Cancer statistics for African American/Black People 2022. *CA Cancer J Clin.* 2022;72(3):202-29. Epub 20220210. doi: 10.3322/caac.21718. PubMed PMID: 35143040.

44. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin.* 2022;72(1):7-33. Epub 20220112. doi: 10.3322/caac.21708. PubMed PMID: 35020204.

45. Siontis KC, Noseworthy PA, Ruddy KJ. Atrial Fibrillation and Cancer: Where Biology and Epidemiology Intertwine. *JACC CardioOncol.* 2021;3(2):233-5. Epub 20210615. doi: 10.1016/j.jacc.2021.04.003. PubMed PMID: 34396328; PubMed Central PMCID: PMC8352332.

46. Assuncao B, Handschumacher MD, Brunner AM, Yucel E, Bartko PE, Cheng KH, et al. Acute Leukemia is Associated with Cardiac Alterations before Chemotherapy. *J Am Soc Echocardiogr.* 2017;30(11):1111-8. Epub 20170915. doi: 10.1016/j.echo.2017.07.016. PubMed PMID: 28927558.

47. Asteggiano R, Norbiato C, Marengo S, Parrini I. Cancer and arrhythmias. *Journal of Cardiology Practice.* 2021;19(21).

48. Lee DH, Chandrasekhar S, Fradley MG. Electrophysiologic Complications in Cancer Patients. *Methodist Debakey Cardiovasc J.* 2019;15(4):282-8. doi: 10.14797/mdcj-15-4-282. PubMed PMID: 31988689; PubMed Central PMCID: PMC6977558.

49. Buza V, Rajagopalan B, Curtis AB. Cancer Treatment-Induced Arrhythmias: Focus on Chemotherapy and Targeted Therapies. *Circ Arrhythm Electrophysiol.* 2017;10(8). doi: 10.1161/CIRCEP.117.005443. PubMed PMID: 28798022.

50. Bagheri R, Yousefi Y, Rezai R, Azemonfar V, Keshtan FG. Atrial fibrillation after lung surgery: incidence, underlying factors, and predictors. *Kardiochir Torakochirurgia Pol.* 2019;16(2):53-6. Epub 20190628. doi: 10.5114/kitp.2019.86355. PubMed PMID: 31410090; PubMed Central PMCID: PMC6690155.

51. Ciriaco P, Mazzone P, Canneto B, Zannini P. Supraventricular arrhythmia following lung resection for non-small cell lung cancer and its treatment with amiodarone. *Eur J Cardiothorac Surg.* 2000;18(1):12-6. doi: 10.1016/s1010-7940(00)00428-0. PubMed PMID: 10869934.

52. Imperatori A, Mariscalco G, Riganti G, Rotolo N, Conti V, Dominioni L. Atrial fibrillation after pulmonary lobectomy for lung cancer affects long-term survival in a prospective single-center study. *J Cardiothorac Surg.* 2012;7:4. Epub 20120110. doi: 10.1186/1749-8090-7-4. PubMed PMID: 22233837; PubMed Central PMCID: PMC3287133.

53. Walsh SR, Oates JE, Anderson JA, Blair SD, Makin CA, Walsh CJ. Postoperative arrhythmias in colorectal surgical patients: incidence and clinical correlates. *Colorectal Dis.* 2006;8(3):212-6. doi: 10.1111/j.1463-1318.2005.00881.x. PubMed PMID: 16466562.

54. O'Neal WT, Lakoski SG, Qureshi W, Judd SE, Howard G, Howard VJ, et al. Relation between cancer and atrial fibrillation (from the REasons for Geographic And Racial Differences in Stroke Study). *Am J Cardiol.* 2015;115(8):1090-4. Epub 20150131. doi: 10.1016/j.amjcard.2015.01.540. PubMed PMID: 25711434; PubMed Central PMCID: PMC4380860.

55. Guzzetti S, Costantino G, Vernocchi A, Sada S, Fundaro C. First diagnosis of colorectal or breast cancer and prevalence of atrial fibrillation. *Intern Emerg Med.* 2008;3(3):227-31. Epub 20080305. doi: 10.1007/s11739-008-0124-4. PubMed PMID: 18320149.

56. Erichsen R, Christiansen CF, Mehnert F, Weiss NS, Baron JA, Sorensen HT. Colorectal cancer and risk of atrial fibrillation and flutter: a population-based case-control study. *Intern Emerg Med.* 2012;7(5):431-8. Epub 20111004. doi: 10.1007/s11739-011-0701-9. PubMed PMID: 21968511.

57. Ostfeld EB, Erichsen R, Pedersen L, Farkas DK, Weiss NS, Sorensen HT. Atrial fibrillation as a marker of occult cancer. *PLoS One.* 2014;9(8):e102861. Epub 20140813. doi: 10.1371/journal.pone.0102861. PubMed PMID: 25119880; PubMed Central PMCID: PMC4138009.