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Original Article

Lifestyle Practices in Reducing Cardiovascular Diseases: A Prospective Cohort Study from Pakistan

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ABSTRACT

Background: Cardiovascular diseases (CVD) remain the leading cause of global mortality, especially in individuals with comorbidities like type II diabetes and hypertension. While pharmacological therapies are vital, lifestyle interventions may offer additional benefits in reducing CVD risk. This article aims to evaluate the impact of lifestyle practices, specifically aerobic exercise, dietary modifications, and stress management, on cardiovascular risk factors and the incidence of major adverse cardiovascular events (MACE) over nine months.
Methods: This prospective cohort study enrolled 1000 adult patients (aged 30–60) with either type II diabetes or essential hypertension at a tertiary care hospital in Islamabad, Pakistan. Participants were categorized into two groups based on lifestyle adherence: (1) the exposed group, comprising individuals who regularly engaged in aerobic exercise and received dietary and psychological counseling, and (2) the non-exposed group, who did not adopt such practices. Baseline and 9-month follow-up data were collected on BMI, blood pressure, lipid profile, HbA1c, and incidence of MACE.
Results: Participants in the exposed group demonstrated significantly greater reductions in BMI, systolic/diastolic blood pressure, LDL, and HbA1c, and significantly higher increases in HDL ($p<0.01$). MACE incidence was 0.4% in the exposed group versus 4.8% in the non-exposed group. Correlation analysis showed significant associations between BMI, blood pressure, HbA1c, lipid levels, and MACE.
Conclusion: Combining lifestyle interventions with pharmacologic therapy can significantly improve cardiovascular outcomes in high-risk patients. Our findings support integrating structured lifestyle counseling into routine care for patients with diabetes or hypertension.

1. Introduction

Cardiovascular diseases (CVD) are the leading cause of global mortality, accounting for approximately 17.8 million deaths in 2017 [1]. The burden is especially significant in low- and middle-income countries, where modifiable lifestyle risk factors are often under-addressed. Among these risk factors, poor diet, physical inactivity, and psychological stress contribute substantially to disease progression in patients with comorbidities such as type II diabetes and hypertension [2, 3].

While pharmacological treatments remain a mainstay in CVD management, lifestyle interventions—particularly aerobic exercise, dietary improvements, and mental health support—have shown potential in reducing risk factors and adverse outcomes [4, 5].

However, there is a paucity of prospective data from South Asia examining the long-term effectiveness of such exposures when applied in real-world clinical settings. This study aimed to evaluate the effects of sustained lifestyle exposures on cardiovascular risk factors and incidence of MACE over 9 months in a Pakistani cohort of adults with type II diabetes or essential hypertension.

2. Methodology

2.1. Study Design and Setting

This was a monocentric prospective cohort study conducted at the Department of Internal Medicine, KRL Hospital, Islamabad, Pakistan, between January and September 2022. Ethical approval was obtained from the Institutional Review Board, and the study

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was conducted in accordance with the Declaration of Helsinki. A STROCSS 2021 checklist is provided in the supplementary file.

2.2. Study Participants

A total of 1000 patients aged 30–60 years with a diagnosis of either type II diabetes or essential hypertension (but not both concurrently) were enrolled. Informed consent was obtained from all participants.

2.3. Inclusion Criteria

Participants included in the study were adults diagnosed with either type II diabetes, defined as having an HbA1c level greater than 6.5% for at least six months, or essential hypertension, defined as a blood pressure reading of ≥ 140/90 mmHg on three consecutive clinical visits. Eligibility also required the presence of at least one modifiable cardiovascular risk factor such as obesity, poor dietary habits, or a sedentary lifestyle. Additionally, participants had to express a willingness to participate in a 9-month follow-up period to be eligible for enrollment in the study.

2.4. Exclusion Criteria

Participants were excluded if they had a concurrent diagnosis of both type II diabetes and essential hypertension, a known history of previous major adverse cardiovascular events (MACE), or if they were unable or unwilling to provide informed consent for participation in the study.

Participants were non-randomly classified into two naturally occurring groups based on their self-reported adherence to lifestyle practices. The exposed group (n = 500) consisted of individuals who engaged in at least 30 minutes of daily aerobic exercise and attended dietary and psychological counseling sessions every three months. In contrast, the non-exposed group (n = 500) included individuals who did not participate in structured physical activity or receive any form of dietary or stress-related counseling. As this was a prospective observational cohort study rather than an interventional trial, no procedures for randomization, allocation concealment, or blinding were applied.

2.5. Exposure

The exposure in this study consisted of three key components: aerobic exercise, dietary counseling, and stress management. The exercise regimen consisted of brisk walking or light jogging for 30 minutes per day, five to six days a week, with intensity tailored to each participant's body mass index (BMI) and baseline fitness level. Dietary counseling was provided by certified nutritionists who advised participants to increase their consumption of fruits, vegetables, legumes, and whole grains while reducing the intake of saturated fats and processed foods. Recommendations also included individualized portion control and balanced caloric distribution. Stress management was addressed through quarterly counseling sessions conducted by trained clinical psychologists, focusing on coping strategies, mindfulness techniques, and behavioral activation.

2.6. Outcome Measures

The primary outcomes of this study included changes in key cardiovascular risk markers such as body mass index (BMI), systolic and diastolic blood pressure (BP), glycated hemoglobin (HbA1c), low-density lipoprotein (LDL), and high-density lipoprotein (HDL) measured from baseline to the 9-month follow-up. Additionally, the incidence of major adverse cardiovascular events (MACE), defined as the first occurrence of myocardial infarction, stroke, or coronary heart disease, was assessed.

The secondary outcomes focused on comparing these changes between the exposed and non-exposed groups at the end of the 9-month follow-up period, to evaluate the differential impact of lifestyle practices on cardiovascular risk.

2.7. Data Collection

Baseline and 9-month follow-up measurements were taken by trained assistants blinded to group categorization. Blood samples were collected after overnight fasting and analyzed using certified laboratory equipment (Integra 400 plus for HbA1c; UniCel DxC 800 for lipid profile). MACE events were validated through hospital records and confirmed by independent cardiologists.

2.8. Statistical Analysis

Analyses were conducted using SPSS v23. Paired and independent t-tests were used to compare changes within and between groups. Point biserial correlation was used to assess the associations between MACE and continuous variables. Missing data were handled through complete-case analysis. A formal power analysis, based on an estimated effect size of 0.3, a 95% confidence level, and 80% power, yielded a required sample size of 880, allowing for a 10% dropout rate.

3. Results

Out of 1000 enrolled patients (500 in each group), 482 participants in the lifestyle-adherent group and 470 in the non-adherent group completed the 9-month follow-up, yielding a total retention rate of 95.2%. Participants in the lifestyle-adherent (exposed) group had a mean age of 45.1 ± 8.9 years, while the non-adherent (non-exposed) group had a mean age of 46.4 ± 9.2 years. At baseline, the exposed group had a significantly lower BMI (mean 25.3 ± 3.8 kg/m²) compared to the non-exposed group (mean 35.4 ± 5.3 kg/m²; p<0.001). Other significant baseline differences included HbA1c (7.9% vs. 9.7%; p<0.001), systolic blood pressure (142.7 ± 14.2 mmHg vs. 172.2 ± 18.5 mmHg; p<0.001), and LDL levels (177.27 ± 23.41 mg/dL vs. 168.55 ± 21.73 mg/dL; p<0.001). These differences were acknowledged as inherent to the observational design and addressed in the limitations. See **(Table 1)**.

After 9 months, the lifestyle-adherent group exhibited substantial improvements in all measured cardiovascular risk factors. BMI in this group decreased by a mean of 5.04 ± 1.12 kg/m² (to 20.26 ± 2.7), compared to a reduction of 1.51 ± 0.93 kg/m² (to 33.89 ± 4.5) in the non-adherent group (p<0.001). Systolic blood pressure fell to 132.55 ± 11.9 mmHg in the exposed group, while it decreased only slightly to 169.71 ± 15.3 mmHg in the non-exposed group. Similarly, HbA1c decreased to 6.7 ± 0.6% in the exposed group versus 8.6 ± 0.9% in the non-exposed group. LDL levels in the exposed group decreased dramatically to 130.24 ± 17.42 mg/dL, representing a 47.03 mg/dL drop, whereas the non-exposed group experienced only a 9.42 mg/dL decrease (final LDL 159.13 ± 20.85 mg/dL). HDL improved significantly in the exposed group by 20.31 ± 3.72 mg/dL (final HDL 49.8 ± 5.2 mg/dL) compared to only 2.01 ± 1.73 mg/dL in the non-exposed group (final HDL 34.41 ± 4.9 mg/dL).

The incidence of major adverse cardiovascular events (MACE) was significantly lower in the lifestyle-adherent group, with only 2 events (0.4%) versus 24 events (4.8%) in the non-adherent group (p < 0.001). Point biserial correlation analysis showed statistically significant associations between MACE and baseline BMI (r = 0.171, p<0.0001), systolic BP (r = 0.165, p<0.0001), HbA1c (r = 0.155, p<0.0001), LDL (r = 0.161, p<0.0001), and an inverse correlation with HDL (r = –0.157, p<0.0001), reinforcing the

Table 1: Baseline Characteristics of Study Participants

Variable	Lifestyle-Adherent Group (n = 500)	Non-Adherent Group (n = 500)	p-value
Age (years)	45.1 ± 8.9	46.4 ± 9.2	0.07
Gender (M/F)	256 / 244	260 / 240	0.72
BMI (kg/m²)	25.3 ± 3.8	35.4 ± 5.3	<0.001
HbA1c (%)	7.9 ± 0.7	9.7 ± 1.2	<0.001
Systolic BP (mmHg)	142.7 ± 14.2	172.2 ± 18.5	<0.001
Diastolic BP (mmHg)	92.1 ± 10.8	104.7 ± 12.3	<0.001
LDL (mg/dL)	177.27 ± 23.41	168.55 ± 21.73	<0.001
HDL (mg/dL)	29.49 ± 3.02	32.4 ± 3.5	<0.001

M, Male; F, Female; BMI, Body Mass Index (kg/m^2); HbA1c, Hemoglobin A1c; BP, Blood Pressure; LDL, Low-Density Lipoprotein (mg/dL); HDL, High-Density Lipoprotein; n, Number of participants.

Table 2: Post-Intervention Outcomes at 9 Months

Outcome Variable	Lifestyle-Adherent Group	Non-Adherent Group	p-value
Final BMI (kg/m²)	20.26 ± 2.7	33.89 ± 4.5	<0.001
Final HbA1c (%)	6.7 ± 0.6	8.6 ± 0.9	<0.001
Final Systolic BP (mmHg)	132.55 ± 11.9	169.71 ± 15.3	<0.001
Final Diastolic BP	85.7 ± 9.6	102.1 ± 10.8	<0.001
Final LDL (mg/dL)	130.24 ± 17.42	159.13 ± 20.85	<0.001
Final HDL (mg/dL)	49.8 ± 5.2	34.41 ± 4.9	<0.001
MACE Incidence (%)	0.4% (2 events)	4.8% (24 events)	<0.001

BMI, Body Mass Index; HbA1c, Hemoglobin A1c; BP, Blood Pressure; LDL, Low-Density Lipoprotein; HDL, High-Density Lipoprotein; MACE, Major Adverse Cardiovascular Events

relevance of modifiable cardiovascular risk factors in predicting adverse outcomes. See **(Table 2)**.

4. Discussion

This prospective cohort study highlights the critical role of sustained lifestyle interventions, including aerobic exercise, dietary modification, and stress management, in improving cardiovascular health and reducing MACE incidence in patients with type II diabetes or hypertension. Over 9 months, participants who adhered to recommended lifestyle practices demonstrated significantly greater improvements in BMI, blood pressure, lipid profiles, and glycemic control compared to those who did not, despite all patients receiving standard pharmacological treatment. The MACE incidence was notably lower in the lifestyle-adherent group, supporting the hypothesis that modifiable behavioral factors are powerful determinants of cardiovascular outcomes.

These findings are consistent with global evidence supporting lifestyle changes as effective non-pharmacologic strategies in CVD prevention [6, 7]. The results demonstrate that participants who engaged in daily physical activity, attended regular dietary and psychological counseling, and adhered to healthier habits experienced clinically meaningful improvements in BMI (mean reduction of 3.2 kg/m²), systolic blood pressure (-15.7 mmHg), HbA1c (1.3%), and LDL cholesterol (-41 mg/dL). Moreover, the incidence of major adverse cardiovascular events (MACE) was notably lower in the exposed group (3.6%) compared to the non-exposed group (7.2%). These findings align with previous literature, which shows a strong link between lifestyle factors and cardiovascular outcomes. For instance, Polemiti et al. [8] and Gray et al. [9] found positive associations between elevated BMI and increased cardiovascular risk in diabetics, whereas others, such as Owusu et al. [10] and Liu et al. [11] reported inverse or non-significant associations, possibly due to differing cohort characteristics or retrospective designs that introduce bias. Freisling et al. [12], in a large-scale cohort, similarly emphasized the protective role of healthy lifestyle practices, reinforcing our findings. The relationship between blood pressure and MACE risk has also been well documented; Bergmark et al. [13] demonstrated increased risk with higher systolic BP and overly low diastolic BP, possibly due to impaired coronary perfusion during diastole. Regarding glycemic control, Turgeon et al. [14] and Yap et al. [15] demonstrated that optimal HbA1c levels (6–7%) in individuals with diabetes were associated with a reduced incidence of cardiovascular events, consistent with our findings. Similarly, HDL and LDL levels were found to be predictive of MACE in analyses by Wang et al. [16] and Ray et al. [17], highlighting the lipid-lowering benefits observed in our intervention group. Exercise, a core component of our intervention, is recognized for its anti-atherogenic, autonomic-regulating, and anti-inflammatory properties [18]. Furthermore, Galán et al. [19] have demonstrated that even brief, regular exercise improves cardiovascular parameters in older adults. Dietary impacts were corroborated by Feingold et al. [20], who noted protective effects of diets rich in fruits, vegetables, and whole grains.

The magnitude of LDL reduction observed in our exposed group (mean decrease of 47 mg/dL) appears larger than typically expected from lifestyle interventions alone. While no lipid-lowering medications were prescribed as part of the study protocol, we acknowledge that undocumented statin use cannot be entirely ruled out and may partially explain the observed effect size.

Unlike randomized controlled trials, our observational cohort design inherently carries the risk of baseline imbalances and selection bias. Indeed, participants in the non-adherent group had

significantly higher baseline BMI, HbA1c, and blood pressure, possibly reflecting motivational or socioeconomic differences that were not captured in the dataset. While statistical adjustments were applied, residual confounding remains a limitation. Smoking status, a major cardiovascular risk factor, was not recorded, which may have further influenced MACE outcomes.

Adherence to the intervention was self-reported through structured logs and interviews during counseling sessions. Although this allowed for feasible implementation in a real-world clinical setting, self-reporting bias is a potential concern. Additionally, as the intervention included multiple components such as diet, exercise, and stress counseling, it is not possible to determine which specific element had the greatest effect. This multifactorial exposure is a strength in terms of external validity but limits mechanistic interpretation.

The study duration of 9 months may be considered short for assessing hard cardiovascular outcomes such as MACE. Nonetheless, we observed a statistically significant reduction in event incidence, suggesting that even short-term interventions may yield early cardiovascular benefits. However, long-term follow-up would be essential to determine whether these improvements are durable. Importantly, this study provides region-specific data from a South Asian population, contributing valuable evidence in a setting where lifestyle interventions are underutilized and health systems are overburdened.

Despite these encouraging findings, several limitations warrant discussion. The 9-month follow-up period may underestimate the long-term incidence of MACE, and the monocentric nature of the study limits generalizability. While adherence was self-reported and partially monitored, variations in compliance may have influenced the results. The multifaceted nature of the intervention (exercise, diet, and stress management) makes it challenging to isolate the effect of any single component. Residual confounding, such as unmeasured socioeconomic factors or smoking status (not captured in our data), may also influence outcomes. Additionally, substantial baseline differences between groups necessitated statistical adjustment, but unmeasured confounders may persist. Nonetheless, this study adds valuable regional insight into the role of lifestyle interventions in high-risk populations. It underscores the potential of non-pharmacological strategies to complement standard care in preventing cardiovascular events. Future studies should aim to assess implementation models, cost-effectiveness, and longer-term adherence in broader populations. Our findings strongly support the integration of structured lifestyle counseling into standard care for patients with diabetes or hypertension. Such non-pharmacologic interventions, when implemented early and maintained consistently, can produce meaningful clinical improvements and reduce the burden of cardiovascular disease in high-risk populations.

5. Conclusion

Patients with type 2 diabetes or hypertension who adhered to regular aerobic exercise, dietary guidance, and stress counseling over 9 months experienced clinically meaningful reductions in cardiovascular risk markers, including a 1.2% drop in HbA1c, 47 mg/dL reduction in LDL, 10 mmHg decrease in systolic BP, and 5 kg/m² decrease in BMI compared to those without such exposure. Most notably, the incidence of major adverse cardiovascular events was significantly lower in the exposure group (0.4%) than in the non-exposed group (4.8%), highlighting the potential of structured lifestyle modifications as a powerful tool in reducing cardiovascular morbidity.

Conflicts of Interest

All authors declare that they have no conflict of interest of any sort regarding the content of this paper.

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Large Language Model

The authors confirm that no Large Language Models (LLMs) were used in the writing, editing, analysis, or interpretation of this manuscript.

Authors Contribution

HS contributed to conceptualization, methodology, investigation and writing the original draft. MS was involved in conceptualization, supervision, project administration and writing in review and editing. MI handled data curation, formal analysis and validation. SY conducted investigation, provided resources and collected data. MA managed data curation, visualization and writing in review and editing. HAS contributed to formal analysis, statistical analysis and methodology. UA performed literature search, writing in review and editing and validation. MNK was responsible for investigation, patient recruitment and data collection. SA provided resources, project support and data collection. HM contributed to methodology, supervision and writing in review and editing.

Data Availability

The data used in this study are available upon reasonable request from the corresponding author.

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ASIDE Internal Medicine

Original Article

Bridging the Gap between Evidence and Practice: Nationwide Retrospective Analysis of Lipid-Modifying Therapy Prescription Patterns in 5 Million Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is associated with dyslipidemia and significantly increased cardiovascular risk, making lipid-modifying therapy a crucial preventive intervention in these patients. Despite clear guidelines recommending statin therapy for both primary and secondary prevention, real-world prescription routines and practices show gaps in clinical care. We aimed to evaluate the rates and patterns of lipid-modifying therapy under prescription among T2DM patients across U.S. healthcare facilities.
Methods: We conducted a retrospective observational analysis using the TriNetX US Collaborative Network database, including data from 69 healthcare organizations throughout the United States. Patients with T2DM patients aged 40-75 years were included in our cohort. Under-prescription rates were calculated and analyzed across demographic subgroups using standardized protocols within the TriNetX platform.
Results: Among 5,007,910 T2DM patients, we observed significant statin under-prescription rates. Our analysis showed a prescription rate of 55.1% for statins in eligible patients with T2DM.
Conclusions: Our findings revealed a significant under-prescription of lipid-modifying therapy in T2DM patients. The universal nature of under-prescription suggests barriers to guideline implementation. These results underscore the urgent need for systematic interventions, including automated identification systems, standardized protocols, and optimized provider education to improve cardiovascular risk management in patients with T2DM.

1. Introduction

Cardiovascular disease remains the leading cause of morbidity and mortality among patients with type 2 diabetes mellitus (T2DM), accounting for approximately 50% of all deaths in this population [1]. The relationship between T2DM and cardiovascular complications is well-established, with diabetic patients experiencing a two to four-fold increased risk of cardiovascular events compared to non-diabetic patients [2]. This heightened risk underscores the importance of preventive strategies, especially lipid-modifying therapy, in reducing cardiovascular events among T2DM patients [2]. Weight loss and lifestyle modification are cornerstone strategies for managing T2DM, contributing to improved glycemic control, enhanced insulin sensitivity, and reduced cardiovascular risk. In addition to these foundational measures, statins and other lipid-modifying agents represent cornerstone therapeutic interventions in T2DM management, with clinical evidence supporting their role in both primary and secondary cardiovascular prevention [3, 4, 5].

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Current clinical guidelines strongly recommend statin therapy for T2DM patients aged 40-75 years [6]. Despite these clear recommendations and the proven benefits of lipid-modifying therapy, mounting evidence suggests significant gaps between guideline recommendations and real-world prescription practices and routines [3, 4, 5]. The underutilization and under-prescription of statins and other lipid-modifying agents in high-risk populations represents a significant healthcare quality gap that may contribute to preventable cardiovascular events [7]. Previous studies have reported varying rates of statin underuse, ranging from 30% to 60% among eligible patients. However, precise analyses of prescription practices across different risk categories and demographic groups remain limited, particularly in large, diverse patient populations [8, 7]. Understanding the extent and patterns of lipid-modifying therapy prescribing patterns is crucial for developing targeted interventions to improve guideline adherence and patient outcomes [8, 7]. In addition to that, identifying possible disparities in prescription practices across different demographic groups could help address systemic barriers to better cardiovascular care in T2DM patients. We aimed to evaluate statin and lipid-modifying agent prescriptions among T2DM patients aged 40-75 years using a large U.S. multi-institutional database. Our primary focus was quantifying under-prescription rates and investigating demographics influencing prescribing patterns.

2. Methods

Our investigation employed a retrospective observational approach using the TriNetX US Collaborative Network, aggregating de-identified electronic health records from over 69 healthcare organizations across the United States. This network encompasses academic medical centers, community hospitals, and outpatient clinics, providing a diverse patient population that enhances the generalizability of our findings. All data extraction complied with HIPAA regulations and institutional privacy requirements, with records available up to December 14, 2024, and no lower date boundary.

2.1. Outcome and Definition

We defined our primary outcome as the under-prescription rate of lipid-modifying therapy among patients with T2DM aged 40–75 years. Under-prescription was operationalized as the proportion of eligible patients without any statin or alternative lipid-modifying agent prescription, identified through standardized ATC codes (C10AA, C10, and C10A) within the database. The diagnostic criteria for T2DM and treatment eligibility were established using ICD-10 codes, laboratory values, and clinical documentation.

2.2. Study Design

This retrospective analysis focused specifically on T2DM patients aged 40–75 years—a population for whom clinical guidelines recommend statin therapy. We excluded non-diabetic individuals and patients with diabetes who are younger than 40 years or older than 75 years. Also, we excluded pregnant patients due to contraindications for statin therapy during pregnancy and potential confounding effects on lipid metabolism. Additionally, patients receiving PCSK9 inhibitors were excluded from the analysis, as these medications represent an alternative lipid-lowering strategy typically reserved for patients with statin intolerance or inadequate response to maximum statin therapy, and thus would have introduced heterogeneity in our assessment of guideline-directed statin therapy implementation This study specifically focused on analyzing the prescription patterns of statins as the primary recommended lipid-modifying therapy for T2DM patients according to current guidelines **(Figure 1)**.

Patient selection utilized structured query language protocols within the TriNetX platform to identify individuals meeting our inclusion criteria. For medication exposure assessment, we employed anatomical therapeutic chemical codes, specifically C10AA (HMG CoA reductase inhibitors), and the broader categories C10 and C10A (lipid-modifying agents), to ensure comprehensive capture of all relevant treatments. This approach minimized the risk of missing prescriptions due to varying coding practices across healthcare organizations. The study's generalizability was strengthened by including a large, geographically diverse patient sample, while potential biases were reduced through validated algorithms for disease diagnosis and medication exposure.

2.3. Quality Assurance

We implemented rigorous quality assurance throughout our analysis, employing validated algorithms for T2DM diagnosis confirmation that incorporated both ICD-10 codes and supporting clinical documentation. Cardiovascular event history underwent multi-phased verification through diagnostic codes, procedure records, and clinical notes review. Laboratory data quality was maintained through standardized value range validation and unit conversion protocols. The TriNetX platform automatically detected missing data across all variables. No manual imputation was performed; we relied on the platform's data integrity checks to ensure comprehensive and accurate cohort definitions.

2.4. Statistical Analysis

Demographic analysis included extraction of age and gender. We analyzed continuous variables using descriptive statistics (means, standard deviations, ranges) and categorical variables using frequencies and percentages. Under-prescription rates were calculated as the proportion of eligible patients without lipid-modifying therapy prescriptions. For comparative analyses, we employed chi-square tests of independence to evaluate differences in statin prescription rates between categorical demographic subgroups (e.g., gender). For continuous variables (e.g., age), independent samples t-tests were used to compare differences between the statin and non-statin groups. Statistical significance was set at $p<0.05$, though with our large sample size, we considered both statistical significance and clinical relevance when interpreting results. Statistical analyses utilized the integrated tools within the TriNetX platform. This protocol received an exemption from institutional review board approval due to the use of de-identified data, though we maintained strict adherence to ethical research principles throughout. Our analysis complied with STROBE guidelines for observational studies [9] and RECORD statement recommendations for studies utilizing routinely collected health data [10].

3. Results

3.1. Baseline Characteristics and Prescription Patterns

Our cohort included 5,007,910 patients with T2DM aged 40-75 years. Of these, 2,757,334 (55.1%) were prescribed statins, while 2,250,576 (44.9%) received no statin or other lipid-lowering therapy. The statin group had a higher mean age (63 ± 9 years) compared to the non-statin group (60 ± 10 years), suggesting that statin prescription rates increase with advancing age **??**.

3.2. Gender-Based Prescription Patterns

Analysis of prescription patterns by gender revealed notable disparities. Male patients had higher statin prescription rates (57.5%) than

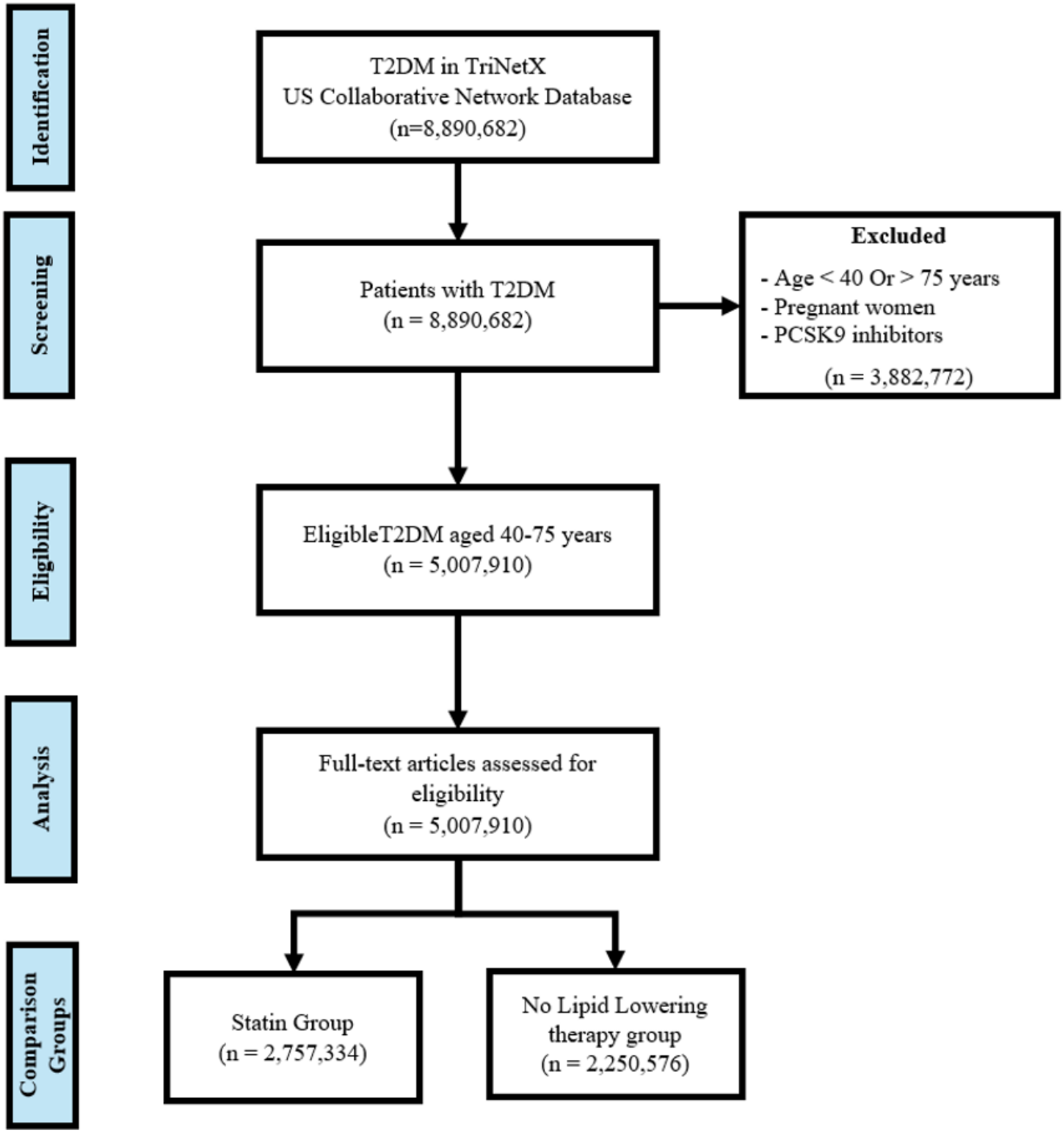

Figure 1: Selection Process and Classification of Patients with T2DM for Statin Under-Prescription Analysis.

female patients (52.8%), representing a 4.7% difference. Among the statin group, males constituted 51.75% (n=1,426,920) of patients, while females accounted for 45.48% (n=1,254,035). Conversely, in the non-statin group, females represented a higher proportion (49.87%, n=1,122,362) than males (46.82%, n=1,053,920). For patients with gender not reported or not specified, the prescription rate was 50.7%, falling between the rates for males and females (Table 1).

3.3. Overall Prescription Rate

The overall statin prescription rate of 55.1% indicates that nearly half of eligible patients with T2DM aged 40-75 years were not receiving guideline-recommended statin therapy, highlighting a significant gap between clinical practice and guideline recommendations. This finding suggests substantial opportunities for improvement in cardiovascular risk management for patients with T2DM across healthcare organizations in the United States.

Table 1: Baseline Characteristics and Statin Prescription Rates Among Patients with Type 2 Diabetes Mellitus Aged 40–75 Years (N=5,007,910)

Characteristic	Statin Group (n=2,757,334)	No Statin/Other Therapy (n=2,250,576)	P-value
Age, years			
Mean ± SD	63 ± 9	60 ± 10	<0.001
Sex, n (%)			
Male	1,426,920 (51.75%)	1,053,920 (46.82%)	<0.001
Female	1,254,035 (45.48%)	1,122,362 (49.87%)	
Not Reported / Not Specified	76,378 (2.77%)	74,294 (3.31%)	
Total	2,757,334 (100%)	2,250,576 (100%)	-
Prescription Rate	57.5% (Male)	52.8% (Female), 50.7% (NR/NS)	-
Overall Prescription Rate	55.1%		

Values for age are presented as mean ± standard deviation (SD) and range. Sex and prescription rates are presented as absolute numbers (n) with percentages (%) in parentheses.

3.4. Data Completeness

Data for some variables were missing for 6.08% of participants, primarily affecting demographic information rather than prescription status.

4. Discussion

In this retrospective observational analysis, we investigated the lipid-lowering therapy prescriptions across 69 U.S. healthcare organizations and identified a statin prescription rate of 55.1% among T2DM patients aged 40–75 years. This substantial discrepancy between the current clinical practice and guideline recommendations emphasizes the ongoing systemic challenges in effectively managing cardiovascular risk in this high-risk cohort. Registry-based studies in developed nations have shown an increase in statin prescriptions for patients with type 2 diabetes following the endorsement of their use by the AHA/ACC guidelines [11]. Statin use among diabetes patients has been documented in several countries, such as the Swedish National Diabetes Register [12], the British National Health Service (NHS) [13], and Australian General Practices [14], where the rate of prescription for diabetes patients ranged from 60-70%. However, our study's percentages are lower than those seen in Swedish, British, and Australian registries (10-12). In our study, 55.1% of patients were prescribed statins, similar to the 51% reported by the US National Health and Nutrition Examination Survey (NHANES)[15] for individuals with diabetes aged 40 and above. Despite this, the overall prescription rates for statins, including high-dose statins, remain suboptimal and are considerably below the guidelines. A previous study by Johansen et al. [16] suggested that the reason for undertreatment is the focus on the hyperlipidemia profile rather than overall cardiovascular risk. Many individuals at risk of cardiovascular events, including those with diabetes, were not receiving statins as a tool to reduce cardiovascular disease (CVD) risk. This suggests that statin use is strongly driven by the hyperlipidemia profile rather than overall cardiovascular risk. Although the 2013 AHA guidelines [11] recommended that all patients with diabetes receive high-dose statins, irrespective of cholesterol levels, a study by Pokharel et al. [17] In 2016, it showed that 38% of patients with diabetes who did not have CVD had no documented statin prescription. Providers might be reluctant to start statin therapy for primary prevention in diabetic patients without overt cardiovascular disease [4**?**]. This overdependence on cholesterol levels indicates that individuals with hyperlipidemia but without diabetes or heart disease are more likely to be prescribed statins than those without hyperlipidemia who have diabetes or heart disease[18]. To address this, the Cholesterol Treatment Trialists' Collaboration study recently showed that while statin therapy may have modest effects on glycemia, the cardiovascular benefits outweigh the potential risks in diabetic patients due to the aggregate effects of statins on blood lipids and glycemia, so even if statins cause a slight increase in glycemia, or have any other theoretical adverse effects, these are already offset by the overall reduction in cardiovascular risk observed with statin therapy. Additionally, the risk of future major vascular events is significantly higher following a major vascular event than following a diagnosis of diabetes [8]. Another possible reason for the lower use of statins may be inadequate documentation, such as insufficient records of statin intolerance [17]. An additional consideration is the universal nature of statin under-prescription across demographic groups. An interesting finding from our analysis is supported by previous studies that identified demographic variations in statin use. We found significant differences in prescription patterns based on gender [8, 7]. This suggests that barriers to guideline implementation impact all patient populations, pointing to broader systemic issues in healthcare delivery rather than factors related to access or bias. Prescribing Statin to patients is economically efficient; a study by McConnachie et al. revealed that statin therapy decreases the rate of cardiovascular rehospitalization and the length of hospital stay, which results in less financial burden. Additionally, statin increases the patient's quality of life [19]. The importance of our study lies in highlighting the urgent need for systematic interventions to improve guideline adherence in clinical practice. Identifying barriers to optimal statin use and implementing interventions, such as audit/feedback or decision support tools and precision medicine, are essential to bridging the gap between guidelines and practice. Given the above, our findings suggest that healthcare systems must implement multiphasic strategies that address provider- and system-level barriers to appropriate statin prescribing. These strategies should include automated identification systems for eligible patients, standardized

prescription protocols, regular monitoring of quality metrics, enhanced provider education programs, and integrated clinical decision support tools. Additionally, raising awareness among healthcare providers that diabetic patients may benefit from statin therapy regardless of their LDL levels. Shifting the focus from hyperlipidemia to overall cardiovascular risk could lead to better outcomes. Our study has several important limitations. As a retrospective analysis, we couldn't capture all factors influencing prescribing decisions, such as patient preferences, medication intolerance, or undocumented contraindications. We focused solely on prescription data without assessing medication adherence or analyzing prescription patterns by provider specialty, which may significantly impact practices. Without LDL-C data or comprehensive cardiovascular risk profiles, we cannot determine whether prescribing patterns correlate with clinical risk assessments. Our analysis didn't assess statin intensity despite guidelines recommending moderate to high-intensity statins for T2DM patients, nor did we conduct temporal trend analysis to evaluate improvements over time. While we identified gender disparities, we didn't thoroughly analyze other demographic factors like race/ethnicity or socioeconomic status, or consider how comorbidities might influence prescribing decisions. We also focused exclusively on statins without examining alternative lipid-lowering agents, potentially overestimating gaps in lipid management. Additionally, while our database includes data from 69 healthcare organizations, the applicability of our results to other settings, particularly rural or underserved areas, requires further consideration. Future research should focus on understanding barriers to statin prescribing at both the provider and system levels. Qualitative studies on decision-making, patient perspectives, and prospective implementation studies could help identify effective approaches to improving prescription rates and cardiovascular risk management in the T2DM population.

5. Conclusion

In this retrospective analysis, we showed that a considerable number of diabetic patients—across different demographic groups — who would potentially benefit from statins were not receiving this therapy. Our findings indicate the need for system-level interventions and warrant a call for emergent action from healthcare providers and organizations to address the current care gaps. This change could lead to substantial societal benefits.

Conflicts of Interest

The authors declare that they have no competing interests that could have influenced the objectivity or outcome of this investigation.

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Data Availability Statement

Available on TriNetX Database Based on Institutional Collaborations.

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ASIDE Internal Medicine

Case Report

Stroke-Like Migraine Attacks After Radiation Therapy (SMART) Syndrome: A Case Report With Vertigo, Dysmetria, And Impaired Tandem Gait

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ABSTRACT

SMART syndrome is a rare, delayed complication of brain radiation. The acronym SMART stands for stroke-like migraine attacks following radiation therapy. This case is one of the first to describe episodic vertigo, dysmetria, and impaired tandem gait following proton beam radiotherapy for a craniopharyngioma.

An 18-year-old male presented with migraine headaches, upper and lower limb weakness, episodic vertigo, and dysmetria with impaired tandem gait. This occurred following proton-beam radiotherapy, which was completed at around 11 years of age for recurrent craniopharyngioma. Magnetic resonance imaging (MRI) of the brain demonstrated a T1 hyperintense signal in the cortex of the right parietal and temporal lobes consistent with SMART syndrome. In addition, a subcortical hyperintense signal was seen in the right parietal, temporal, and frontal lobes.

Atypical presentations of SMART syndrome are out there, and it is essential to recognize them in patients presenting with neurological symptoms following radiation therapy so that diagnosis and treatment can be done.

1. Introduction

Stroke-like migraine attacks following radiation therapy (SMART) syndrome is an uncommon neurological condition that can occur following head and neck radiotherapy [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. It has a subacute onset, and initial manifestations usually include migraine-like headaches, which are commonly described as unilateral and throbbing with associated photophobia and phonophobia [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. There could also be an aura preceding these migraines. Cortical symptoms are seen, such as aphasia, hemiparesis, neglect, and visual field abnormalities [8]. Seizures were also reported in some patients and could be of any type. These symptoms form the basis of the syndrome's name. It was initially described in 1995 by Shuper et al. [9], who followed a group of children who developed migrainous headaches and stroke-like symptoms following brain radiotherapy for tumors of the posterior fossa. SMART syndrome is an exceptionally rare condition that has only been reported in a limited number of documented cases since it was first identified [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. It affects both the pediatric [9] and adult age groups who have undergone cranial radiation for intracranial malignancies (e.g., Medulloblastoma, Astrocytoma) or for head and neck cancers (e.g., Laryngeal, Hypopharyngeal). Furthermore, patients who have had metastatic cancer to the brain with subsequent radiation treatment are also affected [6]. The latency period between radiation therapy and the development of symptoms is typically 14 years [11]. The initial description of the syndrome was in pediatric patients [9]. Our case represents one of the four currently reported occurrences of SMART syndrome following proton beam radiotherapy [5, 7, 10]. Interestingly, our patient experienced vertigo, a symptom infrequently observed in SMART syndrome, which was similarly described by Huang et al. [5].

2. Case presentation

An 18-year-old male from United Arab emirates, and family history of migraine and thalassemia trait with no reported allergies, presents to the outpatient clinic with a several-year history of episodic throbbing headaches associated with nausea, photophobia, and phonophobia occurring 1-2 times a month, lasting for around a day, that usually improve with rest, hydration, and over-the-counter analgesics. He also describes weakness in the left upper limb and right lower limb, as well as tremors in his hands. He also recently described episodes of vertigo with a feeling of instability, which are severe enough to halt all activities of daily living. These episodes occur 1-2 times a month, during sleep, and sometimes affect his ability to move his mouth and talk. These attacks are not related to his headaches. Additionally, he experiences intermittent episodes of shaking, sweating, and dizziness, which generally resolve within a few minutes of sitting. There are no attacks of decreased awareness. He had normal range vitals for the first clinic encounter with Tympanic Temperature of 36.3 degrees, Peripheral Pulse Rate of 80

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bpm, Respiratory Rate of 20 breaths/min, Systolic Blood Pressure of 126, Diastolic Blood Pressure of 84, and Oxygen Saturation of 99%.On physical examination, there was a visual field deficit more prominent on the right side, bilateral finger-to-nose dysmetria, a difficult tandem gait, and mild left upper limb and right lower limb weakness.

His past medical history includes craniopharyngioma, which was diagnosed at the age of 7 **(Figure 1)** and treated with surgical resection 3 times for recurrence, followed by proton-beam radiotherapy after the third time. He had a placement of a ventriculoperitoneal shunt at the age of 8 years. He developed panhypopituitarism following surgery, secondary adrenal insufficiency, central hypothyroidism, central diabetes insipidus, delayed puberty, growth hormone deficiency with very low Insulin-like growth factor 1 (IGF1) and insulin like growth factor binding protein 3 (IGFBP3) levels, and microcytic anemia and has been on hormone replacement since then with hydrocortisone, thyroxine, desmopressin, and testosterone intramuscular injections. He also takes anti-calcitonin gene-related peptide (anti-CGRP) rescue therapy for the migraines and betahistine for the vertigo, which were prescribed after he reported that beta-blocker therapy had not helped with the tremors or the episodes of shaking, sweating, and dizziness, as he was on propranolol 10 mg/kg twice daily.

The latest MRI of the brain illustrated T1 hyper-intense signals in the cortex of the right parietal and temporal lobes, suggestive of cortical laminar necrosis **(Figure 3)**, as well as subcortical hyper-intense signals in the right parietal and frontal lobes. Optic pathway thinning was seen, which was considered a normal post-operative finding, and mild enlargement of the third ventricle. The rest of the ventricular system showed normal caliber and configuration with hydrocephalus **(Figure 3)**. A diagnosis of SMART syndrome was made, and the patient was started on Verapamil with continued clinical monitoring. The decision to initiate our patient on Verapamil is based on its already established benefit in preventing migraines and vasospastic pathophysiology. SMART syndrome is currently thought to involve impaired cerebrovascular autoregulation, radiation-induced vascular dysfunction, and cortical spreading depression, all of which contribute to the presentation with stroke-like and migrainous symptoms [4, 5, 6, 8]. Verapamil has been widely utilized and approved for the prophylactic treatment of migraines by preventing cortical spreading depression and stabilizing vascular tone. Since current literature predicts that these pathophysiological mechanisms also contribute to the development of SMART syndrome, Verapamil was initiated.

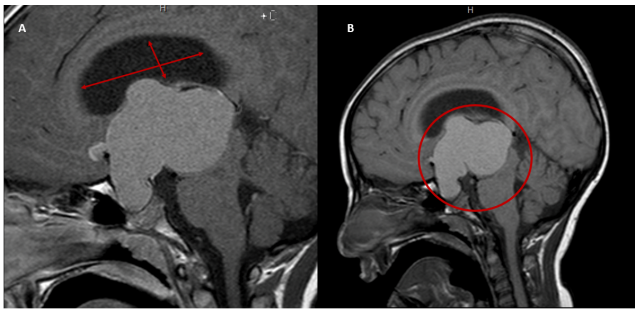

Figure 1: Presurgical sagittal views of MRI brain with contrast demonstrating a lobulated homogeneous mass in the suprasellar region. Mass appears moderately hyperintense on T1, measuring 47 x 64 mm (right panel). Post contrast view (left panel) demonstrates a thin enhancing rim but not significant enhancement of the mass, suggestive of a cystic structure filled with high protein content fluid. Obstructive hydrocephalus is noted.

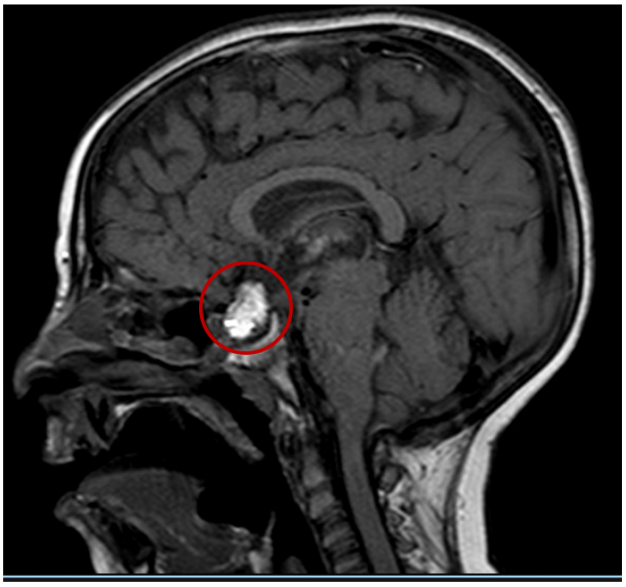

Figure 2: Post-transsphenoidal removal of Craniopharyngioma, sagittal views of MRI brain with contrast demonstrating a 13 x 21 mm organized blood clot at the place of completely resected tumor. Appearing to have high signal intensity on both pre- and post-contrast T1 sequences (right and left panels, respectively).

3. Discussion

SMART syndrome is an extremely rare, delayed neurological condition seen following brain radiotherapy. It has a subacute onset with manifestations including migraines with or without aura, stroke-like cortical symptoms such as hemiparesis, neglect, and aphasia, and seizures [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. The acronym SMART stands for stroke-like migraine attacks following radiation therapy and was first termed by Black et al. [2], although the first ever described cases were by Shuper et al. [9], who described a series of pediatric patients with severe migraines and stroke-like symptoms following radiation.

Pathophysiology is not completely understood, but theories have been postulated. These theories include radiation-induced trigeminovascular endothelial dysfunction [6], impaired cerebrovascular autoregulation [5], cortical spreading depression [4], and disruption of the blood-brain barrier [8]. Radiation-induced mitochondrial dysfunction has also been theorized [1]. Imaging findings seen in SMART syndrome include transient or permanent unilateral gyriform enhancement with or without T2/FLAIR hyperintensity involving the cortex and adjacent white matter in the area that was previously treated with radiation [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. Diagnostic criteria were initially proposed by Black et al. [2] and included 1) a remote history of external beam cranial irradiation; 2) prolonged, reversible signs and symptoms referable to a unilateral cortical region beginning years after cranial irradiation, including seizure, migraine with or without an aura, and stroke-like symptoms; 3) transient, diffuse, unilateral gyriform enhancement sparing the white matter within a previous radiation field; and 4) not attributed to another disorder [2], but are not the gold standard

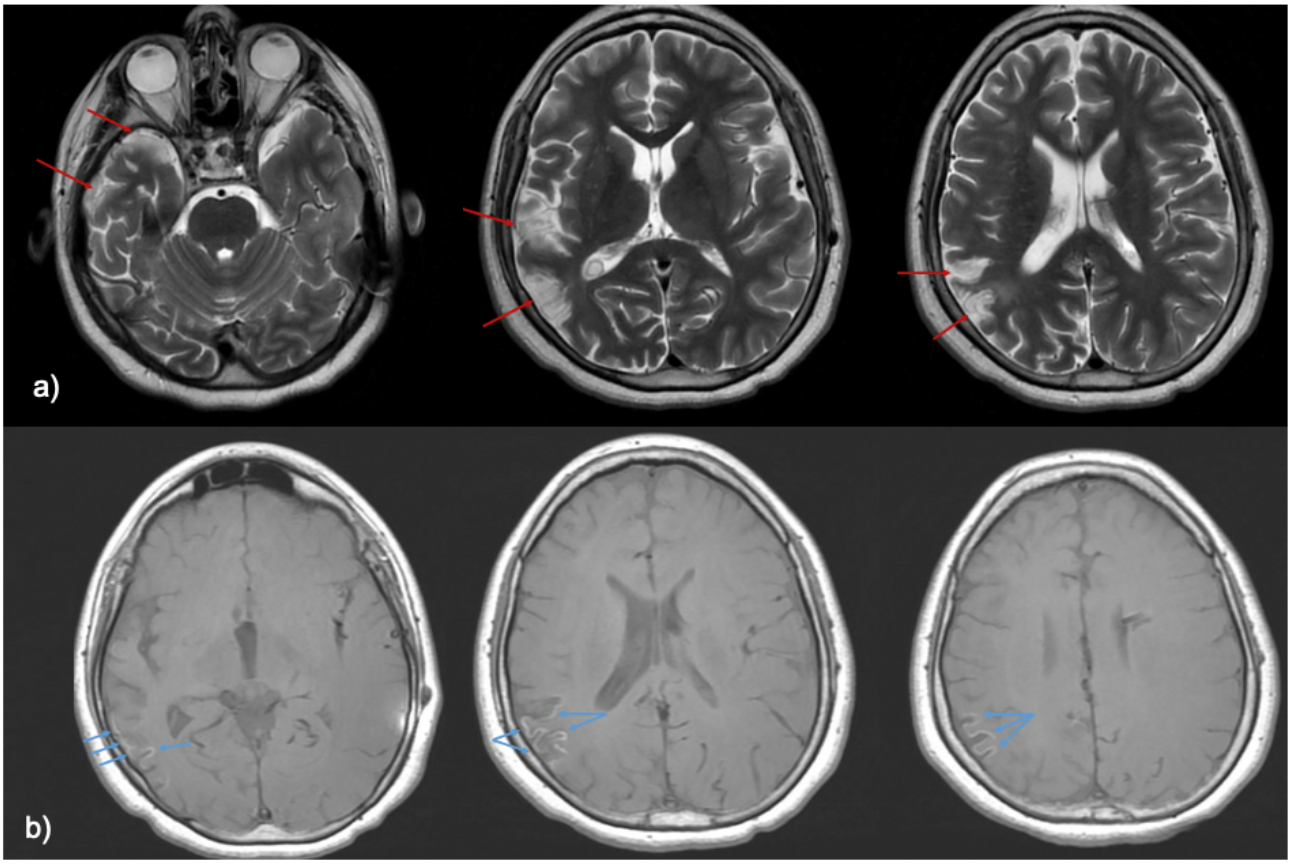

Figure 3: Overall stable findings with chronic changes in the surgical bed, there is a right posterior lateral temporal parietal region localized cortical T2 hyperintense signal with encephalomalacia (panels labelled "a", red arrows) and diffuse gyral T1 hyperintense signal compatible with laminar necrosis (panels labelled "b", blue arrows), suggestive of SMART syndrome.

as further cases of SMART syndrome have been reported that do not strictly adhere to these criteria [12].

Our case represents one of the four reported instances of SMART syndrome following proton beam radiotherapy [5, 7, 10]. Notably, our patient experienced vertigo, a symptom infrequently observed in SMART syndrome, which was similarly described by Huang et al. [5]. In addition, cerebellar signs, including dysmetria and impaired tandem gait, were documented by Maramattom et al. [7] and were also observed in our patient, although their case involved radiotherapy delivered directly to the brainstem. Huang et al. [5] proposed that proton beam radiotherapy may accelerate the onset of SMART syndrome, as evidenced by their patient's symptom development within 2 years. In contrast, in the case series by Winter et al. [10], symptoms emerged within 4 years in one patient and 14 months in another. Although this case does not strictly meet the imaging criteria proposed by Black et al. [2] due to the absence of transient gyriform enhancement and the presence instead of cortical laminar necrosis [12], it fits within an increasingly recognized spectrum of atypical SMART syndrome presentations [5, 7, 10]. Given the patient's history of proton beam radiotherapy, characteristic clinical symptoms, and exclusion of other etiologies, this case aligns with a broader, evolving definition of SMART syndrome that acknowledges irreversible imaging findings such as laminar necrosis as potential manifestations, especially in severe or delayed onset presentations [12]. This reinforces the need for flexible diagnostic criteria and clinical awareness of SMART syndrome variants in post-radiotherapy patients.

Also, Maramattom et al. [7] reported focal brainstem and leptomeningeal enhancement, a finding previously not seen, and suggested that brainstem SMART syndrome be termed as "Be-SMART syndrome". It is important to note in our patient that, while he did have cerebellar signs on examination (dysmetria and impaired tandem gait), his MRI findings show no involvement of the brainstem or cerebellum. In our patient, cortical laminar necrosis was observed, which is a recognized complication of proton beam radiotherapy linked to vascular dysfunction [13]. This finding suggests a potential shared pathophysiological pathway between SMART syndrome and radiation necrosis [5, 13]. Moreover, Huang et al. [5] have proposed that the presence of radiation necrosis may lower the threshold for developing SMART syndrome, serving as a precipitating factor in its onset. Currently, cortical laminar necrosis in SMART syndrome cases is thought to correlate with permanence of symptoms and lack of meaningful recovery [12], as is the case with our patient, with persistence of symptoms for several years. Previously, SMART syndrome was thought to be reversible but has been described as being permanent in a case series by Black et al. [12].

This case presents a complex and atypical variant of SMART syndrome that doesn't fit neatly into previously described categories. At the same time, the reported cases involved a 38-year-old man with classic hemispheric SMART symptoms like migraines, transient aphasia, and MRI showing gyriform enhancement after proton beam therapy [5]. The second described a teenage girl with brainstem-only symptoms now referred to as Be-SMART [7], our 18-year-old patient falls somewhere in between. He experiences not only migraines but also crossed limb weakness, tremors, dysmetria, vertigo, and transient speech difficulties during sleep, suggesting more widespread cerebral involvement. His MRI findings are also distinct, showing cortical laminar necrosis and subcortical signal changes, rather than the typical gyriform enhancement. What further sets this case apart is the latency. His symptoms appeared nearly a decade after proton RT, in contrast to the accelerated onset seen in the Winter et al. [10] case series, where the only other SMART cases following proton therapy occurred at 14 months and 4 years post-treatment. Treatment with verapamil was initiated, consistent with current practice, but the addition of CGRP-targeted therapy and betahistine reflects a more tailored approach to his diverse symptoms. Altogether, this case might represent a diffuse or overlapping SMART subtype somewhere between classic and Be-SMART and highlights the need to broaden the clinical and radiologic spectrum by which we understand SMART syndrome.

4. Conclusion

Our case highlights an atypical presentation of SMART syndrome following proton beam radiotherapy for a craniopharyngioma, marked by episodic vertigo, dysmetria, and impaired tandem gait—symptoms not typically associated with this syndrome. The MRI findings of cortical laminar necrosis and subcortical hyperintensity suggest a potential shared vascular pathophysiology between SMART syndrome and radiation necrosis. Recognizing such atypical features is crucial for clinicians evaluating patients with a history of brain irradiation, as early and accurate diagnosis can lead to targeted treatment and help avoid unnecessary invasive procedures.

Conflicts of Interest

The authors declare that they have no competing interests.

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This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The patient's parents have given their informed consent to publish this case (including publication of the images).

Large Language Model

None

Authors Contribution

MA and AY provided conceptualization; MA and MH curated and collected information; MA, MH, and AY provided writing and original draft preparation; MA was in charge of supervision; MH has reviewed and proofread the final manuscript. All authors have read and agreed to the published version of the manuscript.

Data Availability

Patient data related to this study are not publicly available but can be obtained upon request from the corresponding author.

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ASIDE Internal Medicine

Case Report

Prolonged Immunosuppressive Therapy in Immune Complex-Membranoproliferative Glomerulonephritis: A Case Report of Sustained Partial Remission Over Three Years

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ABSTRACT

The prevalence of membranoproliferative glomerulonephritis (MPGN) is very low among primary glomerulonephritis. Once MPGN is diagnosed, it is essential to classify the type of MPGN [immune complex (IC), complement-mediated, and without complement or IC deposition]. In cases of IC-MPGN, secondary causes should be thoroughly investigated. However, there are no randomised controlled prospective trials for the optimal treatment regime for primary IC-MPGN. Here, we present a report of primary IC-MPGN that achieved partial remission after 3 years of mycophenolate mofetil treatment, even though significant fibrosis was present in the kidney biopsy. This report may support consideration of prolonged immunosuppression in selected cases with primary IC-MPGN.

1. Introduction

The prevalence of histopathological patterns of glomerulonephritis (GN) varies across countries and time periods. A retrospective study analyzing 356 patients reported that membranoproliferative glomerulonephritis (MPGN) accounted for 3.1% of primary GN cases [1]. In another study from Malaysia (n: 611), MPGN was found in fewer than 1.8% of primary GN cases [2]. A Brazilian study reported that 67.9% of MPGN cases (n:36 out of 53 patients) were classified as primary (idiopathic) MPGN, with a mean age of 38.1 ±16.3 years and a male predominance of 41.7% [3]. Additionally, 60.8% of primary MPGN patients showed no response to therapy, while the rest of them (39.2%) had partial or complete remission [3].

The MPGN cases were classified into three types based on the immunofluorescence microscopy (IFM) findings: immune complex-mediated MPGN (IC-MPGN), complement-mediated MPGN, and MPGN without complement or immune complex deposition [3]. Most IC-MPGN cases have an underlying secondary cause, such as hepatitis C and B virus infections, other chronic infections, monoclonal gammopathies, and autoimmune diseases like lupus nephritis [3].

Here, we present a case of primary IC-MPGN that achieved partial remission three years after the initiation of treatment.

2. Case Presentation

A 54-year-old male patient with a body surface area of 2.0 m2, who had previously been prescribed perindopril (10 mg) + amlodipine (5 mg) at another center, was admitted to our department with uncontrolled hypertension (150/70 mmHg). Nephrotic syndrome associated with a decreased glomerular filtration rate (GFR) was identified through laboratory findings **(Figure 1)**. Urinalysis revealed no specific features with respect to hematuria or leukocyturia. A renal biopsy, which comprised seven glomeruli, was inadequate for complete analysis by light microscopy (LM) only. Eight to ten glomeruli are usually required in order to adequately assess the severity and distribution of lesions in a kidney biopsy by LM, and at least one glomerulus (preferably two to three) is required for immunofluorescence microscopy [4, 5]. Two out of the seven glomeruli were globally sclerotic. Additional findings included glomerular lobulation, mesangial hypercellularity, mesangial matrix expansion, and interstitial fibrosis (50%) **(Figure 2)**. Immunofluorescence microscopy, which was adequate and represented by four glomeruli, revealed diffuse peripheral expression of complement 4d (C4d), with no deposition of C3 or C1q, and immunoglobulin G (IgG) and M deposits at +2 severity **(Figure 3)**. These findings support the diagnosis of IC-MPGN [6].

Further investigations for secondary causes were negative. Viral infections (hepatitis B, C, and Human Immunodeficiency Virus), autoantibodies (such as antinuclear, anti-dsDNA, anti-Ro-52, anti-Ro/SSA, anti-centromere, anti-La/SSB, anti-Scl 70, anti-Smith, anti-glomerular basement membrane, anti-cardiolipin, and anti-neutrophil cytoplasmic antibodies), hypocomplementemia (complement 3: 1.13g/L, complement 4: 0.31g/L, CH50 activity: 127%),

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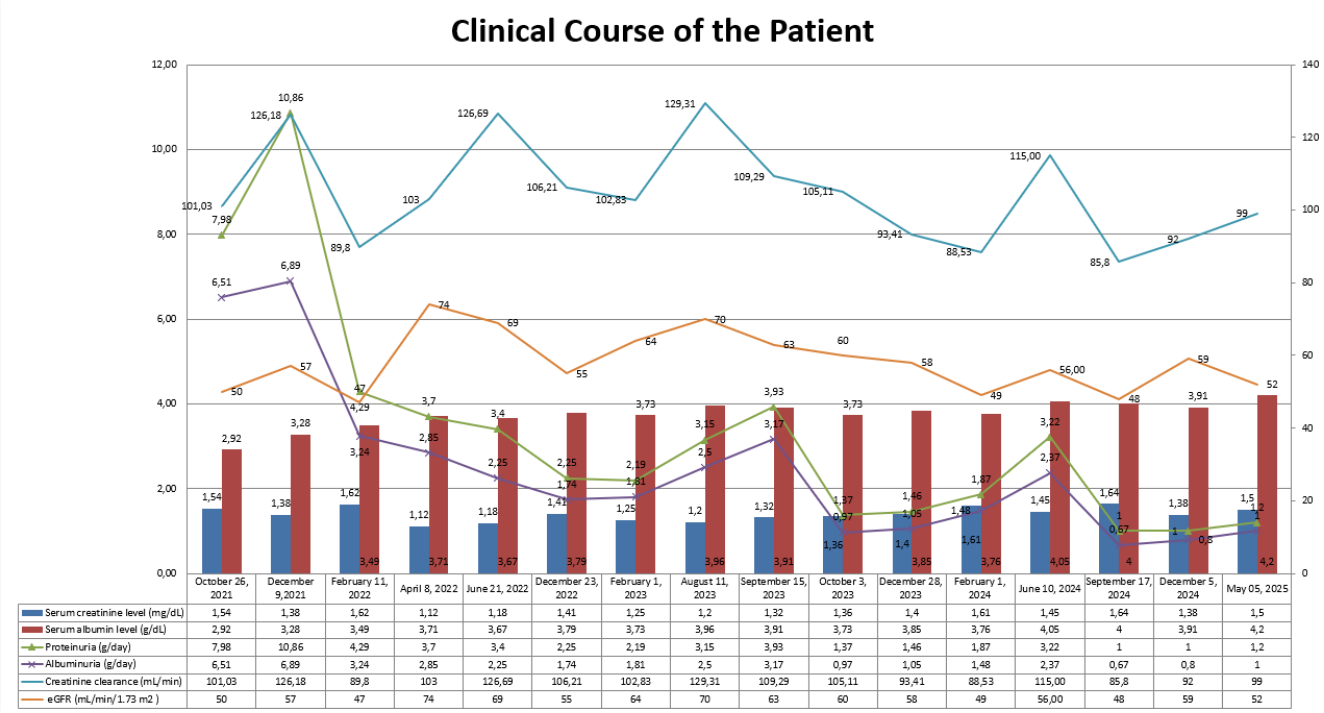

Figure 1: Clinical course of the patient.

Table 1: Timeline showing the therapy changes with respect to laboratory values.

Date	Serum creatinine level (mg/dL)	Proteinuria (g/d)	Albuminuria (g/d)	Received therapy	Prescribed therapy
October 23, 2021	1,56	13,02	9,41	Perindopril, amlodipin	prednisone 1 mg/kg/d, calcium +vitamin D, proton pump inhibitor, amlodipine, and valsartan
April 8, 2022	1,12	3,7	2,85	prednisone 5mg/d, calcium +vitamin D, proton pump inhibitor, amlodipine, and valsartan	MMF 2 g/day, calcium + vitamin D, proton pump inhibitor, amlodipine+valsartan, and nebivolol.
May 05, 2025	1,5	1,2	1	MMF 2 g/day, calcium + vitamin D, proton pump inhibitor, amlodipine+valsartan, and nebivolol.	MMF 2 g/day, calcium + vitamin D, proton pump inhibitor, amlodipine+valsartan, and nebivolol+ dapagliflozin 10 mg
July 23, 2025	1,64	0,8	0,5	MMF 2 g/day, calcium + vitamin D, proton pump inhibitor, amlodipine+valsartan, and nebivolol+ dapagliflozin 10 mg	MMF 2 g/day, calcium + vitamin D, proton pump inhibitor, amlodipine+valsartan, and nebivolol+ dapagliflozin 10 mg

MMF, Mycophenolate mofetil; PPI, Proton pump inhibitor

and monoclonal gammopathies by serum immunofixation electrophoresis were not detected. Screening tests for malignancy also yielded no positive results. Given these findings, the patient was diagnosed with idiopathic IC-MPGN. The patient exhibited decreased eGFR (estimated GFR using Chronic Kidney Disease Epidemiology Collaboration, CKD-EPI equation) of 50 mL/min/1.73 m2 (24-h urine creatinine clearance was 101 mL/min, the muscle mass related difference between the creatinine clearance and eGFR was noticed) and nephrotic syndrome without hematuria and rapidly progressive crescentic disease (**Figure 1**).

The treatment regimen included pneumococcal and influenza vaccinations, prednisone 1 mg/kg/d, calcium +vitamin D, proton pump inhibitor, amlodipine, and valsartan. After three months, prednisone was gradually tapered to 20 mg/day. Proteinuria decreased from 7.98 g/d to 3.7 g/d, and serum albumin levels increased from 2.9 g/dL to 3.7 g/dL in six months of therapy. Given the unsatisfactory response, mycophenolate mofetil (MMF) 500 mg twice daily was added to the treatment regimen. The dose of MMF was prescribed at 2 g/day in the following visit. Throughout follow-up, fluctuations in proteinuria and blood pressure levels were noted. Consequently, the patient continued with a regimen of prednisolone

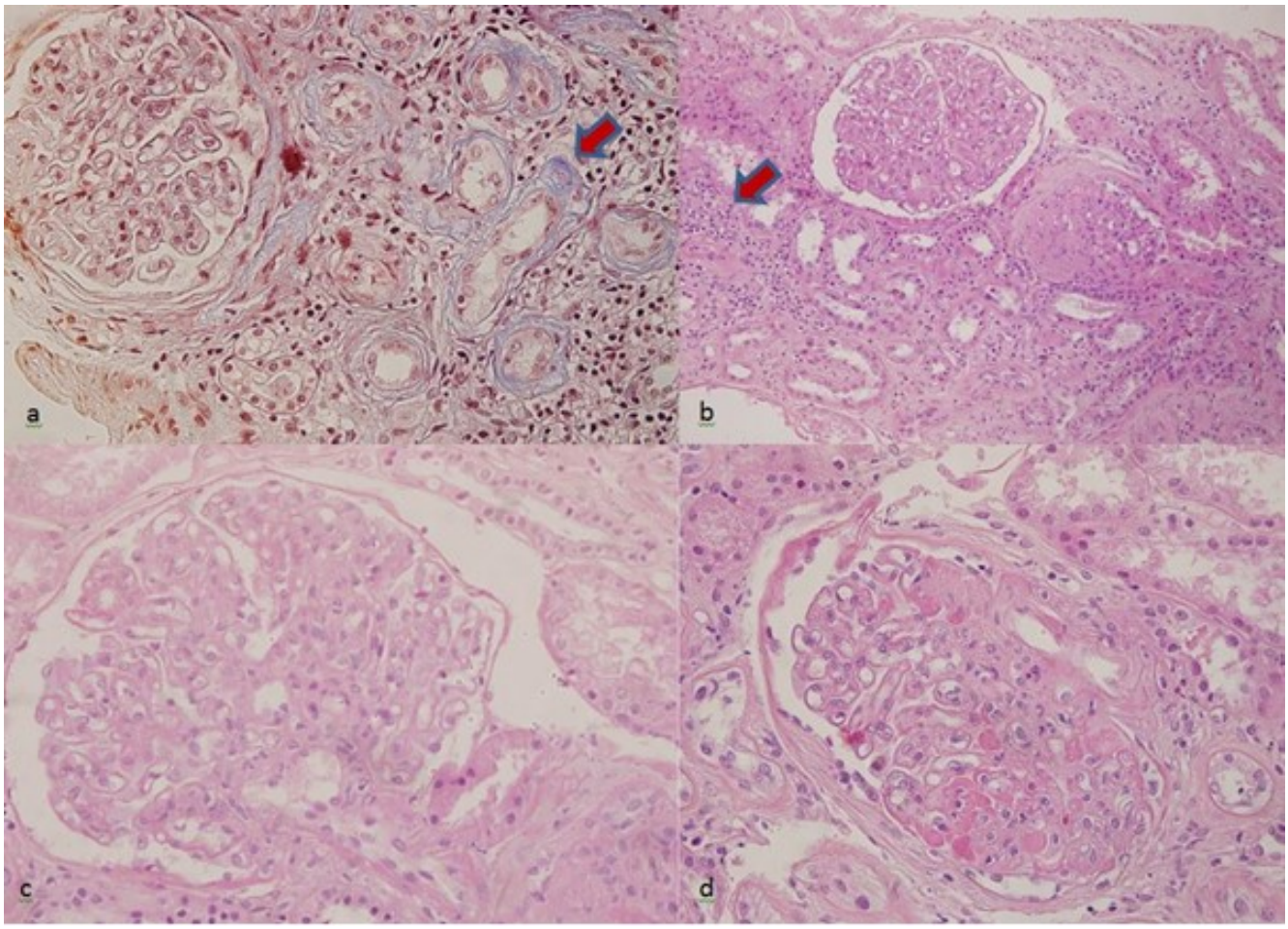

Figure 2: Light microscopy findings showing (a) tubular atrophy and peritubular fibrosis, Masson Trichrome stain × 200; (b) interstitial inflammation H&E × 200; (c) glomerular lobulation and mesangial proliferation, H&E × 400; (d) glomerular fibrin microthrombi H&E × 400.

5 mg/day, MMF 2 g/day, calcium + vitamin D, proton pump inhibitor, amlodipine+valsartan, and nebivolol. After three years, kidney function was better, proteinuria decreased to ≥ 1 g/day and eGFR increased to 59 mL/min/1.73 m2. In addition, sodium-glucose co-transporter 2 inhibitors have recently been added to the treatment list as recommended to all patients [6]. The benefit of this addition was a greater reduction in albuminuria (500 mg/d), which was observed three months later.

3. Discussion

Complement-mediated MPGN is diagnosed when IFM detects dominant C3 or C4 depositions. IC-MPGN is diagnosed when IFM shows subendothelial and mesangial depositions of Ig ± C3. MPGN without Ig or complement deposition is diagnosed when IFM reveals no staining for Ig, C3, or C4 in patients with characteristic MPGN histology [3, 6, 7]. After a definitive diagnosis of IC-MPGN, it is essential to perform a thorough evaluation to rule out secondary causes. In this case, no secondary causes, including malignancy and hepatitis B infection, which are more common in IC-MPGN cases, were identified, leading to the diagnosis of idiopathic IC-MPGN [8]. The kidney biopsy of our patient was adequate with respect to the number of glomeruli by immunofluorescence microscopy, but had inadequate glomeruli to evaluate by LM.

The initial clinical manifestations of patients with IC-MPGN can vary widely among patients and across different geographical regions [9, 10]. Our patient presented with decreased eGFR and nephrotic syndrome without hematuria, which is consistent with other studies. Nakagawa et al. reported that 20.9% of the 67 IC-MPGN patients in Japan presented without hematuria in their study [10]. On the other hand, most of those patients (56.7%) presented with nephrotic syndrome. Unfortunately, 38.8% of patients, like our case, had the first presentation of IC-MPGN as chronic glomerulonephritis (GN). The study by Nakagawa et al. outlined several treatment regimens for IC-MPGN, including intravenous methylprednisolone (43.3%), cyclosporine (25.4%), cyclophosphamide (10.4%), mizoribine (6%), azathioprine (3%), and mycophenolate mofetil (4.5%). Despite these interventions, the long-term outcomes included: complete remission in 25.4% of patients, end-stage kidney disease in 26.9%, and all-cause death in 17.9 % after a median follow-up of 4.6 years [10]. On the other hand, Elahi T et al. found that most of the IC-MPGN patients (65%) from Pakistan presented with acute kidney injury [9]. In their cohort of 163 patients, 4.9% of IC-MPGN patients did not present with hematuria. The patients were treated with steroids alone or cyclophosphamide, resulting in 34.3% achieving complete remission, 41.71% partial remission, and 19.63% progressing to end-stage kidney disease after a follow-up period of 29.45 ± 21.28 months [9].

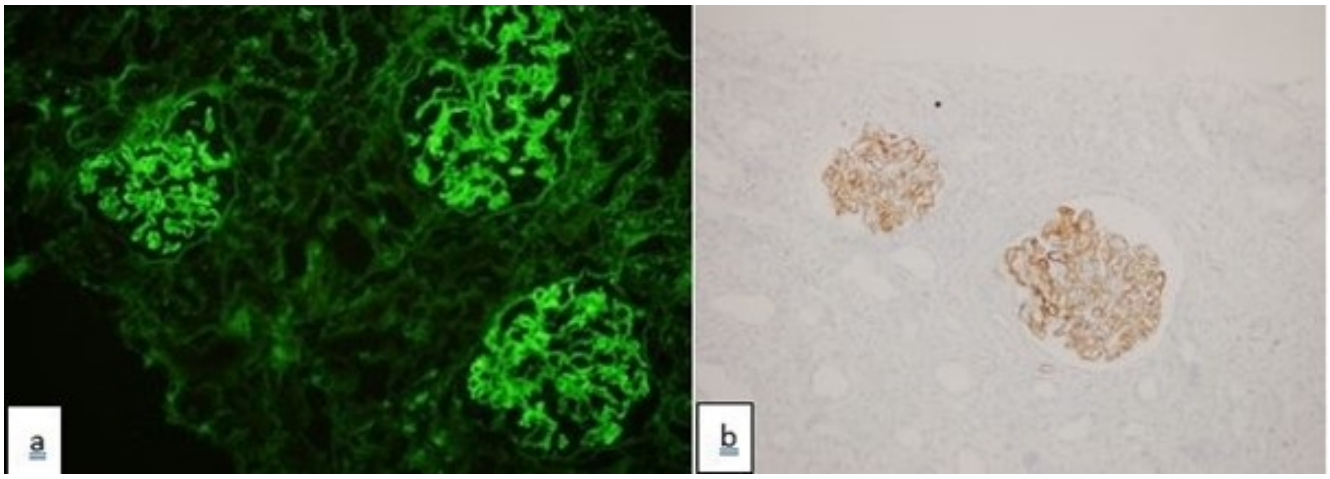

Figure 3: Light microscopy findings showing (a) tubular atrophy and peritubular fibrosis, Masson Trichrome stain × 200; (b) interstitial inflammation H&E × 200; (c) glomerular lobulation and mesangial proliferation, H&E × 400; (d) glomerular fibrin microthrombi H&E × 400.

The treatment options of idiopathic IC-MPGN are not based on randomized controlled intervention trials [11]. Nevertheless, the choice and duration of immunosuppressive drugs depend on the clinical parameters of patients with IC-MPGN. For patients with normal kidney function and nephrotic-range proteinuria, a regimen of prednisone and calcineurin inhibitors (CNI) is typically recommended. In contrast, patients with abnormal kidney function (arbitrarily defined as an estimated GFR [eGFR] <60 mL/min/1.73 m2) without rapidly progressive crescentic disease with varying degrees of proteinuria and hematuria are generally treated with prednisone and MMF [6]. Our patient was in the latter group. Prednisone for 3-6 months and MMF for 6-12 months are typical immunosuppressive treatments for these patients, as in our case [6]. However, even complete remission was achieved after cessation of MMF, and half of these patients were reported to have relapses [11]. So, we had to continue with MMF due to the persistence of proteinuria. However, the long-term benefits of these treatments are not certain [12, 13]. So, this was a limitation for this extended usage of MMF treatment.

For assessment of proteinuria, 24-hour urine protein excretion is considered a gold standard diagnostic tool despite its handicaps [14]. Serum creatinine, 24-hour urine protein excretion, and a urinalysis at least every two to three months are required to assess the response to treatment for all GN [6]. Aiming for a mycophenolic acid trough level of 1 to 3 ng/mL is suggested for cases like ours. However, it is not easily accessible to explore mycophenolic acid trough levels everywhere. It is also wise to prevent and monitor infectious complications of the kidney diseases and the immunosuppressive drugs [15].

Hypertension is also closely related to kidney health, both directly by podocyte injury and indirectly by leading to cardiovascular disease [16]. Drugs such as angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), which target the renin-angiotensin-aldosterone system (RAAS), slow the progression of chronic kidney disease (CKD) by reducing intraglomerular pressure, proteinuria, and inflammation [17]. Many guidelines recommend these RAAS blockers as the first-line treatments in hypertensive patients with CKD and proteinuria [6, 18].

4. Conclusions

Interstitial fibrosis and tubular atrophy have been reported to be key predictors of long-term kidney survival. Our patient had severe glomerulosclerosis and interstitial fibrosis at the initial presentation. However, the chosen treatment regimen has been effective in preserving kidney function. At the third-year follow-up, his kidney function improved compared to the eGFR and proteinuria levels at the time of initial diagnosis, despite severe renal fibrosis. Finally, the early detection of GN is critical in determining patient and kidney survival. Therefore, routine urinalysis to assess proteinuria and hematuria should be a standard procedure for all patients to ensure early diagnosis and intervention.

Conflicts of Interest

All of the authors declare no conflict of interest.

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Large Language Model

No support from artificial intelligence was taken.

Authors Contribution

KK contributed to conception, design, analysis, and interpretation of data, drafting the article, and revising it. YD contributed to literature research and interpretation of data. MK contributed to

literature research and interpretation of data. SM contributed to interpretation of pathological findings.

Data Availability

All data supporting the findings of this single-patient case report are contained within the article.

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Original Article

Trends in Mortality from Leukemia and Ischemic Heart Disease: A 22-Year Analysis in the U.S. (1999-2020)

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ABSTRACT

Introduction: Leukemia and ischemic heart disease (IHD) are major U.S. mortality causes. This study analyzes national mortality trends from 1999 to 2020 to assess the impact of public health efforts in leukemia-associated IHD mortality rates.
Methods: This retrospective study analyzed death certificate data from the CDC-WONDER database spanning 1999 to 2020, focusing on leukemia (ICD-10: C91–C95) and ischemic heart disease (ICD-10: I20–I25) as multiple causes of mortality in the U.S. population. Crude mortality rates (CMR) and age-adjusted mortality rates (AAMR) per 100,000 population were calculated. JoinPoint analysis was performed to estimate annual percent change (APC) and average annual percent change (AAPC).
Results: From 1999 to 2020, there were 53,603 deaths from combined leukemia and ischemic heart disease among U.S. adults aged 25+, with the AAMR declining from 1.39 to 1.09 per 100,000 (AAPC= -1.30%; 95% CI: -1.90 to -0.68; P= 0.000034). A significant decrease occurred from 1999 to 2018 (AAMR: 1.39 to 0.95; APC= -2.1894%; 95% CI: -2.3995 to -1.9788, P < 0.000001), followed by a period where the trend shifted upward which is statistically significant for the certain subgroups, except men and older adults. Men had higher AAMR than women (1.87 vs. 0.62). Regional AAMRs were highest in the Midwest (1.3). Non-Hispanic Whites had the highest AAMR (1.25). Adults 65+ had a CMR of 5.27 vs. 0.26 for ages 45–64.
Conclusion: Significant health disparities exist, as mortality from combined leukemia and IHD is highest among men, older adults, rural populations, and non-Hispanic White individuals.

1. Introduction

Over the past few years, there have been significant improvements in diagnostic approaches, medical care, and community health actions for many diseases [1, 2]. Although these advancements, leukemia and ischemic heart diseases (IHD) are considered the leading causes of death among the adult population in the United States (U.S.). Leukemia is a group of bone marrow and blood cancers that comprises several variants [3], including acute and chronic types [4]. It is considered as the primary contributor of cancer-associated fatalities worldwide [5, 6], with an estimated 60,000 recently detected cases per year in the U.S. [7]. Furthermore, IHD is also referred to as coronary heart disease (CHD) which remains to be the primary cause of fatality, involving diseases like sudden cardiac arrest, heart failure, and heart attacks [8]. CHD accounted for 375,476 deaths in the U.S., representing about 42.1% of all mortality associated with cardiovascular disease [9]. There are nearly 805,000 individuals in the U.S. who suffer from a heart attack every year [10]. IHD has historically improved due to continuous enhancements in cardiovascular treatment, including pharmaceutical therapies [11], procedural interventions [12], and initiatives aimed at addressing contributing factors. These initiatives addressed various conditions, including elevated cholesterol levels, diabetes, hypertension, tobacco consumption, and physical inactivity, that are strongly associated with IHD [13, 14, 15]. Likewise, improvements in targeted therapies, chemotherapy, immunologic treatment, and bone marrow transplantation have markedly enhanced longevity throughout past decades, yet the burden of leukemia continues to be considerably elevated [16]. Leukemia and cardiovascular diseases are closely linked. For example, several leukemia treatments, such

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as anthracyclines [17], tyrosine kinase inhibitors [18, 19], and some targeted therapies [20], can cause cardiotoxicity, leading to heart dysfunction, arrhythmias, and ischemic events. Furthermore, the current heart conditions can limit leukemia treatment and worsen outcomes [21]. These connections underscore the importance of integrated cardio-oncology care in monitoring and managing heart risks in leukemia patients.

These healthcare progresses resulted in consistent declines in age-standardized fatality rates for both diseases during the period between the late 1990s and the early 2010s. Nevertheless, recent findings suggest that this favorable trend may be declining or plateauing in certain populations, raising major concerns regarding the sustainability of medical enhancement [22]. Furthermore, emerging evidence highlights an increase in cardiovascular mortality among adolescents and adults [9] and higher rates of leukemia-associated deaths in specific demographic groups [7]. These transitions may be linked to multiple interrelated variables, including expanding socioeconomic variations, changing disease risk patterns, the lasting consequences of the COVID-19 pandemic, and inequitable access to healthcare services [23], which interrupted preventive and standard medical care.

Despite the importance of this evidence, most prior research has emphasized either leukemia or IHD separately, and there is a lack of comparative and comprehensive evaluations that explore fatality trends for both diseases concurrently among diverse demographics. Furthermore, the existing studies lack detailed stratification by sex, age, geographic region, race/ethnicity, and urban-rural residence [24]. These factors are known to influence disease burden and its associated consequences. This results in a serious gap in interpreting whether the apparent decline in progress underscores a wider challenge in U.S. medical infrastructures. The combined analysis of IHD and leukemia is justified because they are both major causes of mortality in the U.S. Besides, they share common risk factors and healthcare influences, and have treatment-related overlaps. Studying these conditions concurrently offers a broader view of national health trends to guide policy and care.

To resolve this discrepancy, this study considered 22 years of nationwide fatality records from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research (CDC-WONDER) to assess mortality patterns for both IHD and leukemia among individuals aged $\geq$ 25 years old in the period between 1999 and 2020. Furthermore, we aim to identify whether there has been a decline in mortality rate improvement for IHD and leukemia, and to address which populations are most influenced. We hypothesize that after a period of steady decline, mortality rates for both IHD and leukemia have plateaued or increased in certain subgroups, reflecting emerging disparities in healthcare access, prevention, and treatment. Tracking mortality trends in IHD and leukemia helps clinicians target screening, prevention, and resources to populations at risk. For public health, these trends guide priority setting, integrated care planning, and policies to improve healthcare performance and equity.

2. Materials and Methods

2.1. Study Setting and Population

This study is a retrospective epidemiological analysis using national death data from the US over 22 years, from January 1, 1999, to December 31, 2020. The records were gathered from the CDC WONDER platform [25], particularly the Multiple Cause of Death (MCOD) database compiled by the National Center for Health Statistics (NCHS). The MCOD database collects anonymized mortality data covering all deaths recorded in the US, delivering comprehensive geographic and population-based data along with contributing factors of mortality.

We targeted adults aged 25 years and older, as mortality trends, etiological determinants, and contributing factors differ markedly across adult and pediatric groups. However, our eligibility criteria were determined by death certificates that identified leukemia or IHD as the multiple cause of mortality. Individuals with both conditions listed as either the primary cause of death or a contributing factor were included in our analysis. This was categorized by utilizing ICD-10 codes C91–C95 for leukemia and I20–I25 for IHD. Exclusion criteria involved individuals younger than 25 years and documents with missing geographic and demographic data. We chose $\geq$ 25 years to focus on mature adult mortality patterns, as leukemia and IHD risks differ substantially in younger populations. This age cutoff also reduces variability seen in adolescents and young adults. Besides, prior investigations have reported the same in adults $\geq$ 25 years in IHD [26] and leukemia [27].

We conducted this study to investigate the long-term mortality patterns across various U.S. groups and to assess differences by major sociodemographic characteristics. Consequently, we stratified the population depending on age groups (25–44, 45–64, 65+), sex (female, male), geographic region (Northeast, South, Midwest, and West) according to the U.S. Census Bureau [28], and race/ethnicity (American Indian/Alaska Native, Hispanic, Asian/Pacific Islander, Non-Hispanic White, and Non-Hispanic Black). In addition, we integrated the 2013 NCHS Rural–Urban Classification Scheme [29], classifying regions across six categories spanning from peripheral rural settings to central urban areas.

2.2. Data Extraction

We rigorously extracted the included data from the CDC WONDER platform [25] by searching the MCOD database. Moreover, death records were refined through ICD-10 codes for leukemia (C91–C95) and IHD (I20–I25). We extracted annual death rates and population denominators across each year between 1999 and 2020. Besides, both age-adjusted mortality rates (AAMRs) and crude mortality rates were determined per 100,000 individuals. However, age standardization was carried out using the direct approach, adjusted to the 2000 U.S. standard population to ensure comparability over years and demographic subgroups. These comprised sex, race/ethnicity, age based on predefined classification, spatial region, and rural–urban residence. Furthermore, the use of CDC WONDER provided standardized definitions, authenticated data collection, and nationwide representation, which strengthened the applicability and credibility of our results. Data management was executed using R (version 4.3.0) for data preparation and visualization, and Microsoft Excel for preliminary organization. Data integrity verification was conducted to prevent missing data, repetition, or data mislabeling. Additionally, no personal identifiers were applied to guarantee adherence to the ethical guidelines, along with exempting this research from institutional review board (IRB) approval according to STROBE guidelines [30] and CDC regulations on publicly accessible and de-identified datasets. Therefore, this study constituted no risk to participants and did not necessitate informed consent. According to Title 45 Code of Federal Regulations Part 46, it met the standards for exclusion from IRB assessment. All data representation and analysis were developed using GraphPad Prism (version 9) and R to ensure top-tier data visualization and analysis.

2.3. Statistical Analysis

We utilized Joinpoint Regression Analysis, a well-suited approach to assess chronological changes in disease occurrences. Likewise, the Joinpoint Regression software (version 4.9.0.1), developed by the U.S. National Cancer Institute (NCI), was used to identify statistically significant variations ("joinpoints") in mortality patterns. The application of Joinpoint modeling enabled us to locate years in which the extent or direction of death rate variation has shifted. The statistical framework adapts multiple associated linear intervals to the natural logarithm of the AAMRs. It calculates APCs in each segment and a cumulative AAPC for the study duration.

The software employs a Monte Carlo permutation technique to determine the optimal count and location of joinpoints. This is accompanied by the highest number set to three in line with NCI guidelines for long-term information. APCs and AAPCs were documented with 95% confidence intervals. Besides, a two-tailed p-value < 0.05 was reported as statistically significant. Moreover, comparative trend analyses between leukemia and IHD were conducted to investigate whether progress in lowering fatality has been equitable throughout our demographics. In addition, sensitivity analyses were conducted by omitting years affected by outlier events, such as the onset of the COVID-19 pandemic or economic crises, to ensure the reliability of mortality trend predictions over time.

3. Results

3.1. Overall Trends

From 1999 to 2020, mortality trends for combined leukemia and ischemic heart disease in the overall adult population aged 25 and above showed notable changes over time, with 53603 deaths. The AAMR decreased from 1.39 (95% CI: 1.33 to 1.44) in 1999 to 1.09 (95% CI: 1.05 to 1.12) in 2020 (AAPC -1.2953%; 95% CI: -1.9019 to -0.6848, P = 0.000034), indicating an overall decline in mortality rates despite the recent increase. Joinpoint regression analysis identified a single joinpoint in 2018, splitting the trend into two segments. Between 1999 and 2018, AAMR declined significantly from 1.39 to 0.95, respectively (APC -2.1894%; 95% CI: -2.3995 to -1.9788, P < 0.000001). However, from 2018 to 2020, a significant upward trend was observed, with AAMR increasing from 0.95 in 2018 to 1.09 in 2020 (APC = 7.6171%; 95% CI: 0.6808 to 15.0314, P = 0.0327). **(Table S1, Table S2, Table S3, (Figure 1))**

3.2. Gender

Mortality trends stratified by gender revealed significant disparities, with men experiencing a higher overall number of deaths compared to women (35836 vs. 17767). Men also exhibited a higher overall AAMR over the study period (1.87; 95% CI, 1.85 to 1.89) compared to women (0.62; 95% CI, 0.61 to 0.63). Additionally, AAPC showed an increase in mortality rates among men (AAPC = -1.1096%; 95% CI: -1.8943 to -0.3186, P = 0.0060) compared to women (AAPC =-2.3545%; 95% CI: -3.1496 to -1.5529, P < 0.000001).

Further analysis identified that AAMR for women declined from 0.84 in 1999 to 0.53 in 2020, with 2 joinpoints identified in 2009 and 2017.The AAMR for the first segment (1999 – 2009) declined from 0.84 to 0.64 (APC = -2.8766%; 95% CI: -3.4846 to -2.2648, P < 0.000001). This trend showed a more pronounced decline, from 0.64 in 2009 to 0.46 in 2017 (APC = -4.4981%; 95% CI: -5.6668 to -3.3149, P < 0.000001). However, from 2017 to 2020, a significant reversal occurred in AAMR, with a change from 0.46 in 2017 to 0.53 in 2020 (APC: 5.4678%; 95% CI: 0.4197 to 10.7697, P = 0.0354).

In men, the AAMR declined from 2.22 in 1999 to 1.85 in 2020 with one joinpoint detected in 2018. In the first segment (1999-2018), the AAMR declined from 2.22 in 1999 to 1.62 in 2018 (APC = -1.8809%; 95% CI: -2.1568 to -1.6041, P < 0.000001). In the second segment (2018-2020), the mortality trend showed a numerical increase (APC = +6.5%; 95% CI: -2.2% to 16.1%); however, this change was not statistically significant (P = 0.14). **(Table S2, Table S3) (Figure 1)**

3.3. Race/ethnicity Trends

Between 1999 and 2020, Non-Hispanic (NH) White adults experienced the highest overall AAMR (1.25; 95% CI: 1.24 to 1.26) (47998 deaths), followed by NH Black or African American adults (0.71; 95% CI: 0.68 to 0.73) (2895 deaths) while the least mortality was in the Hispanics (0.54; 95% CI: 0.51 to 0.56) (1749 deaths). Among NH Black adults, the AAMR declined from 0.88 in 1999 to 0.64 in 2020 (AAPC = -2.5488%; 95% CI: -3.1178 to -1.9765, P < 0.000001), supporting the consistency of the declining trend with no join points detected.

The mortality trend for the NH White population exhibited a more complex pattern. The AAMR declined from 1.49 in 1999 to 1.25 in 2020; AAPC = -1.0167% (95% CI: -1.6526 to -0.3767, P = 0.001885), indicating an overall reduction in mortality with one joinpoint detected in 2018. In the first segment (1999-2018), AAMR declined from 1.49 to 1.08, respectively (APC = -1.9035% (95% CI: -2.0988 to -1.7068, P < 0.000001). However, a notable reversal occurred from 2018 to 2020, with a significant increase in mortality rates, as the AAMR rose from 1.08 in 2018 to 1.25 in 2020 (APC = 7.8179%, 95% CI: 0.4969 to 15.6733, P = 0.037844).

For the Hispanic adults, the mortality trend for leukemia and ischemic heart disease showed a significant decline in AAMR from 0.74 in 1999 to 0.57 in 2020 with no join points detected (AAPC -2.3413%; 95% CI: -3.4604 to -1.2105, P = 0.000356), indicating a statistically significant reduction in mortality rates. **(Table S2, Table S4) (Figure 2)**

3.4. Regional Trends

From 1999 to 2020, the majority of deaths among adults aged 25 and older with leukemias and ischemic heart disease occurred in the Midwest with the highest overall AAMR (1.3; 95% CI: 1.28 to 1.32) (14022 deaths), followed by the Northeast (1.15; 95% CI: 1.13 to 1.17) (11028 deaths), the West (1.07; 95% CI: 1.05 to 1.07) (10819 deaths), then the South (1.03; 95% CI: 1.02 to 1.05) (17734 deaths).

From 1999 to 2020, the Northeast experienced a consistent and statistically significant decline in AAMR, from 1.57 in 1999 to 1.02 in 2020, with no joinpoints detected (AAPC -2.571%; 95% CI: -2.9407 to -2.1999), indicating a sustained and significant decrease in mortality over the 22 years.

In the Midwest, the AAMR decreased from 1.6 in 1999 to 1.23 in 2020 (AAPC = -0.5182%; 95% CI: -2.5415 to -0.4842, P = 0.0041), indicating a mild but statistically significant overall decline, with one joinpoint detected in 2017. From 1999 to 2017, mortality rates significantly declined with an AAMR change from 1.6 in 1999 to 1.05 in 2017 (APC = -2.3545%; 95% CI: -2.8301 to -1.8765, P < 0.0001). However, between 2017 and 2020, there was a non-significant increase in AAMR from 1.05 in 2017 to 1.23 in 2020 (APC = 3.652%; 95% CI: -3.6495 to 11.5068, P = 0.3147)

In the south, the AAMR decreased from 1.2 in 1999 to 1.09 in 2020 (AAPC = -0.6697%; 95% CI: -1.4204 to 0.0701), which was not statistically significant (P = 0.0759) with one joinpoint detected

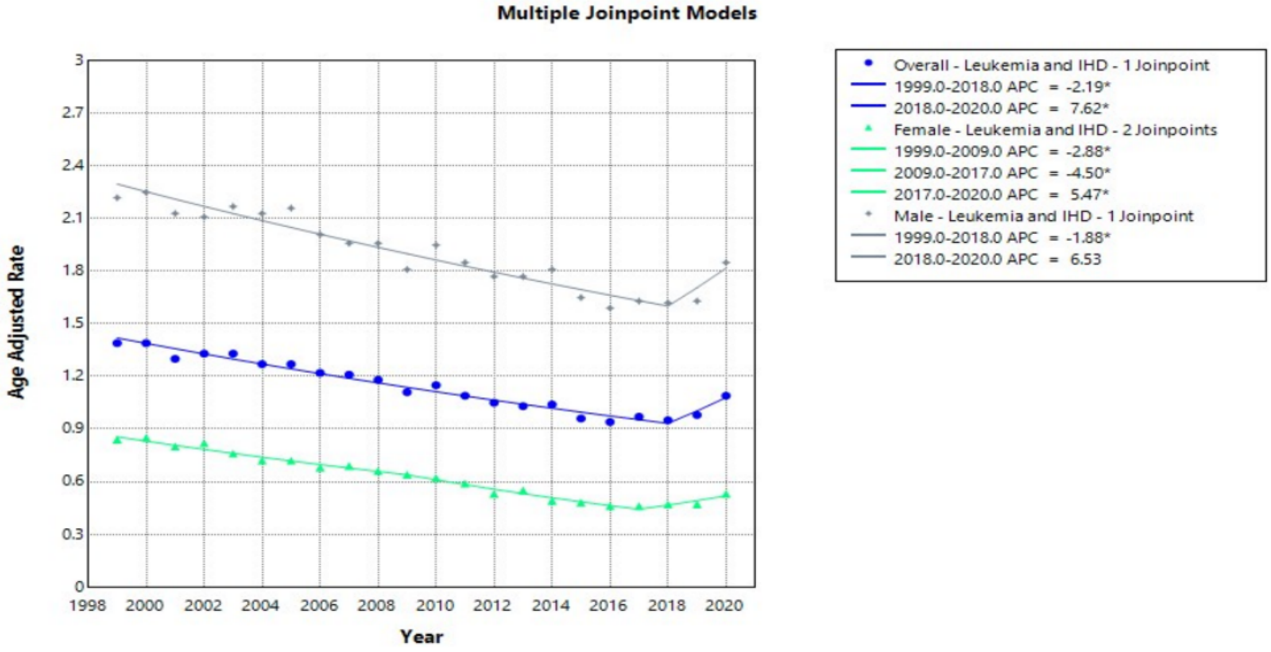

Figure 1: Overall and sex-stratified age-adjusted mortality rates (AAMRs) per 100,000 individuals in the United States, 1999 to 2020.

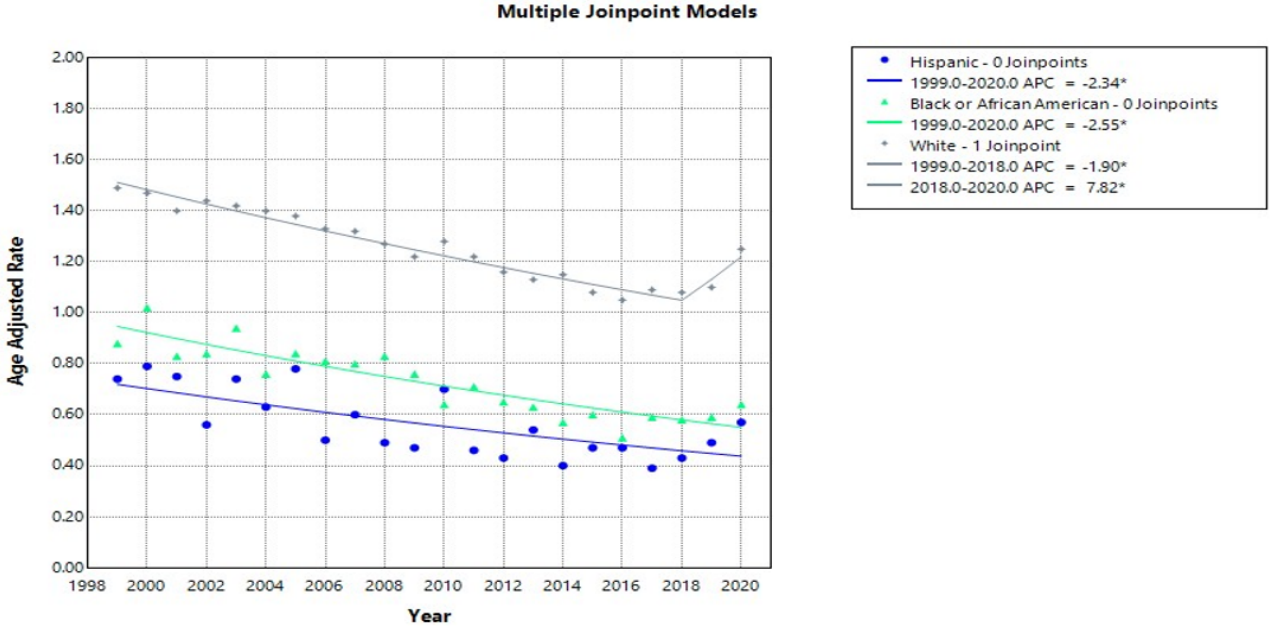

Figure 2: Age-adjusted mortality rates (AAMRs) per 100,000 individuals stratified by race/ethnicity in the United States, 1999 to 2020

in 2018. From 1999 to 2018, AAMR decreased significantly from 1.2 to 0.89, respectively (APC = -1.8211%; 95% CI: -2.2822 to -1.5594, P < 0.0001). From 2018 to 2020, the trend reversed, showing a significant increase in the AAMR from 0.89 to 1.09, respectively (APC = 10.9869%; 95% CI: 2.4799 to 20.2, P = 0.0134).

The West region showed a steady and significant decline in the AAMR from 1.28 in 1999 to 1 in 2020 (AAPC = -1.7657%; 95% CI: -2.0995 to -1.4309, P < 0.0001) with no joinpoints detected. Analysis of state-level data from 1999–2020 revealed significant geographic variation in age-adjusted mortality rates related to leukemia and ischemic heart disease **(Table S6)**. The highest mortality rates were observed in Vermont (1.83 per 100,000; 95% CI, 1.58–2.09), West Virginia (1.79; 95% CI, 1.64–1.93), and North

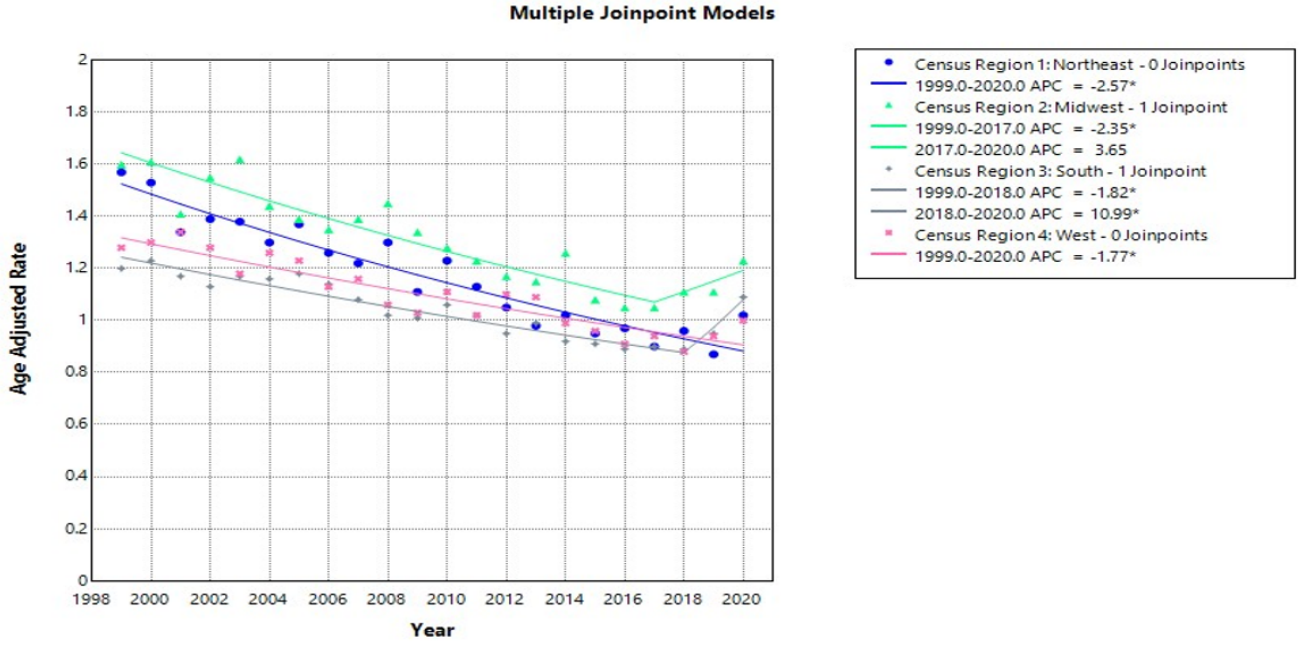

Figure 3: Age-adjusted mortality rates (AAMRs) per 100,000 individuals stratified by Census Region in the United States, 1999 to 2020.

Dakota (1.78; 95% CI, 1.54–2.02). Conversely, the states with the lowest mortality rates were Nevada (0.56 per 100,000; 95% CI, 0.48–0.63), Hawaii (0.66; 95% CI, 0.55–0.77), and Georgia (0.67; 95% CI, 0.63–0.72) **(Table S2, Table S5, Table S6) (Figure 3)**.

3.5. Age-Specific Trends

Age-stratified analysis revealed that the (+65) age group had a higher overall mortality rate with CMR (5.27; 95% CI: 5.22 to 5.32) and 48,933 deaths compared to the (45-64) age group with CMR (0.26; 95% CI: 0.25 to 0.27) and 4,415 deaths.

From 1999 to 2020, adults aged 45-64 years demonstrated a consistent and statistically significant decline in mortality rates for leukemia and ischemic heart disease with an CMR changed from 0.3 in 1999 to 0.29 in 2020 (AAPC = -1.3921%; 95% CI: -1.9549 to -0.8221, P = 0.000058), indicating a sustained reduction in mortality over the study period. For adults aged 65 and older, the mortality trend was more complex. The CMR showed a significant decline from 6.53 in 1999 to 4.81 in 2020 with one joinpoint detected in 2018 (AAPC = -1.3581%; 95% CI: -2.0427 to -0.6688, P = 0.000119), indicating a net reduction in mortality. From 1999 to 2018, there was a significant decline in AAMR from 6.53 in 1999 to 4.28 in 2018 (APC =-2.2183%; 95% CI: -2.4471 to -1.9489, P < 0.000001). However, from 2018 to 2020, the trend shifted direction, with a non-significant increase in mortality rates (APC = +7.2%; 95% CI: -0.6% to 13.6%; P = 0.07). While this recent upward trend did not reach statistical significance, it contrasts sharply with the preceding period of significant decline. **(Figure 4)**

3.6. Urban-Rural Trends

The higher trends of mortality between 1999 and 2020 occurred in nonmetropolitan (rural) areas with higher overall AAMR (1.34; 95% CI: 1.32 to 1.37) (11,460 deaths) compared to metropolitan (urban) areas with overall AAMR (1.08; 95% CI: 1.07 to 1.09) (42,143 deaths).

For urban areas, AAMR decreased from 1.38 in 1999 to 1.02 in 2020 (AAPC = -1.4414%; 95% CI: -1.9505 to -0.9499, P < 0.000001), indicating a net decline in mortality with one joinpoint in 2018. From 1999 to 2018, AAMR showed a significant decline to 0.9 in 2018 (APC = -2.3259%; 95% CI: -2.4981 to -2.1607, P < 0.000001). However, a significant reversal occurred from 2018 to 2020, with mortality rates increasing at an AAMR from 0.9 in 2018 to 1.08 in 2020 (APC = 7.4087%; 95% CI: 1.7848 to 13.3435, P = 0.012207).

In non-metropolitan (rural) areas, mortality rates also exhibited a slight decrease in AAMR from 1.5 in 1999 to 1.46 in 2020, with one joinpoint detected in 2018. (AAPC = -0.6582% ; 95% CI: -1.9919 to 0.0597, P = 0.338281), suggesting no significant overall change in mortality rates. From 1999 to 2018, the AAMR declined from 1.5 in 1999 to 1.15 in 2018 (APC: -1.7541%; 95% CI: -2.2050 to -1.3011, P < 0.000001). From 2018 to 2020, there was an upward trend, with AAMR increasing to 1.46 in 2020 (APC: 10.3821%; 95% CI: -4.6495 to 27.7833, P = 0.17265); however, this change was not statistically significant. **(Table S2, Table S7) (Figure 5)**

3.7. Place of Death Trends

The data reveal significant variation in mortality locations among the study population. The highest proportion of deaths occurred in inpatient medical facilities (22,014 deaths), representing the most common place of death. This was followed by deaths at the decedent's home (14,919 deaths) and nursing home/long-term care facilities (9,130 deaths). In contrast, the lowest mortality counts were observed in medical facilities with unknown status (38 deaths) and among those dead-on arrival (222 deaths). Notably, hospice facilities accounted for 2,280 deaths, while outpatient or emergency room settings recorded 3,031 deaths. **(Table S8)**

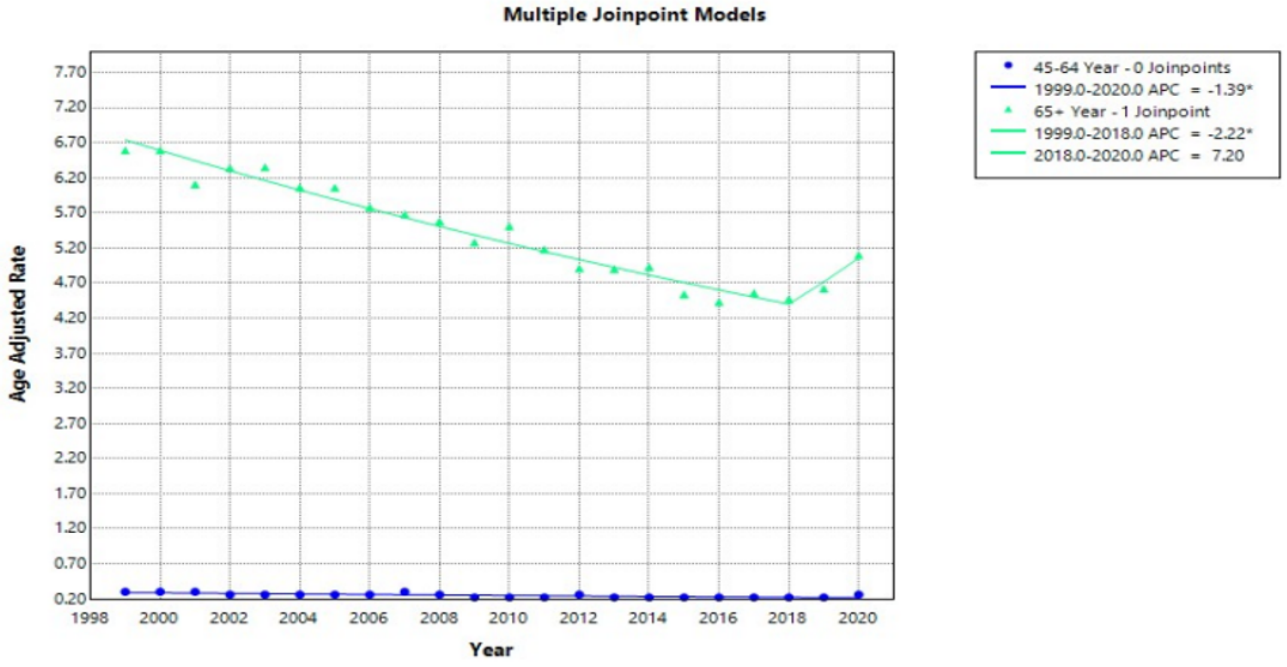

Figure 4: Age-adjusted mortality rates (AAMRs) per 100,000 individuals stratified by Age groups in the United States, 1999 to 2020 .

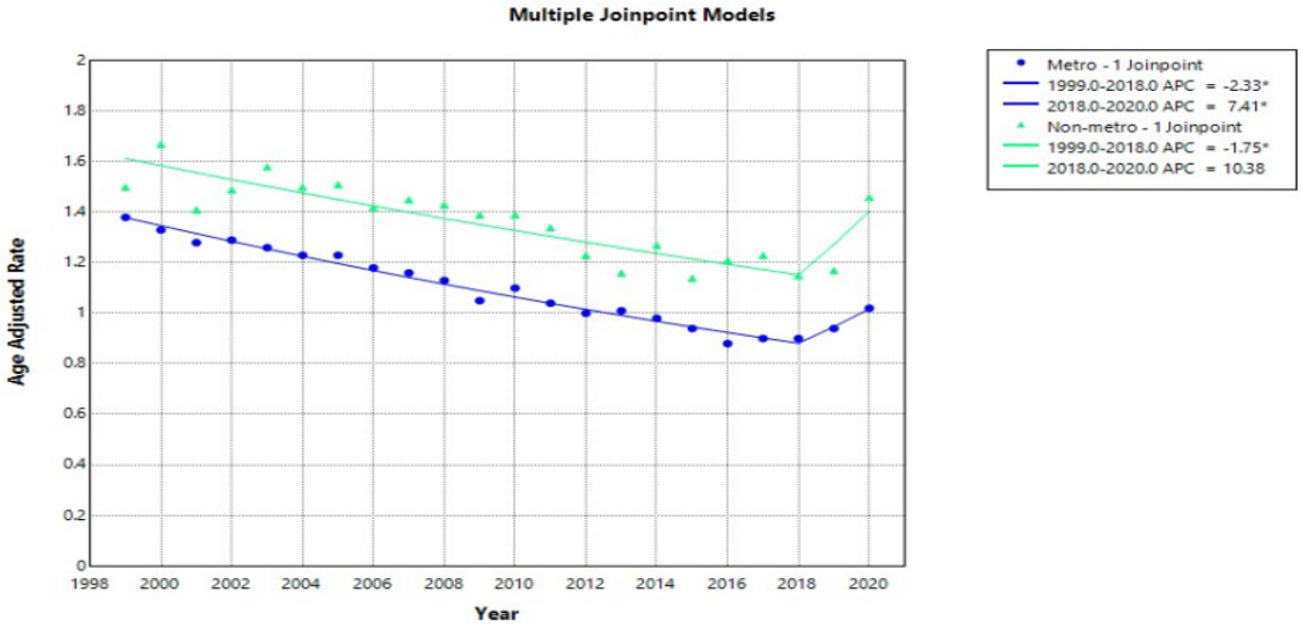

Figure 5: Age-adjusted mortality rates (AAMRs) per 100,000 individuals stratified by Urbanization in the United States, 1999 to 2020.

4. Discussion

This 22-year analysis provides an extensive examination of mortality trends in U.S adults with leukemia and ischemic heart disease (IHD), disease states that frequently co-occur owing to overlapping risk factors, older age, and treatment adverse effects. We observed a general decline in mortality from 1999 to 2018, with a marked reversal in the recent years (2018–2020), indicating the emergence of new concerns in survivorship and management of comorbidities.

Our findings build upon and refine the existing literature on cardiovascular mortality in patients with hematological malignancies. A recent, notable study by Doolub et al. examined temporal trends using a similar dataset and timeframe, reporting that overall cardiovascular mortality among patients with leukemia

decreased by 31.8% between 1999 and 2020 [31]. However, our study differs in several critical aspects, revealing a more urgent and nuanced picture. First, while Doolub et al. took a broad approach by analyzing all cardiovascular causes of death across multiple hematological cancers [31], our study provides a more granular analysis by focusing specifically on the co-occurrence of leukemia and IHD. This focused scope, combined with a more powerful statistical method —"Joinpoint regression analysis" — allowed us to uncover a critical inflection point that was missed by the broader analysis. While Doolub et al.'s findings suggest a consistent decline, our analysis reveals that the long-term decrease in mortality for leukemia and IHD (AAPC = -1.30%) masks a significant and concerning reversal. Specifically, we identified a sharp increase in mortality of +7.62% per year from 2018 to 2020. This recent uptick suggests that the progress in managing this high-risk comorbidity may be stalling or reversing, a critical insight for contemporary cardio-oncology that is not apparent from studies that average trends over two decades.

The 1.39 to 0.95 per 100,000 decrease in age-adjusted mortality rate (AAMR) between 1999 and 2018 (APC = -2.18%) is in line with the national improvements in cancer outcomes and cardiovascular care, as advances in leukemia interventions, notably those for chronic lymphocytic leukemia (CLL) and acute promyelocytic leukemia (APL) have contributed to improved survival [32]. Further, improved primary and secondary prevention of IHD, including greater use of statins, hypertension control, and added revascularization techniques, has likely decreased cardiovascular mortality [33]. Nonetheless, the rise in AAMR from 0.95 in 2018 to 1.09 in 2020 (APC = +7.6%) is concerning.

Men had a significantly larger age-adjusted linked mortality rate (AAMR) than women (1.87 vs. 0.62), reflecting previous literature involving leukemia rates and prevalence of cardiovascular disease [34, 35]. The slower annual percent change (AAPC) for men (-1.11%), in contrast to women (-2.35%), also suggests that female patients may have gained more from improvements in medical services during the study period. Significantly, the mortality change after the 2017 reversal was substantial for women (APC = +5.47%), but there was no change in men, indicating that women with comorbidities may be lagging in recent preventive or compensatory strategies [36, 37].

Racial differences in mortality were evident throughout the study period. White non-Hispanic men and women were the largest group of deaths (47,998) and had the highest age-adjusted mortality risk (AAMR) score (1.25). While the long-term annual age adjusted percentage change (AAPC) of -1.01% shows that the number in this group had improved over time, the reversal in the post 2018 period (APC = +7.8%) highlights the fact that a rapidly aging population may have raised the overall number of women and men that die of IHD, which may exist at a higher prevalence in Whites [38, 39]. Non-Hispanic Black adults showed a more consistent decline (AAPC = -2.55%), without joinpoints, which may reflect more uniform public health outreach in this subgroup or less data volatility due to smaller sample sizes. Hispanic adults demonstrated the steepest decline in AAMR (AAPC = -2.34%) over the time period for the group, as its AAPC demonstrates a trend that reflects what is widely termed and sometimes referred to as the "Hispanic Paradox," suggesting that this group has 'better health' than their socioeconomic status would suggest [40, 41].

The area with the highest mortality burden was in the Midwest (AAMR = 1.3), while the South showed the largest increase in mortality after 2018 (APC = +10.99%). The differences between regions may be attributed to healthcare system differences including infrastructure, access to care, and disease burden, for example, states such as North Dakota and West Virginia, which had the largest state-level AAMRs, are rural Midwest states that had less specialist availability and have higher populations of smoking and obesity, which are two key contributors to both leukemia and IHD mortality [42, 43]. By contrast, the West region showed a steady decrease over time, with no joinpoints (AAPC = -1.76%), indicating that this region has better access to tertiary care centers and has been willing to engage in aggressive, guideline-based treatments and standards of care.

As expected, the population aged 65 years and older represented most deaths (48,933) and had a crude mortality rate (CMR) of 5.27 versus 0.26 in the 45–64 age group. Older adults often carry multimorbidity, have a depressed physiological reserve, and have more exposure to cardiac toxicants (e.g., anthracyclines or tyrosine kinase inhibitors) [44]. The rising mortality trend after 2018 (APC = +7.2%) was not statistically significant, but biologically plausible as treatment-related cardiovascular disease is often temporal to the end of life in cancer survivorship and therefore emphasizes an urgent need for cardioncology interventions and routine surveillance for older leukemia patients [45, 46]. In contrast to standard oncologic care, these cardioncology interventions should include longitudinal cardiac monitoring (e.g., echocardiography, biomarkers), early referral to cardio-oncology services for high-risk individuals, and baseline cardiovascular risk assessment before starting chemotherapy [47]. Long-term cardiac complications may be reduced by implementing structured survivorship programs that emphasize lifestyle modification, cardiotoxicity prevention, and the management of modifiable cardiovascular risk factors (such as diabetes, dyslipidemia, and hypertension). These tactics are particularly important for older adults, who are more susceptible to therapy-induced cardiotoxicity due to their decreased physiological reserve and preexisting comorbidities [48].

The difference in rates between metropolitan (AAMR = 1.08) and non-metropolitan populations (AAMR = 1.34) aligns with existing health disparities. Patients in rural settings are likely to experience longer delays in diagnosis and treatment, as well as limited access to cardiologists and oncologists, and face financial or transportation barriers [49]. Both regions experienced increases in mortality rates after 2018, but the increase in mortality was larger in rural areas (e.g., APC = +7.4%), indicating a need to expand telemedicine and decentralized care [50].

It was noticed that 40% of deaths occurred outside inpatient settings—in people's homes (14,919) or in long-term care facilities (9,130)—suggesting a significant burden of unmonitored or poorly managed end-of-life complication [51]. This matches trends in palliative care across the country, where patients with end-stage hematologic malignancies often deteriorate quickly without going to the hospital [52, 53]. The level of deaths outside of hospice facilities (2,280 deaths) might reflect limited use of palliative services, which is a known deficit in hematologic oncology [54, 55].

5. Strengths and Limitations

Previously identified, the strengths of this study stem from factors such as its population-level representativeness, 22-year duration, and stratification by important demographic and geographic factors. In addition, Joinpoint regression analyzes and statistically tests inflection points in mortality trajectories with great precision.

A significant limitation of our study is that our analysis combined all deaths where both leukemia and ischemic heart disease were

listed on the death certificate, as we used Multiple Cause of Death (MCOD), without stratifying by the Underlying Cause of Death (UCOD). Therefore, our results represent the overall mortality trend for the co-occurrence of these conditions, but do not distinguish between patients dying from leukemia with IHD as a contributing factor and those dying from IHD with leukemia as a contributing factor. These two scenarios have different clinical and etiological implications, and their mortality trends may differ. Future studies using multiple-cause-of-death data should analyze these pathways separately to provide a more granular understanding of this comorbidity. Additionally, the study has limitations due to its ecological design, as the consistency of mortality reporting may be impacted by regional or temporal differences in ICD coding practices, and the use of death certificates may be susceptible to misclassification bias, especially in complex cases. Notably, no sensitivity analyses were conducted to account for potential modifications to coding standards during the 22-year study period.

Furthermore, important clinical factors crucial for assessing results, such as chemotherapy regimens, treatment adherence, baseline cardiac function, and cardiotoxicity monitoring, are not included in the database at the individual level. Information on particular leukemia subtypes, which may vary in prognosis and treatment-related mortality, is also missing. Furthermore, the evaluation of care disparities is limited by the lack of information on socioeconomic factors, such as income, insurance coverage, and access to healthcare. We were unable to directly assess treatment effects or link observed mortality trends to particular interventions due to the ecological nature of the data. These restrictions make it challenging to draw conclusions about causality and underscore the need for more comprehensive, patient-level research.

6. Conclusions

After twenty years of decreasing mortality from comorbid conditions of leukemia and ischemic heart disease, reversals in mortality among key subgroups, particularly those older than 65, women, non-Hispanic Whites, and those in the South and rural areas, have created an urgent need for renewed public health attention. Prioritizing the provision of cardio-oncology services, the equitable delivery of care, and planning for survivorship will be essential to ensure that previous gains are maintained and noted disparities are addressed for this medically disadvantaged population.

Conflicts of Interest

The authors declare no competing interests that could have influenced the objectivity or outcome of this research

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Large Language Model

None

Authors Contribution

MFH and AK contributed to writing the original draft, review and editing, and project administration. AAI contributed to writing the original draft and review and editing. AG contributed to writing the original draft. KP contributed to writing the original draft and data extraction. ZS contributed to writing the original draft and visualization. AWH contributed to writing the original draft and methodology. MA contributed to JP analysis. SUR contributed to tables and visualization. AA contributed to writing the original draft. ZK and AB contributed to writing, review and editing, validation, and supervision.

Data Availability

Data Availability Statement: The data supporting the findings of this study are openly available in CDC-WONDER at https://wonder.cdc.gov/. The data supporting the findings of this study were obtained from the CDC WONDER online database (Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research). The datasets used and analyzed during the current study are publicly available and can be accessed at [CDC WONDER] https://wonder.cdc.gov/. Further inquiries can be directed to the corresponding author.

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