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High cardiovascular mortality risk among older merkel cell carcinoma patients

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Abstract

Objective Previous research has primarily focused on the incidence and mortality rates of Merkel cell carcinoma (MCC), neglecting the examination of cardiovascular mortality (CVM) risk among survivors, particularly older patients. This study aims to assess the risk of CVM in older individuals diagnosed with MCC.

Methods Data pertaining to older MCC patients were obtained from the Surveillance, Epidemiology, and End Results database (SEER). CVM risk was measured using standardized mortality ratio (SMR) and cumulative mortality. Multivariate Fine-Gray's competing risk model was utilized to evaluate the risk factors contributing to CVM.

Results Among the study population of 2,899 MCC patients, 465 (16.0%) experienced CVM during the follow-up period. With the prolongation of the follow-up duration, the cumulative mortality rate for CVM reached 27.36%, indicating that cardiovascular disease (CVD) became the second most common cause of death. MCC patients exhibited a higher CVM risk compared to the general population (SMR: 1.69; 95% CI: 1.54–1.86, $p < 0.05$). Notably, the SMR for other diseases of arteries, arterioles, and capillaries displayed the most significant elevation (SMR: 2.69; 95% CI: 1.16–5.29, $p < 0.05$). Furthermore, age at diagnosis and disease stage were identified as primary risk factors for CVM, whereas undergoing chemotherapy or radiation demonstrated a protective effect.

Conclusion This study emphasizes the significance of CVM as a competing cause of death in older individuals with MCC. MCC patients face a heightened risk of CVM compared to the general population. It is crucial to prioritize cardiovascular health starting from the time of diagnosis and implement personalized CVD monitoring and supportive interventions for MCC patients at high risk. These measures are essential for enhancing survival outcomes.

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Keywords Merkel cell carcinoma (MCC), Cardiovascular mortality (CVM), Surveillance, Epidemiology, And End results database (SEER), Standardized mortality ratio (SMR), Cumulative mortality, Competing risk model, Risk factor, Cardiovascular disease (CVD)

Introduction

Merkel cell carcinoma is an uncommon skin cancer that predominantly affects the older and exhibits aggressive clinical behavior with neuroendocrine characteristics [1]. The incidence of MCC is rising and strongly correlated with age, particularly among individuals aged 85 years or older [2]. Advances in cancer screening, diagnosis, and treatment have led to an increasing population of cancer survivors, resulting in reduced mortality from primary cancers. Consequently, non-cancer causes of death, including CVD, have gained prominence [3].

Heart disease and cancer have long been the top causes of death in the USA and throughout the world [4]. A significant study by Sturgeon et al. revealed that three out of every four cancer patients succumb to heart disease, with cancer patients experiencing a 2–6 times higher risk of cardiovascular mortality compared to the general population. Of all cancer patients, 38% die from the malignant disease process, while 11% succumb to CVD [5]. Since a large portion of patients seen in cardiovascular practice are older adults and there is an increase in the overlap between heart disease and cancer patients as cancer-specific mortality is declining and the surviving population is aging, it is important to identify older MCC patients who are at an increased risk of dying from heart disease [6, 7].

This study aims to investigate CVM among older MCC patients and identify associated risk factors in order to improve health management, enhance survival rates, and optimize quality of life for individuals with MCC.

Materials and methods

Data sources

The data for this study were obtained from the SEER 17 database, which is maintained by the US National Cancer Institute. SEER*Stat software was used for data retrieval [8]. The SEER 17 database covers approximately 26.5% of the U.S. population (based on 2020 census) and provides comprehensive information on cancer patients, including demographic, clinical information and follow-up information. To a certain extent, the sample is representative of the entire US population and across different health care settings and patients, as it includes individuals from 17 registries across the United States. More information about the SEER program can be found at https://seer.cancer.gov/. Since this study used existing de-identified data, it did not require ethics committee approval or patient informed consent.

Study population and data collection

The primary outcome of this study was to determine the causes of death, which were categorized as cancer-specific deaths, cardiovascular disease deaths and other non-cancer deaths. The SEER database provided six specific causes of death related to CVD: aortic aneurysm and dissection; atherosclerosis; cerebrovascular diseases; diseases of heart; hypertension without heart disease; other diseases of arteries, arterioles and capillaries. Follow-up for the study ended either at the occurrence of the primary endpoint event or on December 31, 2018.

Various characteristics were included in the analysis, such as age of diagnosis (65 or older), sex, race (white, black and others), marital status (unmarried, married and others), stage (localized, regional and distant), year of diagnosis (2004–2018), chemotherapy (yes, no/unknown), surgery (yes, no/unknown), radiation (yes, no/unknown), survival months, and cause of death, were selected in this study. Detailed information regarding these characteristics can be found in the SEER research data record description.

The inclusion criteria were as follows: (1) individuals diagnosed with MCC as their only primary cancer in their lifetime; (2) diagnosed between 2004 and 2018; (3) diagnosed at the age of 65 years or older; (4) primary site of cancer in the skin; (5) diagnosed by microscopically confirmed (6) with an obvious cause of death. The following were the exclusion criteria: (1) cases with unknown information; (2) cases with autopsy/death certification reports; (3) cases lost to follow-up; (4) cases from geographic registries including Alaska Natives, following that the database "Incidence - SEER Research Data, 17 Registries (exclAK), Nov 2021 Sub (2000–2019) for SMRs", see: https://seer.cancer.gov/data-software/documentation/seerstat/nov2021/, automatically excludes Alaska natives.

Study Design and statistical analysis

The study calculated the proportions of total cases, causes of death, and survivors within each subgroup, which were categorized based on factors such as age of diagnosis, sex, race, stage, year of diagnosis, radiation, chemotherapy, marital status, and surgery.

SMR was controlled for age and sex (performed according to the SEER data standard "2000 US Std Population (19 age groups·Census P25-1130)). For each subgroup and all causes of CVM in patients with MCC, the SMR was calculated as the ratio of observed to expected CVM and presented as SMR and 95% confidence interval (95% CI). If SMR was more significant than one and the

p value < 0.05, it indicates that the CVM of patients with MCC was higher than that of the general population in the United States, with statistically significant results. The absolute excess risk (AER) reflected the absolute increase in CVM risk within the population [9].

Cumulative mortality and cumulative mortality curves were generated by the cumulative incidence function (CIF) and Nelson-Aalen cumulative risk curves to describe the incidence of death from CVD over time [10]. Differences in variables were assessed using Gray's test.

Furthermore, variance inflation factor (VIF) was used to detect collinearity between variables [11–13]. Then, hazard ratio (HR) and 95%CI were calculated based on the multivariate Fine-Gray's competing risk model to measure the associations between risk factors and CVM [14, 15].

The effect of a variable in any analysis was considered significant when $p < 0.05$. The study design is illustrated in Fig. 1.

Results

Characteristics of the included patients

Within the SEER database, a total of 2,899 patients were diagnosed with MCC between 2004 and 2018. Out of these patients, only 1,079 (37.2%) were found to be alive, while 465 (16.0%) experienced deaths related to CVD during the follow-up period. Patients' baseline characteristics are shown in Table 1. The results of the cumulative mortality curve with confidence intervals for CVM in MCC patients using the Nelson-Aalen cumulative risk curve is displayed in Fig. 2. At the end of follow-up, the result of cumulative mortality of CVM was 27.4% (95%CI: 0.241–0.307). Further details regarding the cumulative mortality of CVM can be found in Table S1.

MCC patients' CVM risk compared to the general population

The overall SMR for CVM in MCC patients was 1.69 (95% CI: 1.54–1.86) and AER was 182.39/10,000. Stratified analysis based on different variables revealed that both the SMR and AER for patients with MCC were

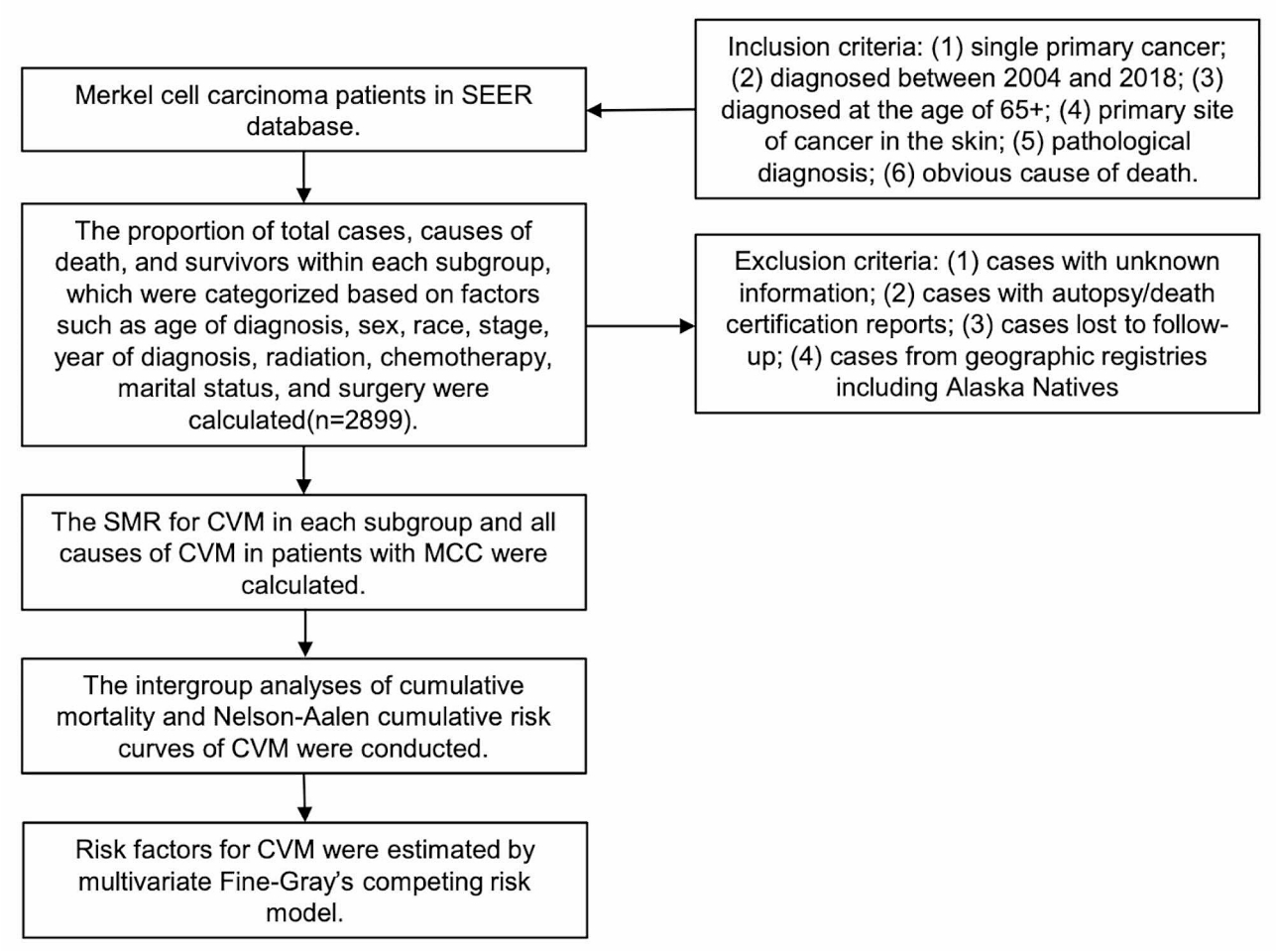

Fig. 1 Study design

Table 1 Characteristics of merkel cell carcinoma patients

Characteristics	Total (*n*, %)	Cancer-specific deaths (*n*, %)	Cardiovascular disease deaths (*n*, %)	Other non-cancer deaths (*n*, %)	Alive (*n*, %)
Total	2899(100.0)	861(29.7)	465(16.0)	494(17.0)	1079(37.2)
Sex					
Male	1703(58.7)	573(33.6)	271(15.9)	285(16.7)	574(33.7)
Female	1196(41.3)	288(24.1)	194(16.2)	209(17.5)	505(42.2)
Race					
White	2759(95.2)	823(29.8)	448(16.2)	474(17.2)	1014(36.8)
Black	39(1.3)	12(30.8)	6(15.4)	6(15.4)	15(38.5)
Other	101(3.5)	26(25.7)	11(10.9)	14(13.9)	50(49.5)
Year of Diagnosis					
2004–2008	806(27.8)	280(34.7)	195(24.2)	207(25.7)	124(15.4)
2009–2013	875(30.2)	287(32.8)	156(17.8)	161(18.4)	271(31.0)
2014–2018	1218(42.0)	294(24.1)	114(9.4)	126(10.3)	684(56.2)
Age of Diagnosis					
65–69	427(14.7)	101(23.7)	21(4.9)	37(8.7)	268(62.8)
70–74	512(17.7)	137(26.8)	48(9.4)	51(10.0)	276(53.9)
75–79	554(19.1)	179(32.3)	80(14.4)	83(15.0)	212(38.3)
80–84	607(20.9)	190(31.3)	123(20.3)	125(20.6)	169(27.8)
85+	799(27.6)	254(31.8)	193(24.2)	198(24.8)	154(19.3)
Stage					
Localized	1794(61.9)	326(18.2)	357(19.9)	358(20.0)	753(42.0)
Regional	801(27.6)	332(41.4)	91(11.4)	100(12.5)	278(34.7)
Distant	304(10.5)	203(66.8)	17(5.6)	36(11.8)	48(15.8)
Chemotherapy					
No/Unknown	2612(90.1)	678(26.0)	448(17.2)	467(17.9)	1019(39.0)
Yes	287(9.9)	183(63.8)	17(5.9)	27(9.4)	60(20.9)
Surgery					
No/Unknown	402(13.9)	194(48.3)	36(9.0)	63(15.7)	109(27.1)
Yes	2497(86.1)	667(26.7)	429(17.2)	431(17.3)	970(38.8)
Radiation					
No/Unknown	1441(49.7)	393(27.3)	283(19.6)	290(20.1)	475(33.0)
Yes	1458(50.3)	468(32.1)	182(12.5)	204(14.0)	604(41.4)
Marital status					
Unmarried	216(7.5)	63(29.2)	33(15.3)	36(16.7)	84(38.9)
Married	1705(58.8)	509(29.9)	240(14.1)	272(16.0)	684(40.1)
DSW	978(33.7)	289(29.6)	192(19.6)	186(19.0)	311(31.8)

Abbreviations: DSW, Divorced, Separated, Widowed; "Other" refers to American Indian/Asian/Pacific Islander; "85+" refers to age 85 or older.

higher compared to the general population. However, patients of black and other races did not exhibit an increased CVM risk relative to the general population. There were no significant differences in the SMR of CVM among patients with distant MCC or those who underwent chemotherapy. Detailed SMR and AER values for CVM can be found in Table 2.

Among the six causes, the most significantly elevated SMR was other diseases of arteries, arterioles, capillaries (SMR: 2.69; 95% CI: 1.16–5.29; AER: 4.80/10,000), followed by hypertension without heart disease (SMR: 2.20; 95% CI: 1.38–3.34; AER: 11.50/10,000), diseases of the heart (SMR: 1.74; 95% CI: 1.57–1.93; AER: 147.53/10,000), and cerebrovascular diseases (SMR: 1.36; 95% CI: 1.05–1.73; AER: 16.34/10,000). There was no significant difference in the SMR of CVM from atherosclerosis and aortic aneurysm and dissection. The SMR and AER from the main causes of CVD in MCC patients are illustrated in Table 3.

Nelson-Aalen cumulative risk curves of CVM

The intergroup analyses of cumulative mortality were conducted, using different variables to determine the higher risk factors of CVM among the MCC patients. The results revealed that marital status was significantly associated with CVM in MCC patients ($p=0.0008$). Additionally, the risk of death from CVD increased with the age of diagnosis ($p<0.0001$). Among different disease stages, patients with localized disease were found to be the main risks for death ($p<0.0001$). Interestingly,

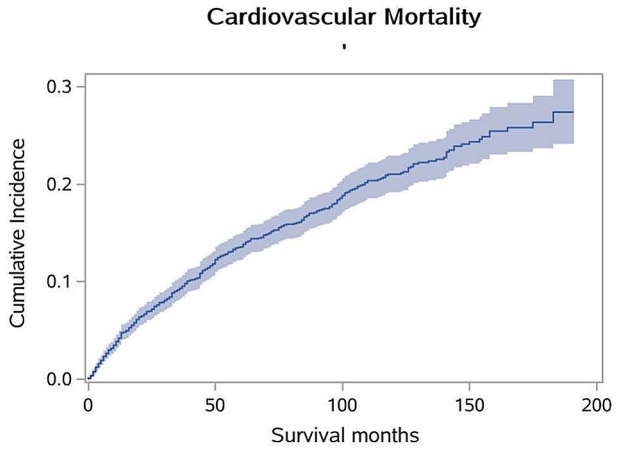

Fig. 2 Nelson-Aalen cumulative risk curve of CVM in MCC patients

surgery was associated with a higher cumulative mortality ($p=0.0005$). However, radiation and chemotherapy were associated with a significantly lower cumulative mortality ($p<0.0001$). The Nelson-Aalen cumulative risk curves for variables in multiple categories are displayed in Fig. 3 and the cumulative mortality results are listed in detail in Table S2-S10.

Risk factors of CVM

The results of the analysis, as previously presented, indicate that age, marital status, stage, surgery, radiation, and chemotherapy statuses were associated with CVM in patients with MCC. The VIF values for all the variables of CVM were close to one, indicating no collinearity among the independent variables.

Subsequently, the variables were estimated using the multivariate Fine-Gray's competing risk model. The findings revealed that age, radiation, chemotherapy, and stage were significant risk factors for CVM, as shown in Table 4. Specifically, older patients demonstrated a higher risk of CVM, with HRs of 1.786 (95% CI: 1.070–2.980), 2.700 (95% CI: 1.672–4.359), 3.693 (95% CI: 2.328–5.857) and 4.539 (95% CI: 2.864–7.194) for age groups 70–74, 75–79, 80–84 and over 85 versus 65–69, respectively. Regarding stage status, patients with regional stage had an HR of 2.113 (95% CI: 1.223–3.650), and those with localized stage had an HR of 2.943 (95% CI: 1.731–5.003), both indicating a higher risk of CVM compared to those with distant stage. Patients who received chemotherapy and radiation exhibited a reduced risk of CVM. In detail, the HR was 0.594 (95% CI: 0.357–0.987) for chemotherapy compared to no chemotherapy, and 0.732 (95% CI: 0.604–0.888) for radiation compared to no radiation treatment.

Discussion

The study's main findings can be summarized as follows: (1) Non-cancer deaths, particularly CVD, account for a significant proportion of deaths in older patients with MCC. As the follow-up time increased, CVD emerged as the second leading cause of death. (2) The SMRs for CVM in older MCC patients were higher than those in the general population, especially, for other diseases of arteries, arterioles, and capillaries. (3) Nelson-Aalen cumulative risk curves of CVM was higher in MCC patients who were diagnosed at age 85 or older, experienced divorced/separated/widowed, had a localized stage, underwent surgical treatment, and did not receive chemotherapy or radiation. (4) Age of diagnosis, stage, and lack of chemotherapy or radiotherapy treatment identified as the main risk factors for CVM through the multivariate Fine-Gray's competing risk model. Therefore, it is crucial for these patients to prioritize the treatment and prevention of non-cancer diseases, such as CVD, alongside primary MCC management.

Common knowledge dictates that certain risk factors, such as age, sex, and race, are beyond our control and have an impact on the occurrence rates of both cancer and CVD. Among these nonmodifiable risk factors, age is a consistent and independent variable in relation to CVD and cancer [16]. It is evident that as the population ages, the fields of geriatrics and cardiac care are becoming increasingly intertwined. This highlights the importance of an individualized approach that assesses risks and benefits based on the patient's overall health status, and involves shared decision-making in their treatment [17].

Sex has a significant impact on both CVD and cancer progression due to the evident differences between male and female organs and hormonal fluctuations [16]. It is widely recognized that biological sex plays a crucial role in normal cardiac physiology and how the heart responds to cardiac diseases. Generally, women exhibit better cardiac function and survival compared to men in the presence of cardiac disease. However, this sex difference diminishes when comparing postmenopausal women with age-matched men, which aligns with the findings of this study [18, 19]. When addressing older patients aged 65 years and above, it is important to acknowledge that the cardioprotective effects observed in premenopausal women are lost after menopause.

In recent years, there has been a growing emphasis on studying the impact of social determinants of health (SDOH) on racial disparities in cardiovascular and cancer mortality [20, 21]. A series of 9 papers published in the JACC Focus Seminar highlight how SDOH such as socioeconomic position, neighborhood environment, sociocultural factors, and racial discrimination within and outside of the healthcare system influence the relationship between race and cardiovascular health [22].

Table 2 Standardized mortality ratios of cardiovascular mortality among Merkel cell carcinoma patients

Characteristics	Observed deaths	Expected deaths	SMR(95% CI)	Excess risk per 10,000	Persons
Total	465	274.34	1.69*(1.54–1.86)	182.39	2899
Sex					
Male	271	145.41	1.86*(1.65–2.10)	223.90	1703
Female	194	128.93	1.50*(1.30–1.73)	134.33	1196
Race					
White	448	263.25	1.70*(1.55–1.87)	186.46	2759
Black	6	3.86	1.55(0.57–3.38)	174.30	39
Other	11	7.23	1.52(0.76–2.72)	89.36	101
Year of diagnosis					
2004–2008	195	118.54	1.64*(1.42–1.89)	191.82	806
2009–2013	156	90.54	1.72*(1.46–2.02)	181.61	875
2014–2018	114	65.26	1.75*(1.44–2.10)	170.24	1218
Age of diagnosis (y)					
65–69	21	12.42	1.69*(1.05–2.58)	44.75	427
70–74	48	25.26	1.90*(1.40–2.52)	100.53	512
75–79	80	48.12	1.66*(1.32–2.07)	141.63	554
80–84	123	81.62	1.51*(1.25–1.80)	195.83	607
85+	193	106.91	1.81*(1.56–2.08)	450.44	799
Stage					
Localized	357	203.96	1.75*(1.57–1.94)	204.48	1794
Regional	91	58.68	1.55*(1.25–1.90)	131.94	801
Distant	17	11.70	1.45(0.85–2.33)	102.01	304
Chemotherapy					
No/Unknown	448	259.15	1.73*(1.57–1.90)	195.83	2612
Yes	17	15.19	1.12(0.65–1.79)	22.38	287
Surgery					
No/Unknown	36	23.45	1.54*(1.08–2.13)	134.64	402
Yes	429	250.89	1.71*(1.55–1.88)	187.06	2497
Radiation					
No/Unknown	283	137.62	2.06*(1.82–2.31)	294.68	1441
Yes	182	136.72	1.33*(1.14–1.54)	82.02	1458
Marital status					
Unmarried	33	19.22	1.72*(1.18–2.41)	183.01	216
Married	240	152.02	1.58*(1.39–1.79)	135.89	1705
DSW	192	103.11	1.86*(1.61–2.14)	275.58	978

Abbreviations: SMR, standardized mortality ratio; CI, confidence interval; DSW, Divorced, Separated, Widowed; * Statistical significance was defined as $p < 0.05$; "Other" refers to American Indian/Asian/Pacific Islander; "85+" refers to age 85 or older.

Accumulating evidence indicates that social determinants of health play a significant role in the racial disparities observed in cardiovascular health [23–25]. While race itself is a nonmodifiable factor, efforts can be directed towards improving the SDOH by addressing adverse social influences, promoting employment opportunities, encouraging healthy lifestyles, fostering social support, and redistributing healthcare management.

Numerous studies have consistently demonstrated that CVM is highest in the early stages of cancer patients [3, 26, 27]. While the stage of cancer itself is beyond an individual's control, patients can play an active role in facilitating early detection and diagnosis. By undergoing regular health checkups, remaining vigilant about bodily changes, undergoing recommended screening tests, and following medical advice, individuals can increase the likelihood of detecting potentially cancerous lesions at an early stage. Early detection allows for timely intervention and treatment before the cancer progresses to advanced stages. Simultaneously, it is crucial to prioritize efforts to reduce CVM in the early stages of cancer to improve patient outcomes.

This study revealed a consistent decrease in CVM among patients diagnosed with MCC in different time periods: 2004–2008, 2009–2013, and 2014–2018. One potential explanation for this finding is the impact of the American Heart Association's recommendation to improve cardiovascular health and reduce deaths from cardiovascular diseases and stroke. The association's goal of achieving a 20% improvement in cardiovascular health

Table 3 Standardized mortality ratios of all causes of cardiovascular mortality in patients with Merkel cell carcinoma

Characteristics	Observed deaths	Expected deaths	SMR(95% CI)	Excess risk per 10,000
Total	465	274.34	1.69*(1.54–1.86)	182.39
Diseases of Heart	362	207.78	1.74*(1.57–1.93)	147.53
Hypertension without Heart Diseases	22	9.98	2.20*(1.38–3.34)	11.50
Cerebrovascular Diseases	65	47.92	1.36*(1.05–1.73)	16.34
Atherosclerosis	4	2.67	1.50(0.41–3.84)	1.27
Aortic Aneurysm and Dissection	4	3.01	1.33(0.36–3.40)	0.94
Other Diseases of Arteries, Arterioles, and Capillaries	8	2.98	2.69*(1.16–5.29)	4.80

Abbreviations: SMR, standardized mortality ratio; CI, confidence interval; * Statistical significance was defined as $p < 0.05$.

by 2020 may have had a positive effect on reducing CVM in the study population [28]. By 2021, the American Heart Association (AHA) had achieved its 2000–2010 goals, including a 25% reduction in heart disease and stroke deaths, as well as reducing unhealthy lifestyles and risk factors. From 2010 to 2020, AHA also largely achieved a 20% reduction in cardiovascular deaths and focused on improving the cardiovascular health of Americans by 20%. Now, AHA's 2024 goal is for every person deserves the opportunity for a full, healthy life [29].

As stated in the results, among the factors affecting the CVM in MCC patients, it is difficult to change the uncontrollable factors, such as age, gender, race, stages and year of diagnosis. However, for other factors, they can be considered controllable.

Indeed, research has consistently shown that marital status can have an impact on health outcomes, including mortality rates. Being married has been associated with lower mortality rates compared to non-married individuals, as indicated in previous studies [30, 31]. The findings of this current study are consistent with those results. The marital status of cancer patients can be a controllable factor as it typically depends on the patient's own choices and decisions. Marital status may have an impact on the treatment and recovery of cancer patients. For example, having a spouse or family support can provide emotional support and encouragement, helping patients cope better with the stress and difficulties of the treatment process. Family members can assist patients in managing daily life affairs, provide companionship and care, and seek medical help when needed. Regardless of a patient's marital status, the medical team is committed to providing the best medical care and support to every patient.

Cancer patients generally experience a heightened risk of CVM throughout their lives. This risk typically peaks in the year of cancer diagnosis, likely due to the interplay of pre-existing CVD, potential cardiovascular toxicities associated with cancer therapies, and CVD risks associated with the tumor burden [5]. Bouillon et al. conducted a study on the long-term impact of radiotherapy for breast cancer on CVM and confirmed that radiotherapy increased the risk of long-term CVM [32]. Fung et al. concluded that there was a significant increase in CVM following chemotherapy treatment for testicular nonseminoma, but not after surgery. They also found that deaths from CVD were primarily observed within the first year after diagnosis [33]. Although this study explores CVM and its association with various treatments for MCC, its findings diverge from previous research. Interestingly, receiving chemotherapy or radiotherapy treatment might serve as protective factors for MCC patients, potentially reducing their CVM risk. In conclusion, MCC patients would benefit from receiving chemotherapy or radiotherapy treatment, as it may help mitigate both cancer-specific mortality and the risk of cardiovascular events. The decision to undergo surgical treatment requires caution.

Nonetheless, it is crucial to acknowledge certain limitations of this study. Firstly, there is a potential risk of missing records and unreliable coding in the SEER database, and the absence of the patients' prior cardiovascular history could have influenced the study's results [34]. Secondly, this study only identified a limited number of factors that could be associated with CVM in MCC patients. The unavailability of lifestyle behavioral habits or genetic risk factors related to cardiovascular disease in the database prevented the exploration of their impact on the results. Thirdly, the exclusive focus on the primary site of cancer in the skin during the research has the potential to overlook MCC of an unknown primary, which typically exhibits a significantly more favorable prognosis [35]. This underscores the importance of exploring a broader range of patient populations and primary sites in future research endeavors. Lastly, the analysis might be constrained by insufficient data due to the small sample size. To enhance the reliability of future studies and further mitigate the risk of CVM while improving the life expectancy of MCC patients, it is imperative to conduct large-scale clinical cohorts that encompass comprehensive clinical information.

Conclusions

This study emphasizes the significance of CVM as a competing cause of death in older individuals with MCC. MCC patients face a heightened risk of CVM compared to the general population. It is crucial to prioritize cardiovascular health starting from the time of diagnosis and implement personalized CVD monitoring and supportive interventions for MCC patients at high risk. These measures are essential for enhancing survival outcomes.

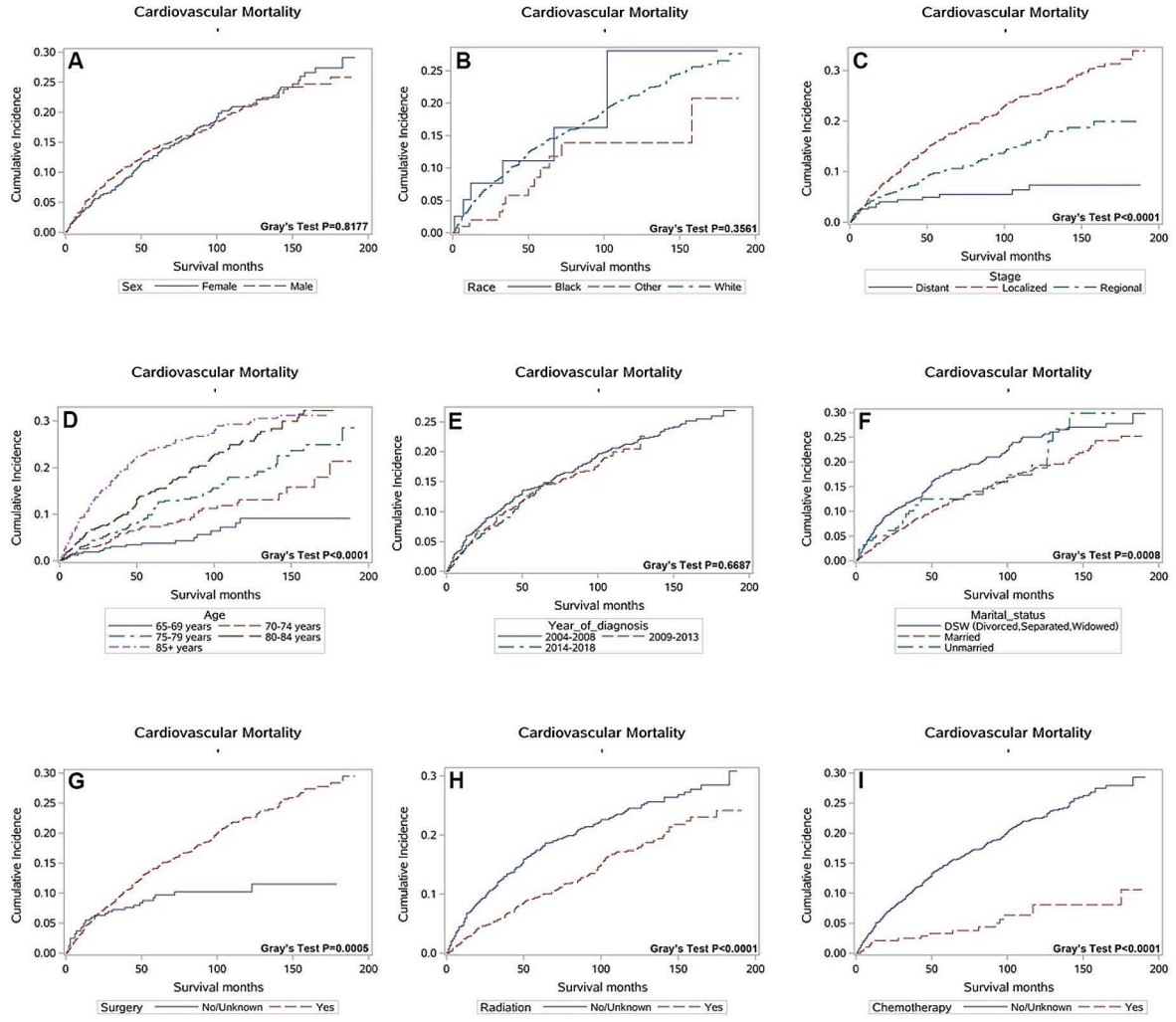

Fig. 3 Nelson-Aalen cumulative risk curves for variables

Table 4 Multivariate competing risk analysis for predictors of cardiovascular mortality in patients with Merkel cell carcinoma

Characteristics	HR	95%CI	*P*Value
Age of Diagnosis (y)			
65–69	Reference		
70–74	1.786	1.070–2.980	0.0264
75–79	2.700	1.672–4.359	< 0.0001
80–84	3.693	2.328–5.857	< 0.0001
85+	4.539	2.864–7.194	< 0.0001
Stage			
Distant	Reference		
Regional	2.113	1.223–3.650	0.0073
Localized	2.943	1.731–5.003	< 0.0001
Chemotherapy			
No/Unknown	Reference		
Yes	0.594	0.357–0.987	0.0443
Surgery			
No/Unknown	Reference		
Yes	1.259	0.870–1.824	0.2219
Radiation			
No/Unknown	Reference		
Yes	0.732	0.604–0.888	0.0015
Marital			
Unmarried	Reference		
Married	0.944	0.656–1.359	0.7572
DSW	1.061	0.733–1.537	0.7528

Abbreviations: HR, hazard ratio; CI, confidence interval; DSW, Divorced, Separated, Widowed; "85+" refers to age 85 or older.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12877-024-05222-8.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

Supplementary Material 10

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Author contributions
All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Data availability
The datasets generated during the current study are available in the SEER repository, (https://seer.cancer.gov/).

Declarations

Ethics statement
All procedures performed in the present study were in accordance with the principles outlined in the 1964 Helsinki Declaration and its later amendments. This study was exempted from obtaining informed consents by the institutional research committee of the First Affiliated Hospital of Jinan University because SEER research data is publicly available and all patient data are de-identified.

Consent for publication
NA.

Competing interests
The authors declare no competing interests.

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