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Association Between the Cardiometabolic Index With Mortality Risk in Adult Hypertensive Patients

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ABSTRACT

Hypertension alone contributes to 10 million deaths annually, highlighting the need for improved risk assessment tools. Currently, the cardiometabolic index (CMI) provides prognostic value in early clinical screening for disease risk in conditions for type 2 diabetes, hypertension, and cardiovascular disease. However, only a few studies assess the relationship between CMI on mortality risk in hypertensive patients, individuals with systolic/diastolic blood pressure exceeding 140/90 mm Hg, compared to existing biomarkers: glycated-hemoglobin (HbA1c) and C-reactive protein (CRP). Thus, this study aims to elucidate the correlation between CMI and mortality risk in hypertensive patients.

578 patients were randomly selected from the 1999-2018 National Health and Nutrition Examination Survey (NHANES) cycle for this study. CMI was calculated by multiplying the triglyceride/high-density lipoprotein cholesterol (HDL). Then, patients were stratified into three groups based on CMI. Furthermore, mortality endpoints include all-cause, cardiovascular, and hypertension-related risk. Multiple statistical analyses were performed to determine associations between CMI and each mortality endpoint. P-values less than 0.05 were considered significant.

Results suggested insignificant associations between CMI and all-cause, hypertension-related, and cardiovascular mortality. Compared to the association between HbA1c and CMI, CRP was significantly associated with all evaluated endpoints [all-cause ($p<0.001$), cardiovascular ($p<0.001$), and hypertension-related mortality ($p<0.001$)].

Hence, CRP can potentially be used as a diagnostic intervention to assess mortality risk in hypertensive patients, representing higher inflammation in patients. Future research can further investigate the diagnostic potential of CMI through evaluating cerebrovascular- or cancer-related mortality risks in clinical contexts.

INTRODUCTION

1.1 Rationale

Obesity affects over 1 billion people, resulting in at least 2.8 million deaths per year globally, according to the World Health Organization (WHO, 2021; WHO, 2024). Obesity may exacerbate existing morbidities, such as hypertension and cardiac death, by dysfunctioning metabolic processes (Landsberg et al., 2013; Piché et al., 2020). Therefore, it is essential to assess cardiometabolic risks associated with obesity to prevent the development of diseases and premature death (Piché et al., 2020).

In previous years, the body mass index (BMI) served as a standard for diagnosing obesity in medical settings and research; nonetheless, the BMI fails to consider variations of obesity and insulin resistance found among the population (Ashwell et al., 2012). In a recent study, Wakabayashi & Daimon (2015) identified a method for quantifying obesity by multiplying the triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratio by the waist-to-height ratio (WHtr), which is referred to as the cardiometabolic index (CMI). Recently, the CMI has been used as a predictor for identifying risk factors for diseases, including non-alcoholic fatty liver disease and cardiovascular diseases. (Tang et al., 2024; Zou et al., 2022). The CMI as a prognostic tool for mortality risk in hypertensive patients has yet to be investigated; thus, this study aims to determine the association between the CMI and all-cause, cardiovascular, and hypertension-related mortality risk.

1.2 Background

1.2.1 Hypertension

Hypertension is described as a condition characterized by high blood pressure, predominantly when the systolic blood pressure/diastolic blood pressure exceeds 140/90 mm Hg (Carey et al., 2019). This continues to rise as a prominent global health issue, resulting in more than 10 million deaths per year (Murray et al., 2020).

Cardiovascular mortality and morbidity continue to affect hypertensive patients even in the presence of advancing technology (Moran et al., 2023; Zhou et al., 2021). Furthermore, patients experiencing shifts in body morphology may alter their hypertension progression and diagnosis (Feng et al., 2024). For example, increasing visceral (abdominal) fat can induce insulin resistance and inflammation, potentially impairing heart functionality (Jin et al., 2023; Kolb, 2022; Shao et al., 2023). Thus, bodily-related changes create challenges in evaluating hypertension. Determining the relationship between CMI and all-cause mortality in hypertension patients is, therefore, necessary for understanding hypertension progression and establishing therapeutic interventions.

1.2.2 Mortality Risk

Cardiovascular diseases remain one of the largest sources of mortality and disability globally; in 2022 alone, the cardiovascular-related mortality rates found in high-income regions of North America ranged from 99.4 to 191.6 per 100,000 (Mensah et al., 2023). Hypertension is one of the major contributors to cardiovascular mortality and disease worldwide, accounting for 7.5 million deaths per year (Chong et al., 2025; Mensah et al., 2023; Waquas et al., 2025; WHO, 2023). Additionally, treated uncontrolled-hypertensive patients had a 1.57-fold risk for all-cause mortality and a 1.74-fold risk for cardiovascular mortality (Gu et al., 2010). In other words, there is an urgent need to examine the potential of health indicators in hypertensive patients for early mortality or disease intervention.

1.2.3 Cardiometabolic Index

The cardiometabolic index (CMI) involves multiplying the triglyceride/high-density lipoprotein cholesterol by the waist-to-height ratio to reflect obesity (Wakabayashi & Daimon, 2015). Traditionally, the CMI is used to calculate risks for diseases associated with the cardiometabolic systems; current research indicates a correlation between cardiometabolic diseases and mortality (Zhu et al., 2025). Yet, limited information exists regarding the ability of CMI to predict mortality risk, a gap that may provide valuable insight into diagnostic tools for medicine.

1.3 Objective Statement/Hypothesis

1.3.1 Objective Statement

Previous studies suggested that visceral fat disrupts the nervous system, further dysfunctioning the immune system, damaging cardiac output and cardiovascular function (Hall et al., 2015; Paranova et al., 2023). Consequently, these symptoms can exacerbate the progression of hypertension and obstruct the treatment and evaluation of hypertension in patients. For that reason, I will analyze data from the National Health and Nutrition Examination Survey (NHANES) using the Cox regression model to inform how mortality risks are affected in comparison to CMI tertiles in hypertensive patients. This approach aims to ascertain the current understanding of CMI as a diagnostic tool in hypertensive patients and provide information regarding health preservation.

1.3.2 Hypothesis

I hypothesized that CMI is positively associated with mortality endpoint. The primary mortality endpoint in this study is all-cause mortality risk. The secondary mortality endpoints are hypertension-related and cardiovascular mortality risk.

METHODS

**All of the below protocols were completed by the student researcher unless otherwise noted*

2.1 Study Designs and Population

I have used data collected from the National Health and Nutrition Examination Survey (NHANES). The NHANES is a longitudinal study created by the Centers for Disease Control and Prevention to evaluate the nutritional and health conditions across the United States. The NHANES consists of a multistage sampling method to collect data, which oversamples minority groups to ensure precise and reliable statistical analyses. In addition, mortality data was linked to the baseline data. NHANES data include information from physical examinations, laboratory tests, and household interviews. Furthermore, the National Center for Health Statistics Institutional Review Board has approved the study, and all the participants were informed before their inclusion in the longitudinal study.

Laboratory and examination data were collected at the Mobile Examination Centre (MEC) in two-year cycles. Additionally, phlebotomists extracted blood through venipuncture for the collection of laboratory biomarkers.

My study analyzed the 1999-2018 NHANES cycle, incorporating a total of 116,876 individuals. Patients were excluded from my analysis based on the following criteria: (1) did not have age data or was younger than 20 years (N = 61,795), (2) no valid mortality information or cause of mortality (N = 2593), (3) without systolic and diastolic blood pressure greater than 140/90 mm Hg (N = 31,583), (4) without valid CMI data (N = 15,945), (5) without information on laboratory biomarkers (N = 1664), (6) no eligible data in smoking or drinking habits (N = 2764), (7) no weight or primary sampling units (N = 181). Since mortality and CMI information were necessary for this study, individuals who lacked available data in these areas were excluded. In some cases, questionnaires restricted information on individuals younger than 20 years of age; to include smoking and drinking habits or other factors as confounding variables, those under the age of 20 years were removed. To continue, survey weights were applied to account for the complex oversampling of certain minority groups. Participants with a survey weight of 0 were excluded from the final analysis after applying the survey weight. Moreover, those who lacked 2 primary sampling units (PSUs) were excluded to minimize technical errors and increase precision during weighted statistical analyses (Chen et al., 2020). I have additionally removed patients who have died within 2 years of the study to reduce reverse causation bias, where an underlying condition could have factored into the results (Øland et al., 2024). As a result, a total of 578 out of the 116,876 individuals were enrolled in this study, as illustrated in **Figure 1**.

2.2 Determining Covariates

To diminish the impact of confounding factors, creatinine, HbA1c, CRP, and cholesterol were introduced as covariates in this study. Given that mortality risk could stem from numerous underlying conditions, I have utilized various health biomarkers to address bias.

Creatinine is an organic compound produced from the degradation of creatine phosphate in muscle (Gowda et al., 2010). Creatinine is an established renal biomarker, previously used to evaluate the influence of kidney function as a factor in mortality risk (Gowda et al., 2010). The presence of chronic kidney disease increases mortality risk due to cardiovascular diseases and non-cardiovascular diseases; additionally, chronic kidney disease is one of the top three growing causes of mortality across the world

(Francis et al., 2024; Thompson et al., 2015). Therefore, it is essential to account for kidney dysfunction when identifying mortality risk relative to the cardiometabolic index, as to achieve accurate results.

HbA1c is hemoglobin, a protein that helps carry oxygen in red blood cells, saturated with glucose (Eyth et al., 2025). Correspondingly, HbA1c represents glucose concentration, which is known as a biomarker for cardiovascular risk and diabetes-mellitus in medical research (Sinning et al., 2021; Weykamp, 2025). I have included this biomarker as a covariate in my analyses to reduce the effect of diabetic and cardiovascular complications on mortality risk.

CRP is produced by the liver in response to inflammation and is extensively utilized as an inflammatory biomarker in research (Singh et al., 2025). In previous research, low-grade inflammation was independently correlated with mortality risk (Bonaccio et al. 2016); hence, it is necessary to factor in the role of inflammation with mortality risk to limit external influence on my findings.

Lipoproteins function by transporting cholesterol and lipids throughout the body, including high-density lipoproteins (HDL) and low-density lipoproteins (LDL) (Lee & Siddiqui, 2023). Though, cholesterol levels are associated with cardiovascular diseases (Lee & Siddiqui, 2023). Conditions involving an elevated level of lipids, increases the risk for cardiovascular disease and mortality risk; thus I have labelled LDL and total cholesterol as covariates in my analyses to prevent bias (Lee & Siddiqui, 2023; Pham et al, 2024).

In addition to the laboratory biomarkers, I have also included age, gender (sex), race, body mass index (BMI), alcohol consumption status, smoking status, and educational level as covariates. Health outcomes may be expressed differently amongst genders, in individuals of varying ages, and between races. Additionally, the body mass index (BMI) reflects the ratio of weight to height, and hence, categorizes obesity (Zierle-Ghosh & Jan, 2023). Earlier studies have established that greater BMIs are associated with greater mortality risk (Calle et al., 1999). Thus, it is necessary to factor in these variables and generate reliable results. Furthermore, educational level was used in place of the poverty index as a socioeconomic covariate to mortality risk to eliminate bias due to varying access to health resources or medical facilities. Education level was split into 3 sections: (1) lower than high school education, (2) high school or GED equivalent of education, and (3) college education or greater.

Smoking and alcohol use can augment mortality risk and compromise the validity of my results; to prevent this, I have listed them as covariates (Rehm et al., 1993). Smoking status has 3 groups: non-smoker, current smoker, and former smoker. Patients who have smoked at least 100 cigarettes in their lifetime and admitted to smoking currently were considered current smokers. Former smokers were individuals who had smoked 100 cigarettes, but had admitted to barely smoking currently. In contrast, non-smokers were identified as individuals who have not smoked 100 cigarettes in their lifetime. Alcohol consumption status was split into 4 groups: non-drinker, mild drinker, moderate drinker, and heavy drinker. Non-drinkers were those who admitted to drinking currently, but do not drink 0 drinks every week. Moderate drinkers were those who drank 3.5 - 8 drinks per week for women and 7 - 15 drinks per

week for men (CDC, 2025). Heavy drinkers were patients who drank over the moderate drink threshold according to gender.

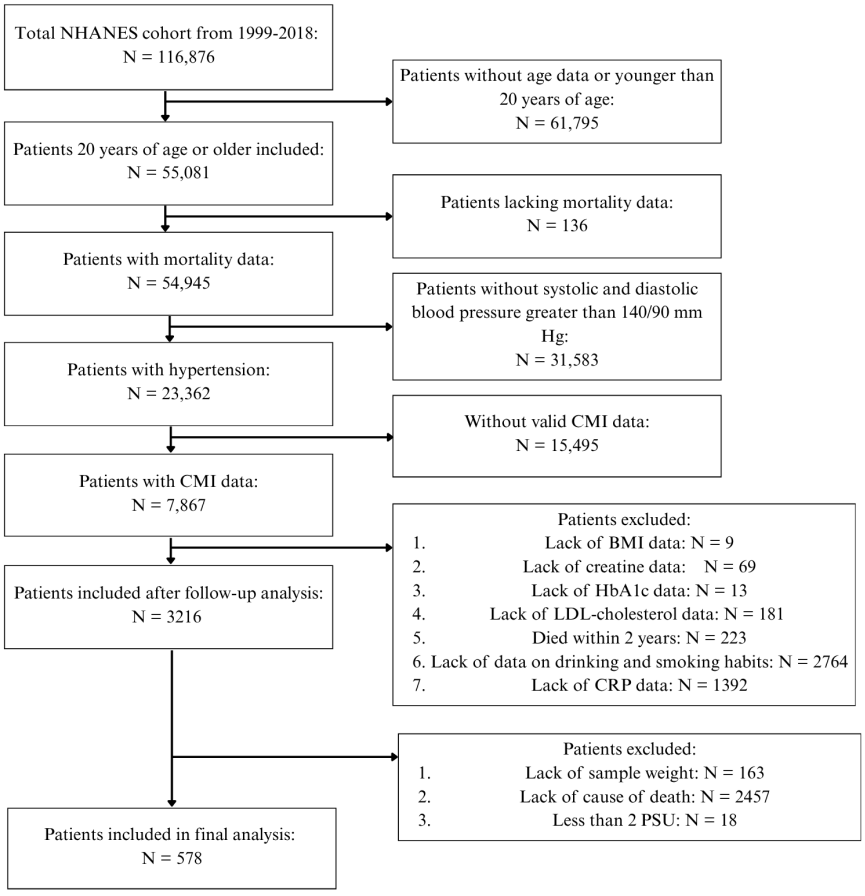

Figure 1. Flow chart representation of the filtering process, including exclusion and inclusion criteria. Abbreviations: cardiometabolic index (CMI), body mass index (BMI), glycated hemoglobin (HbA1c), C-reactive protein (CRP). (Figure created by student researcher using Canva, 2025).

2.3 Definitions of Exposed Variable and Outcome Variables

The main exposure variable in my study is the cardiometabolic index (CMI), which was calculated using the formula created by Wakabayashi & Daimon (2015):

$$\text{CMI} = \frac{\text{Triglyceride Concentration}}{\text{HDL-cholesterol Concentration}} \times \frac{\text{Waist circumference}}{\text{Standing height}}$$

The primary endpoint of this study was defined as all-cause mortality, which involves death from any cause. Furthermore, secondary endpoints were defined as hypertension-related mortality and cardiovascular mortality.

2.4 Statistical Analyses

All statistical analyses were performed using the R language version 4.5.1. The patients were divided into three tertiles based on their CMI, and baseline characteristics of the study population were compared across CMI tertiles. The Kruskal-Wallis test was conducted to evaluate the variances in measurements of the data among the CMI tertiles. In addition, I have used the chi-square test to evaluate the significance of categorical variables. Kaplan-Meier analyses and log-rank tests were used to assess the differences in outcomes among CMI tertiles. Furthermore, the Cox proportional hazard regression model was utilized to quantify the 95% confidence intervals (CI) and hazard ratios (HR) for every 1 unit increase in CMI for each endpoint. Then, I conducted a Cox proportional hazard regression model using CMI tertiles for every endpoint to determine variation in mortality outcomes between the CMI groups. A separate multivariate Cox regression analysis was performed between CMI and endpoints to reduce the impact of confounding variables. In the multivariate Cox regression analysis, I used 4 models to optimize all available data and prevent over-adjusting the covariates to ensure a robust analysis. Model 1 involved CMI, age, gender, and race. Model 2 involved smoking status, alcohol consumption status, education level, BMI, and all the variables in model 1. Model 3 involved C-reactive protein, total cholesterol, and LDL-cholesterol, and all the variables in model 2. Finally, I added HbA1c with all other variables in model 4 to investigate the independent effect of CMI on mortality risk. To validate my findings, I ran a sensitivity analysis on the effect of CMI in subgroups based on age, BMI, and gender. In this study, $p<0.05$ is considered the significance threshold.

Due to time constraints, an additional Restricted Cubic Spline analysis could not be conducted; therefore, CMI was evaluated through the use of continuous and categorical variables for accurate outcomes, regardless of whether the associations were to be linear or non-linear. A continuous approach was done on the Cox proportional regression models to enhance the statistical power of the results; this is because a categorical value would reduce the statistical power as it groups individuals based on thresholds of the CMI. To determine whether associations of the CMI as a categorical variable were significant, the stratified groups were represented by the Kaplan-Meier survival curves, Log-rank tests, and represented on a table on the baseline table.

In this study, Cox proportion hazard models were used to estimate hazard ratios under the proportional hazards assumption (Zhang et al., 2018). No formal assessment of this assumption was performed; however, model estimates were interpreted as average hazard ratios over follow-up time (Bardo et al., 2024).

<u>Sample code for Kaplan Meier Analysis for cardiovascular (referred to as cvd) mortality:</u>

```
library(survey)
library(survminer)
```

```
survival_cvd <- survfit(Surv(permth_exm, ucod_leading==1)~CMI_tertile, data = NHANES_filtered_data2, weights = NHANES_filtered_data2$WTSAF20YR)
ggsurvplot(survival_cvd, xlim=c(0, 210), break.x.by = 40, ylab="Probability of Survival", xlab="Time (months)",
           pval= TRUE, risk.table=TRUE, risk.table.title="Number at Risk",
           surv.scale = "percent", palette=c("blue", "red", "green"),
           title="cardiovascularMortality", conf.int = F, risk.table.height=.45)
summary(kmcurve, times=seq(0, 60, 12))
```

RESULTS

3.1 Baseline Characteristics

To identify an association between CMI and mortality risk, I ran three Kaplan-Meier curves for each endpoint, along with weighted-log rank tests to determine the significance of the distribution of curves between each CMI tertile; using R Language version 4.5.1., I stratified the total participant cohort into 3 equal groups fo varying CMI levels, with approximately 193 individuals stratified across each tertile. To understand the impact of each confounding variable across CMI tertiles, I created a baseline table. Then, I ran a multivariate Cox regression analysis of CMI effect on mortality risk for all endpoints to further verify my findings.

This study enrolled a total of 578 eligible hypertensive patients, and the weighted population was 2,028,490 individuals. The median age was found to be 74 years, 303 patients were male (52%), and 275 were female (48%). To continue, 68% of the study cohort was Non-Hispanic White, 15% were Non-Hispanic Black, 9.7% were Mexican American, and 3.5% were part of other races. The median BMI was found to be 28 kg/m,^{2,} and the median CMI is 1.36 units. With reference to the smoking status, 44% of the study cohort were non-smokers, 16% were current smokers, and 40% were former smokers. On the other hand, 26% of the study cohort were non-drinkers, 11% were moderate drinkers, 54% were mild drinkers, and 8.8% were heavy drinkers. For education level, 42% of the patients reported having less than high school level education, 35% reported having high school level education or GED qualifications, and 23% reported having college level education or higher. Furthermore, the median for creatinine was 0.27 mg/dl, the median for total cholesterol was 191 mg/dl, the median for LDL-cholesterol was 108 mg/dl, and the median for HbA1c concentration was 5.7% in the study population. Age, race, BMI, alcohol consumption status, education level, C-reactive protein, triglycerides, HDL-cholesterol, LDL-cholesterol, HbA1c, and waist circumference were statistically significant amongst the CMI tertiles. In contrast, gender, smoking status, creatinine, total cholesterol, and standing height were not statistically significant amongst the CMI tertiles. Details pertaining to the baseline characteristics can be found in **Table 1, Appendix A**.

Table 2. Observed survival or mortality outcome events distributed across each CMI tertile, using percentage of events out of total number of outcomes. Abbreviations: CMI, cardiometabolic index; T, tertile. (Table created by student researcher using R language version 4.5.1, 2025).

Table 2. Observed Event Counts and Weighted Mortality Rates by CMI Tertile

Survival Status (%)	T1	T2	T3
Alive	232,839 / 252,041 (92%)	699,018 / 821,695 (85%)	3,125,846 / 3,426,013 (91%)
Deceased	19,203 / 252,041 (7.6%)	122,677 / 821,695 (15%)	300,167 / 3,426,013 (8.8%)

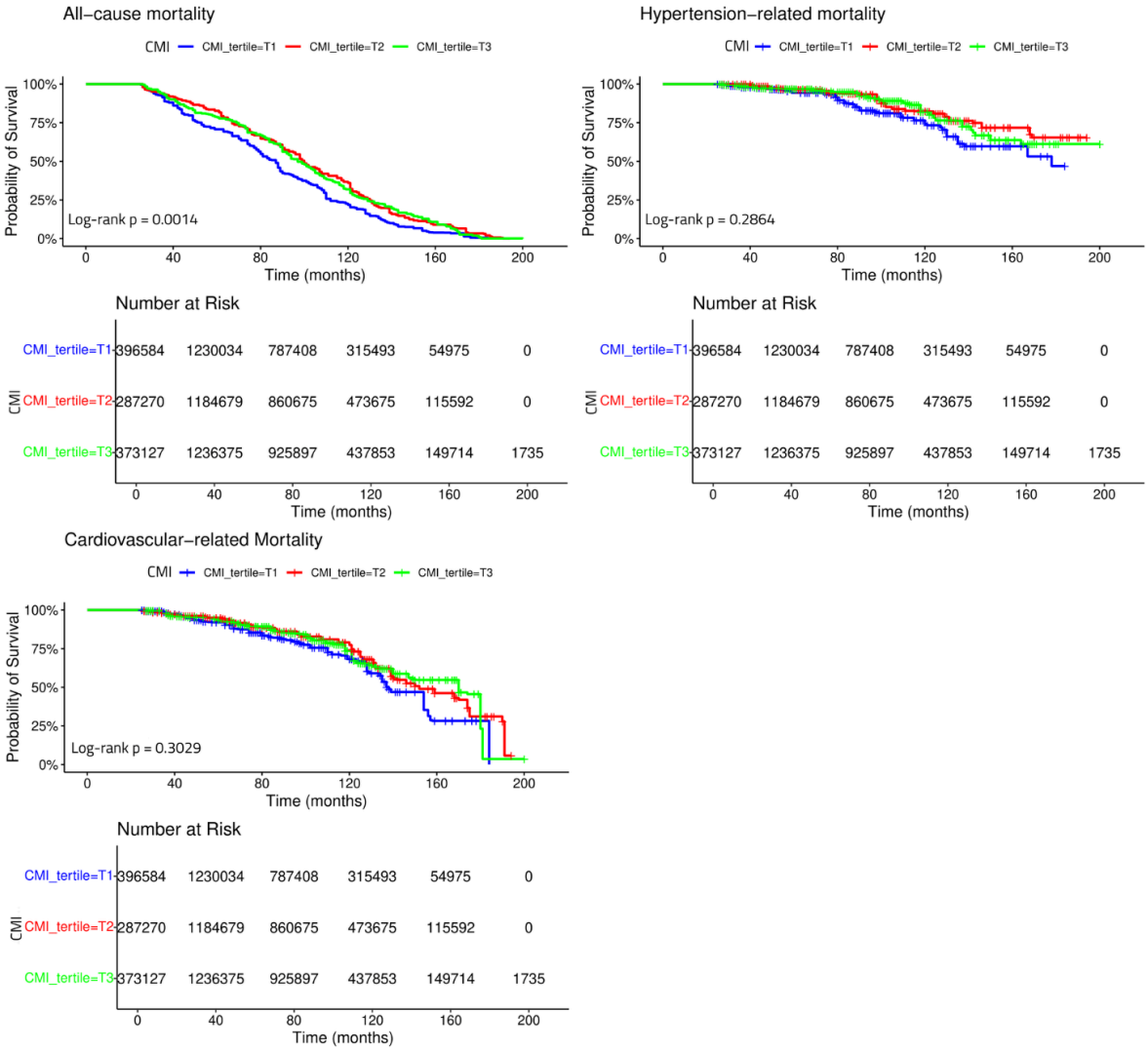

Figure 2. Kaplan-Meier survival analysis of every endpoint in the study cohort. (A) CMI and all-cause mortality; (B) CMI and cardiovascular-mortality; (C) CMI and hypertension-mortality. Abbreviations: CMI, cardiometabolic index. (Figure created by student researcher using R language version 4.5.1, 2025).

3.2 CMI and Mortality risk

Overall, there were 578 patients with valid mortality information, of which 28.9% consisted of cardiovascular deaths (N = 167) and 16.8% consisted of hypertension-related deaths (N = 97). After applying weights to the population cohort, there were a total of 4,056,981 individuals, of which 1,157,455 were cardiovascular deaths and 676,368 were hypertension-related deaths. Upon cohort stratification, tertile 1 consisted of CMI values lower than 0.998, tertile 2 contained CMi values equal to 0.998 to 1.941, and tertile 3 had values greater than 1.941. In tertile 1, 92% of individuals were alive and 7.6% were deceased; in tertile 2, 85% of individuals were alive, whereas 15% were deceased, and in tertile 3, 91% of individuals were alive, whereas 8.8% were deceased (**Table 2**).

Findings from the Kaplan-Meier curves and the weighted-log rank tests demonstrated insignificant differences between the CMI tertiles and association with hypertension-related mortality risk (p=0.2864), and with cardiovascular mortality risk (p=0.3029); despite these results, the Kaplan-Meier curves suggested significant differences between the CMI tertiles and all-cause mortality (p=0.0014) (**Figure 2**). Moreover, the univariable Cox regression analysis indicated that a greater CMI reduced mortality risk in all-cause mortality (HR: 0.950, 95% CI: 0.884-1.022, p=0.17). In comparison, a greater CMI correlated to lower hypertension-related mortality risk (HR: 0.917, 95% CI: 0.740-1.135, p=0.426). Yet in contrast, CMI did not affect cardiovascular mortality (HR: 1.000, 95% CI: 0.860-1.161, p=0.995). Nonetheless, all trends and relationships between CMI and mortality risk of all three endpoints were insignificant, thus revealing that CMI is not associated with mortality risk (**Table 3**).

Table 3. CMI lowered the hazard ratio for the incidence of all-cause and hypertension-related mortality. CMI has a hazard ratio of 1 for cardiovascular mortality, signifying no effect. (Table created by student researcher using R language version 4.5.1, 2025).

Table 3. Univariable Cox regression results of all endpoints

	All-cause Mortality			**Cardiovascular Mortality**			**Hypertension-related Mortality**		
Characteristic	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
CMI	0.950	0.884,1.022	0.170	1.000	0.860, 1.161	0.995	0.917	0.740, 1.135	0.426

Abbreviations: CI = Confidence Interval, HR = Hazard Ratio

3.2.1 CMI and All-cause Mortality Risk

Results from the multivariate Cox regression analysis indicated that the CMI was insignificant after adjusting for multiple variables through models 1-4 for all endpoints (**Figure 3**). These results

demonstrate that CMI is not independently associated with mortality risk. Although this may be the case, other confounding variables have a greater effect on mortality risk throughout each endpoint. For example, the non-smoking status (HR: 0.67, 95% CI: 0.49-0.91, p=0.011) and former smoking status (HR: 0.65, 95% CI: 0.46-0.93, p=0.019) were associated with decreased risk for all-cause mortality in model 2. Yet, education level was associated with greater all-cause mortality risk (HR: 1.23, 95% CI: 1.13-1.48, p<0.001). After adjusting for variables in model 4, the same results were seen in model 2; additionally, moderate drinker was associated with lower risk for mortality (HR: 0.64, 95% CI: 0.43-0.97, p=0.034) and CRP (HR: 1.17, 95% CI: 1.09-1.25, p<0.001) increased the risk of all-cause mortality in model 4 as well.

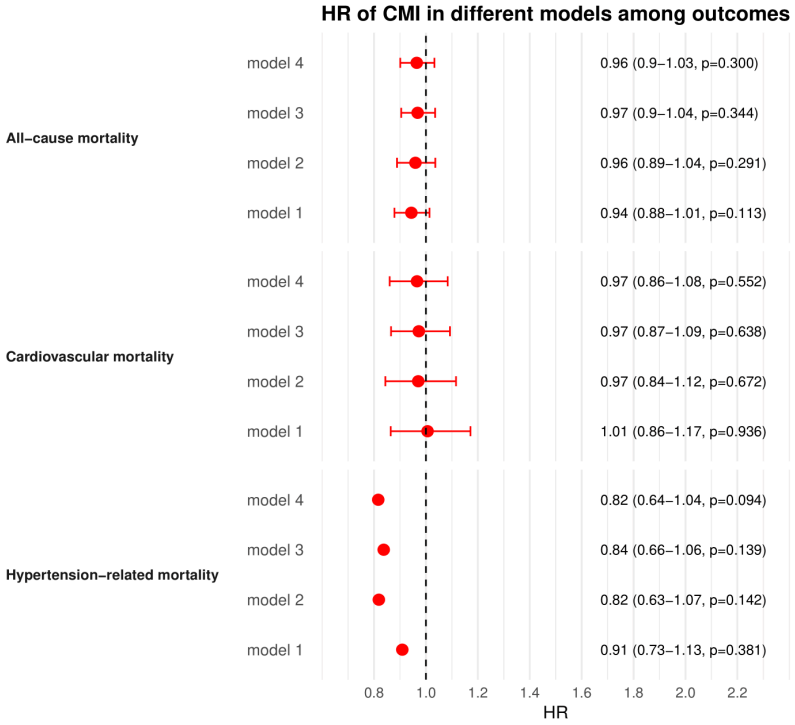

Figure 3. Forest plot of results from multivariate Cox regression analysis. Model 1 contained CMI, age, gender, and race. Model 2 included all the variables from Model 1 and alcohol consumption status, smoking status, education level, and BMI. Model 3 included creatinine, TC, CRP, and LDL-C, and variables from Model 2. Model 4 added HbA1c and the variables in Model 3. Abbreviations: CMI, cardiometabolic index; BMI, body mass index; TC, total cholesterol; CRP, C-reactive protein; LDL-C, low-density lipoprotein; HbA1c, glycated hemoglobin. (Figure created by student researcher using R language version 4.5.1, 2025).

3.2.2 CMI and Cardiovascular Mortality Risk

Contrary to the all-cause mortality models, age (HR: 1.03, 95% CI: 1.01-1.04, p=0.006) increased the cardiovascular-mortality risk significantly, whereas gender (HR: 0.68, 95% CI: 0.48-0.96, p=0.0302) was significantly associated with lower cardiovascular-mortality risk in models 1, 2, and 3. After adjusting for the variables in model 4, similar trends found in models 1, 2, and 3 were observed in model 4; furthermore, CRP (HR: 1.23, 95% CI: 1.11-1.51, p<0.001) was also significantly associated with greater cardiovascular-mortality risk in model 4.

3.2.3 CMI and Hypertension-related Mortality Risk

Opposed to the variables seen in other models, BMI (HR: 1.05, 95% CI: 1.01-1.09, p=0.0096) was significantly associated with higher hypertension-mortality risk beginning from models 2. After adjusting for all the confounding variables in model 4, the correlation between BMI and greater hypertension-mortality risk became insignificant (p=0.059); despite this, CRP (HR: 1.23, 95% CI: 1.08-1.40, p=0.0022) and HbA1c (HR: 1.24, 95% CI: 1.01-1.51, p=0.0368) corresponded to higher hypertension-mortality risk. Results from model 4 from all-cause mortality risk, hypertension-related mortality risk, and cardiovascular mortality risk indicated that CRP has a greater association with mortality risk opposed to the CMI. CMI does not have any significant association with mortality risk, which was supported by the sensitivity analysis (**Figure 4**).

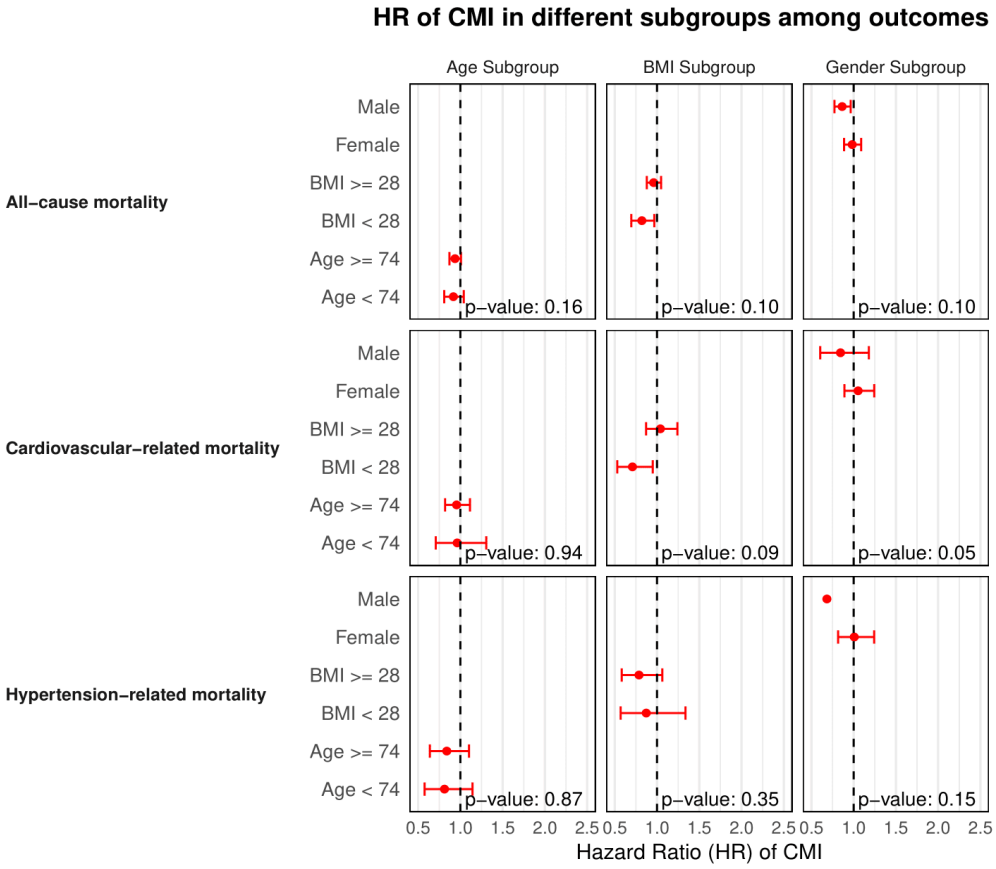

Figure 4. Forest plot outcomes of subgroup analyses of CMI and mortality risk of all endpoints. Subgroups for BMI consisted of greater than or equal to 28 kg/m^2 and less than 28 kg/m^2. Subgroups for age consisted of those greater than or equal to 74 and those less than 74 years of age. Gender subgroups were split between male and female. The p-values represent the interaction between CMI and the incidence of each endpoint. (Figure created by student researcher using R language version 4.5.1, 2025).

DISCUSSION

The main objective of this study was to determine whether the CMI is associated with mortality risk in hypertensive patients. I hypothesized that CMI would have a significant association with all-cause, hypertension-specific, and cardiovascular mortality risk. However, this hypothesis was not supported, as the relationships between CMI and each mortality incidence were insignificant (**Figure 3 & Figure 4**). Despite the Kaplan-Meier curves suggesting significant differences among the CMI tertiles and all-cause mortality risk (p=0.0014), differences observed within hypertension-related and cardiovascular mortality were minimal (**Figure 2**). With reference to **Table 3** and **Figure 2**, the univariate and multivariate Cox regression analyses yielded insignificant associations between CMI and each mortality endpoint, suggesting CMI may not correlate with all-cause mortality, hypertension-related mortality risk, and cardiovascular mortality in hypertensive patients.

4.0.1. CMI Statistical Findings

Multiple statistical models were employed within this study to evaluate the relationship between CMI and mortality risk. Notably, discrepancies observed between Kaplan-Meier Survival analyses, log-rank tests, and Cox regression models likely reflect the differences in covariate adjustment. Kaplan-Meier survival analyses and log-rank tests do not account for confounding variables (Shreffler et al., 2023); whereas, Cox regression models estimates for the independent effects of the CMI after adjusting for covariates, reducing the observed significant association (Andrade, 2023). Moreover, Kaplan-Meier analyses capture non-linear effects that are not represented when CMI is modeled as a continuous predictor in the Cox statistical models (Lundgreen et al., 2022). Collectively, these findings suggest that the association between CMI and mortality risk is sensitive to model specifications. Accordingly, Kaplan-Meier differences should be interpreted as descriptive, while the Cox regression results reflect the estimate of the independent association.

Additionally, the CMI was linked to lower risk for all-cause and hypertension-related mortality, but had no notable impact on cardiovascular mortality (**Table 3**). These outcomes remained consistent after adjusting for covariates in the Cox regression analysis, except for a non-significant trend towards lower cardiovascular mortality risk (HR: 0.9656, 95% CI: 0.8603-1.0838, p=0.55) (**Figure 3** & **Figure 4**). Therefore, these results suggest that CMI may not be indicative of all-cause, cardiovascular, and

hypertension-related mortality risks in hypertensive patients. However, the accuracy of these findings is influenced by numerous limitations.

4.0.2. CMI and Mortality Risk

Although current research presents discrepancies regarding CMI and mortality risk, the fundamental importance of the CMI in clinical research remains prominent. In a study conducted by Yang et al. (2025), reported a significant association between the CMI and mortality; researchers deduced that each incremental increase in the CMI rose all-mortality risk by 11.3% (HR = 1.113, 95% CI: 1.112–1.115), while cardiovascular mortality increased by 6.4% (HR = 1.064, 95% CI: 1.062–1.065). Similarly, another study reaffirmed this relationship between CMI and mortality risk, where a unit of CMI considerably amplified all-cause mortality risk (HR=1.14, 95% CI: 1.05-1.24) and cardiovascular-mortality risk (HR=1.17, 95% CI: 1.01-1.35) (Xu et al., 2024). Furthermore, additional studies have established positive correlations between elevated CMI and the prevalence of hypertension, diabetes mellitus, and chronic kidney disease (Guo et al., 2024; Guo et al., 2025; Zha et al., 2023). Collectively, these studies underscore the strong predictive value of CMI for both mortality risk and morbidity.

Despite these parallels, CMI outcomes on mortality risk have not been consistently reproducible. For instance, Lui et al. (2025) concluded insignificant relationships between all-cause mortality and cardiovascular mortality ($p=0.145$ & $p=0.215$, respectively), whereas a significant association between the CMI and diabetes-related mortality was corroborated ($p<0.001$). Additionally, a study by Li et al. (2025) emphasized a positive relationship between CMI and every mortality endpoint in women ($p<0.05$); however, in men, the relationship between the CMI and cardiovascular-mortality risk was statistically insignificant ($p=0.1367$). These findings align with mine because they deviate from current research concerning CMI and mortality risk. Moreover, this study observed a negative relationship between CMI and all-cause and hypertension-related mortality risk, where greater CMI values are associated with lower risk for mortality. These findings illustrate the necessity for further experimentation and comprehensive assessment of the CMI applications to health, disease, and mortality risk.

4.1 Biological Significance

4.1.2 HbA1c and Hypertension-Related Mortality risk

High blood glucose concentrations furthers mortality risk complications (Balkau et al., 1998). In this study, HbA1c was significantly, positively associated with hypertension-related mortality only (HR: 1.24, 95% CI: 1.01-1.51, $p=0.0368$), demonstrating elevated concentrations of HbA1c, or glucose, concentrations may increase mortality risk. Dysregulation of glucose concentrations may have accelerated hypertension-related mortality through several physiological pathways. Additionally, one specific mechanism is the production of advanced glycated end products (AGEs) via glycation, a process attaching sugar molecules to proteins or lipids (Lee et al., 2022). Through the production of AGEs, greater oxidative stress and unstable molecules are generated from non-enzymatic reactions, which activates inflammatory pathways such as polylol, hexosamine, and protein kinase C pathways (Lee et al.,

2022); hence, AGEs alter proteins via unwanted interactions between molecules (Lee et al., 2022). These processes complicate cellular homeostasis and function. For example, AGEs can bind with the receptor for AGE which amplifies reaction oxygen species, molecules such as hydrogen peroxide, and induces tissue damage (Lee et al., 2022;Yamaguchi et Yamaguchi, 2025).

Overall, elevated concentrations of glucose, or HbA1c, promote cellular dysfunction and inflammatory signaling, impairing vascular integrity. A greater occurrence of HbA1c reflects hypertension-related mortality risk via inflammatory and disruption to homeostasis in hypertension patients.

4.1.2 C-Reactive Protein and Mortality risk

Inflammation mediates the progression of cardiovascular diseases and mortality risk through diverse mechanisms. For example, low-grade inflammation encourages gut microbiota to stimulate cardiovascular disease (Liberale et al., 2023). Additionally, inflammation magnifies the growth of pro-inflammatory cytokines in the artery wall, contributing to atherosclerosis (Willerson et al., 2004). This process occurs as oxidized LDL-cholesterol activates the stimulation of smooth muscle cells (SMCs) along the arterial wall, thus enabling plaque rupture in the arteries (Willerson et al., 2004). In turn, this prompts the migration of inflammatory molecules to vascular tissue (Willerson et al., 2004). These messenger proteins are released into the circulatory system, promoting inflammatory responses by generating CRP and amyloid A (abnormal protein clumps) from the liver (Willerson et al., 2004). Moreover, protein complexes, such as interleukin-6 and CRP, give rise to fibrinogen and tissue factors (proteins), which initiate coagulation, or clotting of the blood (Raaz-Schrauder et al., 2014; Pasceri et al., 2000; Willerson et al., 2004). Coagulation greatly augments mortality risk, as exemplified in research from Yap et al. (2023), which highlighted a positive association between fibrinogen factor 10 and fibrinogen factor 11 with cardiac death. With higher levels of fibrinogen factors, there is heightened risk for all-cause mortality (HR 1.26, 95% CI: 1.09-1.45, p=0.002) (Hu et al., 2025). Therefore, inflammation may be the key mediator between escalated mortality risk and CRP, as it exacerbates these inflammatory mechanisms.

CRP was positively associated with every mortality endpoint in this study ($p<0.001$). CRP has countless pathways that modulate inflammation, thereby intensifying mortality risk. CRP mainly relies on expressing adhesion molecules, leading to monocyte (white blood cells) activation and recruitment to the vascular wall, and precipitating in endothelial dysfunction (of the lining of the blood vessels) (Hein et al., 2010; Pasceri et al., 2000; Woollard et al., 2002). In addition to this, CRP amplifies the expression of interleukin-6 and other pro-coagulative cytokines, thus escalating inflammation (Raaz-Schrauder et al., 2014). Furthermore, CRP mitigates endothelium-derived nitric oxide (eNO) from suppressing SMCs, fostering adherence of monocytes to the heart; coagulation perpetuates via uncoupling through phosphorylation of eNO (Singh et al. 2007; Willerson et al., 2004). Altogether, these inflammatory functions of CRP may have raised the mortality risk in hypertensive patients observed in this study.

CRP was eminently associated with hypertension, blood pressure, and cardiovascular disease (Burger et al., 2023; Smith et al., 2005). Greater CRP levels corresponded with heightened risk for all-cause mortality and correlated with mortality in patients with type 2 diabetes (HR: 1.95 ;HR: 1.94, 95% CI:

1.45–2.61, p<0.001 respectively) (Maluf et al., 2020; Yan et al., 2025). Hence, CRP may be advantageous in evaluating morbidity and mortality, and should be further explored in patients with hypertension.

4.2 Limitations

Several limitations compromise the validity of these present findings. Primarily, data from this investigation utilized a limited sample size of 578 individuals, which may have contributed to insignificant correlations between CMI and each mortality risk (**Figure 3 & Figure 4**). This current cohort was derived after an extensive exclusion process to ensure complete data availability for all study variables and outcomes. While these exclusions reduced potential statistical measurement errors, they substantially decreased the available patient cohort and introduced selection bias, as individuals excluded may have differed systematically in demographic or clinical characteristics compared to included participants. Hence, with an inadequate number of observations, statistical power may have been insufficient for the Cox regression analyses, Kaplan-Meier, and Log-rank tests. Furthermore, a smaller sample size would limit the number of events available for the analyses, reducing the ability of these statistical models to detect strong associations between the CMI and mortality risk; true associations would have been missed due to insufficient statistical power. The final study population may not be fully representative of the broader hypertensive population, thereby limiting the generalizability of the findings.

Though efforts were made to restrict external factors on the results, I could not eliminate all residual confounding factors related to the environment, nutritional health, or the effect of cancer on mortality risk. Therefore, the study may have introduced inaccuracy in the correlations between each mortality endpoint and the CMI or amongst other variables.

Potential multicollinearity may exist between CMI and several covariates included in the regression models, including BMI, waist circumference, triglycerides, and HDL-cholesterol. Considering that CMI is derived from anthropometric and lipid measures, the inclusion of these variables in the same model may inflate standard error and produce unstable hazard ratio estimates. Due to these factors, the independent contribution of CMI to mortality risk may be attenuated through the shared variance between variables.

Moreover, a Restricted Cubic Spline Analysis was not performed, and thus I could not determine whether I should use the continuous or categorical variables for the CMI. As represented by the Kaplan-Meier survival curves, there may have been a significant non-linear association between the CMI and all-cause mortality risk, since the differences amongst the curves were significant (p=0.0014). This may have produced biased results since the CMI may have had non-linear associations with the mortality endpoints, and thus was inaccurately represented as a continuous variable as used in the Cox proportional hazard regression models.

Another limitation that may affect the validity of my results is that the proportional hazards assumption for the Cox proportional hazards model was not formally assessed. Consequently, the reported hazard ratios represent an average effect over the entire follow-up period (Bardo et al., 2024). If the hazard ratios

were to be non-proportional and change over time, this single estimate may not accurately reflect the time-varying nature of the variable, affecting the interpretation of my findings.

Lastly, I was not able to classify levels of hypertension. This is a major constraint since mortality risk varies considerably between stages of hypertension. A study by Peng et al. (2023) demonstrated this: patients who progressed from stage 1 to stage 2 hypertension were found to have a 129% lifetime increase in mortality (HR: 2.29, 95% CI: 1.89–2.77). Therefore, failing to account for the disparate stages of hypertension may have flawed the outcomes of this experiment.

CONCLUSION

The main objective of this study is to determine whether CMI is associated with all-cause, hypertension-related, and cardiovascular mortality risk. I hypothesized that CMI would be positively associated with each mortality outcome. However, no statistically significant associations were observed between CMI and with all-cause, hypertension-related, and cardiovascular mortality risks ($p>0.05$). These findings do not provide evidence supporting CMI as an independent prognostic marker for mortality risk within this hypertensive cohort. Despite this, further investigations should be made with CMI and mortality risk to verify these trends. In contrast, the C-reactive protein is positively associated with each mortality endpoint ($p<0.001$) and HbA1c was positively associated with hypertension-related mortality only ($p=0.037$). In conclusion, C-reactive protein and HbA1c continue to serve as clinically relevant biomarkers of mortality risk and may improve hypertensive patient management through therapeutic interventions targeting inflammation and metabolic control.

5.1 Future research

Future investigations in this field should elucidate the outcomes of CMI on the multifaceted causes of mortality. There are limited studies on CMI and cerebrovascular-related mortality risk, cancer-related mortality risk, and others. These comparisons can clarify the prognostic ability of the CMI. Moreover, Li et al. (2025) illustrated the need for gender-specific differences in the CMI outcomes on mortality risk. Researchers observed that the relationship between the CMI and men was insignificant compared to the women's cohort. Therefore, exploring how gender moderates the relationship between the CMI and mortality risk could enhance understanding of the mechanisms behind the CMI. Lastly, studies should prioritize expanding their sample size to broaden their statistical power and reinforce the generalizability of their results. Nonetheless, this study presents novel insights into diagnostic interventions of the CMI to assess mortality risk in hypertensive patients.

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DATA STATEMENT

The raw data supporting the conclusions of this article can be found at https://www.cdc.gov/nchs/nhanes/.

DECLARATION OF COMPETING INTERESTS

This research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A

Table 1, Appendix A. Laboratory biomarkers and relevant examination variables distribution is shown across CMI tertiles. BMI involves units of kg/m^2. Continuous variables are expressed in interquartile ranges, and categorical variables are expressed as percentages. (Table created by student researcher using R language version 4.5.1, 2025).

Table 1, Appendix A. Baseline Characteristics

Baseline characteristics	**Overall** N = 578	**T1** N = 193	**T2** N = 192	**T3** N = 193	**p-value**
CMI (median [IQR])	1.36 (0.86, 2.40)	0.66 (0.53, 0.86)	1.36 (1.17, 1.62)	2.92 (2.40, 3.69)	<0.001
Gender, (%)					0.051
Male	303 (52%)	94 (49%)	94 (49%)	115 (60%)	
Female	275 (48%)	99 (51%)	98 (51%)	78 (40%)	
Age, (median [IQR])	74 (64, 80)	77 (65, 80)	75 (64, 80)	72 (63, 79)	0.001
Race, (%)					0.015
Mexican American	56 (9.7%)	11 (5.7%)	19 (9.9%)	26 (13%)	
Other Hispanic	24 (4.2%)	5 (2.6%)	7 (3.6%)	12 (6.2%)	
Non-Hispanic White	392 (68%)	138 (72%)	125 (65%)	129 (67%)	
Non-Hispanic Black	86 (15%)	36 (19%)	31 (16%)	19 (9.8%)	
Other Race - Including Multi-Racial	20 (3.5%)	3 (1.6%)	10 (5.2%)	7 (3.6%)	
BMI, (median [IQR])	28 (24, 32)	25 (22, 29)	27 (25, 32)	31 (28, 35)	<0.001
Smoking status, (%)					0.4
Current smoker	94 (16%)	31 (16%)	26 (14%)	37 (19%)	
Former smoker	232 (40%)	78 (40%)	73 (38%)	81 (42%)	
Non-smoker	252 (44%)	84 (44%)	93 (48%)	75 (39%)	

Alcohol consumption status, (%)					0.031
Heavy drinker	51 (8.8%)	27 (14%)	11 (5.7%)	13 (6.7%)	
Mild drinker	311 (54%)	90 (47%)	107 (56%)	114 (59%)	
Moderate drinker	63 (11%)	25 (13%)	22 (11%)	16 (8.3%)	
Non-drinker	153 (26%)	51 (26%)	52 (27%)	50 (26%)	
Education level, (%)					0.021
Lower than High School education	244 (42%)	66 (34%)	82 (43%)	96 (50%)	
High school/GED education	201 (35%)	73 (38%)	72 (38%)	56 (29%)	
College education or greater	133 (23%)	54 (28%)	38 (20%)	41 (21%)	
Creatinine (mg/dl), (median [IQR])	103 (66, 142)	95 (63, 139)	104 (63, 145)	106 (74, 142)	0.3
C-reactive protein (mg/dl), (median [IQR])	0.27 (0.12, 0.58)	0.18 (0.09, 0.41)	0.28 (0.11, 0.62)	0.35 (0.19, 0.71)	<0.001
Triglycerides (mg/dl), (median [IQR])	121 (89, 170)	80 (68, 95)	120 (103, 144)	193 (159, 239)	<0.001
Total cholesterol (mg/dl), (median [IQR])	191 (166, 222)	187 (164, 223)	193 (165, 220)	194 (168, 222)	0.8
LDL-cholesterol (mg/dl), (median [IQR])	108 (85, 133)	99 (81, 126)	111 (87, 135)	112 (88, 134)	0.034
HDL-cholesterol (mg/dl), (median [IQR])	54 (44, 68)	70 (61, 81)	54 (47, 63)	42 (37, 47)	<0.001
HbA1c (%), (median [IQR])	5.70 (5.40, 6.20)	5.50 (5.30, 5.90)	5.80 (5.45, 6.20)	5.90 (5.50, 6.50)	<0.001
Waist circumference (cm), (median [IQR])	101 (93, 112)	94 (84, 102)	101 (93, 110)	109 (101, 121)	<0.001
Standing height (cm), (median [IQR])	167 (158, 174)	166 (159, 173)	166 (158, 173)	167 (159, 175)	0.2

Abbreviations: CMI, cardiometabolic index; BMI, body mass index; GED, general education development; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; T, tertile.

ABOUT THE AUTHOR

Geeta Dey is a rising senior at Herricks High School. She takes interest in cardiovascular health and is passionate about exploring the applications of statistics in medical research. In the future, she hopes to study these topics further in college and learn more about the intersections between mathematics and biology.