Impact of Cardiovascular Diseases on Mortality in Gastric Cancer Patients with Preexisting Chronic Disease

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Purpose: Chronic diseases and cardiovascular diseases (CVD) have been independently linked to poorer cancer outcomes. This study investigated whether gastric cancer patients with hypertension, diabetes, or dyslipidemia have higher mortality if diagnosed with CVD in the past year before cancer diagnosis.

Materials and Methods: Data were obtained from the National Health Insurance database for 2002 to 2019. The study population consisted of gastric cancer patients with hypertension, diabetes, or dyslipidemia. The outcome measure was 5-year mortality in relation to incident status of CVD within 1 year before cancer diagnosis. A survival analysis was conducted using the Cox proportional hazards model. Subgroup analysis was conducted according to age, economic status, and type of hospital first visited for cancer treatment.

Results: Of a total of 6458 individuals, 2123 (32.7%) were diagnosed with CVDs in the past year before cancer diagnosis. Compared to participants without a history of CVD, those who were diagnosed with CVD showed a higher risk of 5-year mortality (hazard ratio 1.259, 95% confidence interval 1.138–1.394). The extent to which the mortality risk differed between those with and without CVD was greater for individuals of low economic status and in those receiving their initial cancer treatment in a general hospital.

Conclusion: Patients with gastric cancer and hypertension, diabetes, or dyslipidemia diagnosed with CVD within 1 year before their cancer diagnosis had a higher mortality risk, emphasizing the importance of managing cancer patients with chronic disease and subsequent incidence of CVDs.

Key Words: Cardiovascular disease, gastric cancer, chronic disease, mortality

INTRODUCTION

Cancer is a leading cause of mortality and the largest barrier to enhancing life expectancy worldwide.[1] Specifically, gastric cancer is one of the most globally prevalent cancers. However,

specific regions have a higher risk, such as East Asia.[2] The highest incidence rates for gastric cancer are in the Asia-Pacific region and East Asia, with gastric cancer ranking second highest in cancer incidence and third highest in cancer mortality in South Korea.[3,4] The age-standardized incidence rate for gastric cancer was 29.6 per 100000 individuals, with a mortality rate of 6.7 per 100000 individuals, in 2019.[5] In response, Korea has introduced national, population-based gastric cancer screening to promote early detection in an attempt to decrease age-standardized gastric cancer incidence and mortality.[6] Nonetheless, the absolute number of incident and mortality cases of gastric cancer are expected to escalate due to the aging population, emphasizing the importance of continuously monitoring gastric cancer.[3]

While aging countries face an increased cancer burden, the incidences of chronic medical conditions are also rising, includ-

ing hypertension, diabetes, and dyslipidemia.[7] Chronic diseases can substantially affect cancer risk, especially since they share mutual risk factors, such as smoking, heavy alcohol drinking, diet, and physical inactivity.[8] Furthermore, diabetes and hypertension have also been shown to be associated with an increased risk of developing various cardiovascular complications.[9] For instance, diabetes and cardiovascular disease (CVD) are closely related, and CVDs are the most common cause of morbidity and mortality in diabetic patients.[10] Likewise, high blood pressure is a strong CVD risk factor, and hypertension can considerably escalate CVD risk and severity.[11] Dyslipidemia is another known CVD risk factor, and high low-density lipoproteins and low high-density lipoproteins have been linked to myocardial infarction and stroke.[12,13] This subject is of particular importance because CVD is a relatively common condition, with previous literature reporting a prevalence of approximately 21% and citing it as a leading cause of death, accounting for over one third of global deaths.[14,15] CVD is also a major cause of mortality in East Asian countries, including Korea, responsible for around one in every five deaths.[16]

Although the risk of developing CVD may be exaggerated by diabetes, hyper-tension, or dyslipidemia and although cancer and chronic diseases, such as diabetes, commonly co-occur in aging populations,[17] few studies have investigated the relationship between CVD and mortality in cancer patients with diabetes, hypertension, or dyslipidemia. Therefore, this study aimed to investigate whether recent history of CVD affects the 5-year mortality of patients with gastric cancer and these three chronic diseases. We hypothesized that participants with recently diagnosed CVD would have higher mortality than individuals without CVD. Furthermore, we investigated population subgroups based on age, economic status, insurance coverage type, and the type of healthcare institution first visited for cancer treatment to determine how these factors affect the previously described relationships.

MATERIALS AND METHODS

Study population

This study used the National Health Insurance Service (NHIS) Senior Cohort database, which includes a sample of around 8% (stratified random sampling by age, sex, and health insurance premium) of the entire older adult population aged between 60 to 80 years in 2008 (n=511953) and observed from 2002 to 2019. Additionally, this data included approximately 8% of older adults who turned 60 each year from 2008 to 2019. The NHIS cohort consisted of 545831 individuals. We aimed to analyze the effect of recent CVD history on 5-year mortality after a gastric cancer diagnosis in patients with select chronic diseases (i.e., hypertension, diabetes mellitus, or dyslipidemia). Patients with gastric cancer were defined based on a combination of major diagnosis codes [International Classification of Diseases (ICD)-10: C16] and cancer-specific insurance claim codes (V193) (n=27452). Patients with a history of other cancer types within 5 years of the gastric cancer diagnosis were excluded (n=22163). Furthermore, only those patients diagnosed before 2016 were included to ensure a 5-year observation period, and individuals diagnosed before 2008 (sampling index year) or who died within 90 days after diagnosis were excluded to avoid immortal time bias (n=12614). Also, the study population only included gastric cancer patients who received cancer treatment (e.g., gastrectomy, chemotherapy, or radiation therapy) at general or tertiary (superior general) hospitals within 1 year after diagnosis (n=9318). Finally, only patients with medical records of diagnosed hypertension (ICD-10: I10–I15), diabetes mellitus (ICD-10: E10–E14), or dyslipidemia (ICD-10: E78) within 1 year before their gastric cancer diagnosis (n=6458) were included in the analysis (Fig. 1).

Variables

The primary outcome measure was 5-year mortality. The major diagnosis code (ICD-10: C16) and the cancer-specific insurance claim code (V193) entry dates were used to determine the index date and those patients observed for 5 years or more.
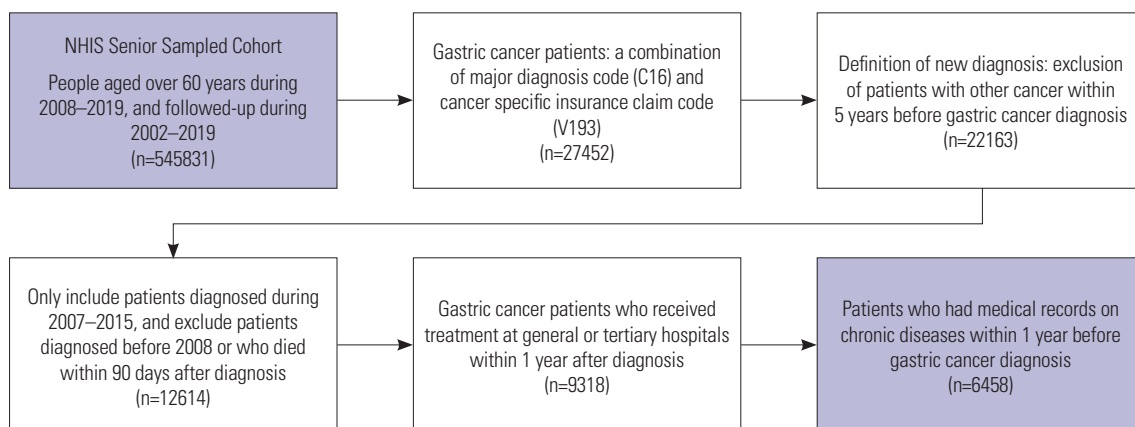

Fig. 1. Selection of the study population. NHIS, National Health Insurance Service.

The patients were classified based on their 5-year survival after diagnosis, categorized as having died or survived.

The primary independent variable was CVD within 1 year before the gastric cancer diagnosis, identified based on the patients' medical records. Patients with CVD (ICD-10: I11.0, I13.0, I13.2, I20–I25, I50, I60–I64, I67, I71, or I97.1) noted in their medical records within 1 year before the gastric cancer diagnosis were considered to have a history of CVD.

We also considered other independent variables, such as sex, age, economic status, insurance coverage type, residential area, Charlson Comorbidity Index (CCI), diagnosis year, cancer treatment type, and the type and size of healthcare institution visited for initial cancer treatment. Age was classified as ~60, 61–65, 66–70, or 70+ years. Regarding economic status and insurance coverage type, approximately 97% of individuals are covered by the NHI in Korea, but they are subdivided into two NHI beneficiary types. The NHI employee group includes employees, employers, and their household members who pay their insurance premiums based on salary. The NHI self-employed group includes all other individuals who pay their premiums based on income, property, and living standards. The remaining 3% of the population is covered by Medical Aid, including economically vulnerable individuals or those with physical disabilities. Medical Aid beneficiaries are exempt from paying insurance premiums. As a result, the type of insurance coverage and the insurance premium level reflect the economic level of the study participants. Thus, economic status was classified as low, middle-low, middle-high, or high based on the insurance premium level. Residential area was categorized as capital area, metropolitan, or rural. CCI was calculated by summing the comorbidities score, excluding cancer and CVD (myocardial infarction, congestive heart failure, peripheral vascular disease, and cerebrovascular disease), present in medical records during the 90 days after the first gastric cancer diagnosis. The diagnosis year was categorized based on the year 2010 (i.e., before or after 2010) because the policy that reduced the copayment level for cancer patients was completed in December 2009. The copayment level for covered medical services decreased from around 20%–30% to 10% in 2005 and from 10% to 5% in the end of 2009. The treatment type (surgery, chemotherapy, or radiation therapy) referred to the patient's treatment within 365 days of the gastric cancer diagnosis and was considered when adjusting for patient severity. The hospital where patients received their initial cancer treatment was characterized based on size (i.e., number of beds, defined based on 1000 or 2000 beds) and type (i.e., tertiary or general hospital) and were used as proxies of quality-of-care.

Statistical analysis
We first used frequencies and percentages and chi-square tests per independent variable to analyze the association between CVD history before gastric cancer diagnosis and 5-year mortality. Survival time was compared using Kaplan-Meier survival curves and the log-rank test according to CVD history. We also conducted survival analysis using a Cox proportional hazards model for 5-year mortality after adjusting for all independent variables. Additionally, Cox regression analyses based on age, economic status, and type of medical institution first visited for cancer treatment were conducted to identify whether differences exist according to these variables in the association between the existence of a CVD history and 5-year mortality. Survival analysis was conducted after adjusting for all covariates. All statistical analyses were performed using SAS statistical software, version 9.4 (SAS Institute, Cary, NC, USA).

Ethics approval
This study was conducted as an observational study in which all data were anonymized, de-identified secondary data. Ethical approval was waived by the Ethics Committee of the National Cancer Center of Korea (NCC2022-0232).

RESULTS

Table 1 presents the general characteristics of the study population. Of 6458 patients with gastric cancer and hypertension, diabetes, or dyslipidemia, 2123 (32.7%) had a history of CVD in the year prior. The total 5-year mortality rate was 24.5%. Individuals with a history of CVD had a higher 5-year mortality rate than those without CVD (31.9% vs. 20.9%).

Table 2 presents the effects of CVD on the 5-year mortality rate for patients with gastric cancer and hypertension, diabetes, or dyslipidemia. Fig. 2 shows the Kaplan-Meier survival curve results for individuals with and without a history of CVD. Patients with a history of CVD had a higher 5-year mortality risk [hazard ratio (HR): 1.259, 95% confidence interval (CI): 1.138–1.394] than those who did not.

Fig. 3 presents the results of additional analyses examining the influence of CVD on 5-year mortality by age, economic status, and type of institution visited for initial cancer treatment. These additional analyses revealed similar trends as those in the primary analysis, indicating that participants with a history of CVD had higher HRs than those without CVD, regardless of the additional factors. For example, individuals with a history of CVD had a higher 5-year mortality risk irrespective of age (~65 years: HR: 1.224, 95% CI: 1.037–1.446; 66+ years: HR: 1.250, 95% CI: 1.116–1.400).

We also found factors affecting how much the 5-year mortality risk differed between those with and without a history of CVD. Specifically, individuals with a history of CVD and low economic status had a higher HR (HR: 1.317, 95% CI: 1.136–1.526) than those with CVD and a high economic status (HR: 1.206, 95% CI: 1.047–1.388). Patients with a history of CVD receiving their initial cancer treatment at a general hospital also showed a higher risk of 5-year mortality (HR: 1.348, 95% CI: 1.142–1.592) than those with CVD at a tertiary hospital (HR:

Table 1. General Characteristics of the Study Population on 5-year mortality

Variables	Total	Died	Survived	p value
History of CVD events				<0.001
With	2123	677 (31.9)	1446 (68.1)	
Without	4335	908 (20.9)	3427 (79.1)	
Sex				0.028
Male	4353	1104 (25.4)	3249 (74.6)	
Female	2105	481 (22.9)	1624 (77.1)	
Age				<0.001
<60 years	1424	100 (7.0)	1324 (93.0)	
61–65 years	1167	262 (22.5)	905 (77.5)	
66–70 years	1433	348 (24.3)	1085 (75.7)	
>70 years	2434	875 (35.9)	1559 (64.1)	
Economic status				0.075
Low	1723	444 (25.8)	1279 (74.2)	
Middle-low	1420	312 (22.0)	1108 (78.0)	
Middle-high	1358	337 (24.8)	1021 (75.2)	
High	1957	492 (25.1)	1465 (74.9)	
Type of insurance coverage				<0.001
Medical aid	312	106 (34.0)	206 (66.0)	
National Health Insurance, self-employed	2022	461 (22.8)	1561 (77.2)	
National Health Insurance, employee	4124	1018 (24.7)	3106 (75.3)	
Residential area				0.034
Capital area	2366	595 (25.1)	1771 (74.9)	
Metropolitan	1591	352 (22.1)	1239 (77.9)	
Rural	2501	638 (25.5)	1863 (74.5)	
Charlson Comorbidity Index				<0.001
0	1170	223 (19.1)	947 (80.9)	
1	2148	461 (21.5)	1687 (78.5)	
2	1574	387 (24.6)	1187 (75.4)	
3+	1566	514 (32.8)	1052 (67.2)	
Year of diagnosis				0.352
Before reducing copayment from 10% to 5% (~2009)	1256	321 (25.6)	935 (74.4)	
After reducing copayment from 10% to 5% (2010~)	5202	1264 (24.3)	3938 (75.7)	
Type of cancer treatment				<0.001
Surgery with chemotherapy or radiation therapy	1116	476 (42.7)	640 (57.3)	
Only surgery	3528	490 (13.9)	3038 (86.1)	
Chemotherapy or radiation therapy	1814	619 (34.1)	1195 (65.9)	
Type of institution				<0.001
Tertiary hospital	4402	1006 (22.9)	3396 (77.1)	
General hospital	2056	579 (28.2)	1477 (71.8)	
Location of healthcare institution				0.841
Capital area	3560	879 (24.7)	2681 (75.3)	
Metropolitan	1776	427 (24.0)	1349 (76.0)	
Rural	1122	279 (24.9)	843 (75.1)	
Size of healthcare institution				0.127
<1000 beds	4211	1066 (25.3)	3145 (74.7)	
1001–1999 beds	1443	338 (23.4)	1105 (76.6)	
>2000 beds	804	181 (22.5)	623 (77.5)	
Total	6458	1585 (24.5)	4873 (75.5)	

Data are presented as n (%).
Cardiovascular diseases (CVD) include myocardial infarction, stable or unstable angina pectoris, heart failure, cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, cerebral arterial aneurysm, and aortic aneurysm.

Table 2. The Impact of CVD on 5-Year Mortality

Variables	HR	95% CI	p value
History of CVD event			
Yes	1.259	1.138–1.394	<0.001
No	1.000	-	-
Sex			
Male	1.189	1.066–1.325	0.002
Female	1.000	-	-
Age			
<60 years	1.000	-	-
61–65 years	3.340	2.651–4.209	<0.001
66–70 years	3.618	2.892–4.525	<0.001
>70 years	5.931	4.802–7.327	<0.001
Economic status			
Low	1.072	0.931–1.235	0.331
Middle-low	1.060	0.916–1.226	0.434
Middle-high	1.143	0.993–1.315	0.063
High	1.000	-	-
Type of insurance coverage			
Medical aid	1.246	0.996–1.557	0.054
National Health Insurance, self-employed	0.994	0.889–1.111	0.919
National Health Insurance, employee	1.000	-	-
Residential area			
Capital area	1.000	-	-
Metropolitan	0.905	0.754–1.085	0.281
Rural	1.006	0.872–1.160	0.935
Charlson Comorbidity Index			
0	1.000	-	-
1	0.932	0.793–1.095	0.393
2	1.011	0.856–1.194	0.898
3+	1.315	1.121–1.544	0.001
Year of diagnosis			
Before reducing copayment from 10% to 5% (~2009)	1.000	-	-
After reducing copayment from 10% to 5% (2010~)	0.797	0.702–0.905	<0.001
Type of cancer treatment			
Surgery with chemotherapy or radiation therapy	3.772	3.321–4.284	<0.001
Only surgery	1.000	-	-
Chemotherapy or radiation therapy	2.874	2.546–3.246	<0.001
Type of institution			
Tertiary hospital	1.000	-	-
General hospital	1.221	1.082–1.378	0.001
Location of healthcare institution			
Capital area	1.000	-	-
Metropolitan	1.015	0.859–1.200	0.862
Rural	0.942	0.793–1.120	0.501
Size of healthcare institution			
<1000 beds	0.939	0.781–1.130	0.506
1001–1999 beds	0.985	0.818–1.186	0.874
>2000 beds	1.000	-	-

CVD, cardiovascular diseases; HR, hazard ratio; CI, confidence interval.
CVD include myocardial infarction, stable or unstable angina pectoris, heart failure, cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage, cerebral arterial aneurysm, and aortic aneurysm.

1.191, 95% CI: 1.046–1.355).

DISCUSSION

This study investigated whether gastric cancer patients with hypertension, diabetes, or dyslipidemia diagnosed with CVD within 1 year before their cancer diagnosis have worse 5-year mortality than those without CVD. We found that individuals diagnosed with CVD had a higher mortality rate than those without, regardless of age, economic status, or the type of hospital visited for initial cancer treatment. Interestingly, however, these factors affected how much the mortality risk differed between those with and without a history of CVD. The difference be-

Fig. 2. Kaplan-Meier survival curves of the study participants. CVD, cardiovascular diseases.

tween the two groups was larger for individuals of lower economic status and those receiving their initial cancer treatment in a general hospital.

Hypertension and diabetes have been shown to be independently associated with increased mortality in cancer patients. A large meta-analysis concluded that pre-existing hypertension in patients with cancer is related to poorer outcomes, including an elevated risk of all-cause mortality.[18] Reports have also presented an association between pre-existing diabetes and mortality in patients with cancer.[19] Diabetic cancer patients have higher mortality rates than non-diabetic patients for most cancer sites, including stomach cancer. Furthermore, patients treated with an oral hypoglycemic agent or insulin had the highest mortality rate.[20] Although the relationship between mortality and hypertension or diabetes in patients with cancer is complex, the higher mortality rate may reflect more comorbidities at the time of the cancer diagnosis, which inevitably correlates with poorer survival.[20] Findings on dyslipidemia and cancer mortality have been less concurrent since most studies have focused on the effects of statin use in patients with dyslipidemia and cancer mortality. Several studies have suggested that statin use decreases cancer risk, whereas others concluded that no significant relationship exists between statin therapy and cancer mortality.[21] Apart from mortality, abnormal serum lipid levels may advance lymph node metastasis in early gastric cancer patients.[22]

This study provides further evidence that, excluding the independent associations described above, individuals with hypertension, diabetes, or dyslipidemia diagnosed with CVD within 1 year before a gastric cancer diagnosis have worse 5-year survival. These results are predictable, considering that hy-
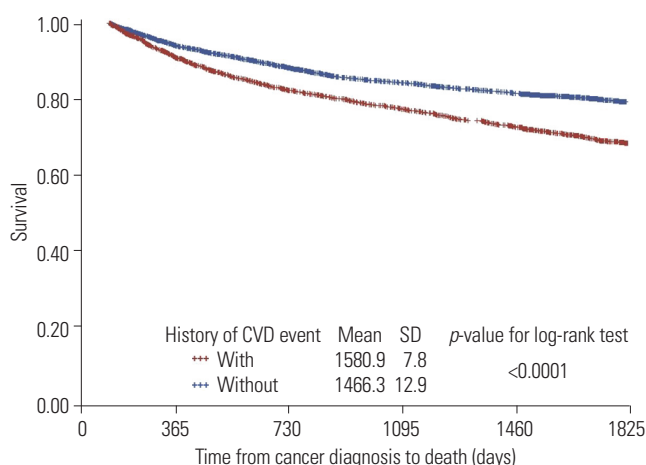

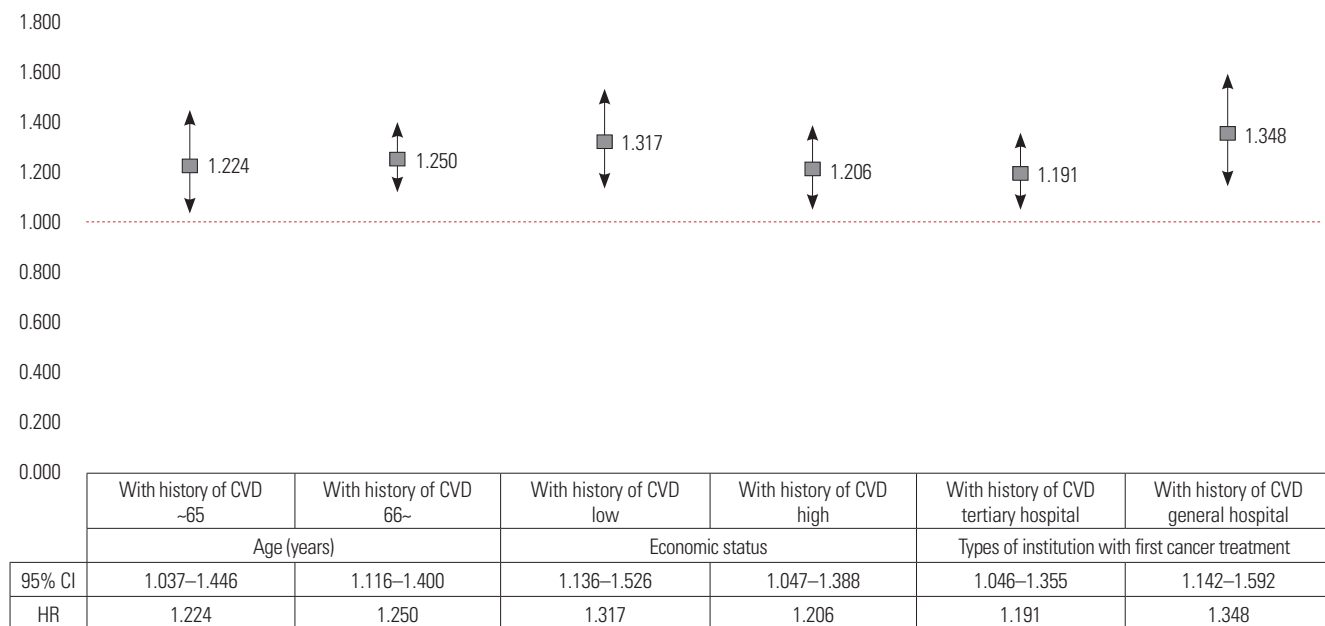|	With history of CVD ~65	With history of CVD 66~	With history of CVD low	With history of CVD high	With history of CVD tertiary hospital	With history of CVD general hospital
	Age (years)		Economic status		Types of institution with first cancer treatment	
95% CI	1.037–1.446	1.116–1.400	1.136–1.526	1.047–1.388	1.046–1.355	1.142–1.592
HR	1.224	1.250	1.317	1.206	1.191	1.348

Fig. 3. Impact of cardiovascular diseases on 5-year mortality according to age, economic status, and type of healthcare institution first visited for cancer treatment. CVD, cardiovascular diseases; HR, hazard ratio; CI, confidence interval.

pertension, diabetes, and dyslipidemia are known risk factors for many CVDs, increasing overall mortality risk.[13,23,24] Unsurprisingly, pre-existing CVD in patients with cancer has also been linked to worse survival in previous analyses, with studies suggesting that such tendencies may persist across different cancer types.[25] In addition, patients with cancer and baseline CVD may be less likely to receive cancer treatment than those without such comorbidities, potentially affecting overall survival.[26] Considering that the prevalence of CVD in patients with cancer is already high, these findings emphasize the importance of identifying and managing pre-existing CVD in patients with gastric cancer and chronic diseases, particularly because hypertension, diabetes, and dyslipidemia are common in older adults.[27]

In this study, higher mortality risk was identified in patients with gastric cancer and hypertension, diabetes, or dyslipidemia complicated by CVD before their cancer diagnosis, regardless of age, economic status, and type of medical institution first visited to receive cancer treatment. However, these factors affected the degree to which the mortality risk differed between patients with and without a history of CVD. The difference between the groups was larger for individuals of lower economic status and those receiving their initial cancer treatment in general hospitals. The economic status trends may reflect associations between a lower socioeconomic status and worse survival, regardless of tumor site.[28] Furthermore, hypertensive and diabetic patients belonging to higher income or education groups are more likely to use tertiary hospitals,[29] and tertiary hospitals are generally perceived to provide higher quality care. For example, there is a noticeable difference in the number of patients attending the five largest tertiary hospitals in Korea between the lowest and highest income group.[30] Overall, our study suggests that patients with gastric cancer and hypertension, diabetes, or dyslipidemia and a recent history of CVD have a higher 5-year mortality risk than those without CVD, highlighting the importance of monitoring and managing the quality of care for this patient population.

This study has some limitations. First, information on cancer severity, such as cancer stage at diagnosis, could not be identified due to data limitations. However, only patients diagnosed with gastric cancer for the first time and with a treatment history were included in the study population, partly overcoming this limitation. Individuals who died within 3 months of diagnosis were also excluded from the study population. Second, although this study accounted for various confounders, the possibility of residual confounding cannot be excluded entirely, as information on variables, such as education level or household size, was not available in the NHI claims data. Third, the level of NHI premium paid was used as a proxy of income to measure economic status. Last, as the outcome measure of this study was 5-year mortality, future studies are needed to further investigate the effect of CVD on long term outcomes of gastric cancer patients. Despite these limitations, this study is unique, as it is the first to investigate the effects of a recent history of CVD on 5-year mortality in patients with gastric cancer and diabetes, hypertension, or dyslipidemia using a large, representative dataset in Korea.

In conclusion, individuals with hypertension, diabetes, or dyslipidemia diagnosed with CVD in the year before their gastric cancer diagnosis had a higher 5-year mortality risk than patients without a history of CVDs. In addition, the extent to which the mortality risk differed between those with and without CVD was greater for individuals of lower economic status and those receiving their initial treatment for cancer in general hospitals. These findings highlight the importance of monitoring and managing patients with gastric cancer and chronic diseases complicated by CVD.

DATA AVAILABILITY STATEMENT

Data can be obtained for research purposes after application to the National Health Insurance Service.

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AUTHOR CONTRIBUTIONS

Conceptualization: Kyu-Tae Han and Woorim Kim. Data curation: Kyu-Tae Han. Formal analysis: Kyu-Tae Han. Funding acquisition: Woorim Kim. Investigation: all authors. Methodology: all authors. Project administration: Woorim Kim. Resources: Kyu-Tae Han. Supervision: Woorim Kim. Validation: all authors. Visualization: Kyu-Tae Han and Woorim Kim. Writing—original draft: Woorim Kim. Writing—review & editing: Kyu-Tae Han and Woorim Kim. Approval of final manuscript: all authors.

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