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Survival benefit of metformin use according to cancer diagnosis in diabetic patients with metabolic syndrome

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ABSTRACT

Background: Metabolic syndrome (MetSyn) is a disease cluster causing cardiovascular disease, cancer, and high mortality. Metformin is the most common antidiabetic agent inhibiting the tumorigenesis and insulin resistance of MetSyn. We describe the association between metformin intake and survival of patients with type 2 diabetes mellitus (T2DM) and MetSyn, according to the presence of cancer.

Methods: We analyzed the clinical characteristics and all-cause mortality of patients with T2DM and MetSyn using a 5-year dataset between January 1, 2009 and December 31, 2013 derived from the Korean National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS). Cox proportional hazards regression models were used to investigate metformin effects adjusted for other potential confounding variables.

Results: Among a total of 43,043 patients with both MetSyn and T2DM, 24,725 patients (57.4 %) received metformin regularly. Female sex, high income, regular exercise, and metformin use were good prognostic factors, whereas hypertension, current smoking, cancer, and diabetes medication (except metformin) were poor prognostic factors. After adjustment for possible confounding variables, metformin showed a significant effect on patient survival (hazard ratio [HR], 0.68; 95 % confidence interval [CI], 0.63–0.75; $p < 0.001$). The effect of metformin was pronounced on the group of patients with liver, lung, colorectal, or prostate cancers (HR, 0.57; CI, 0.46–0.70).

Conclusions: Metformin intake may be related to favorable survival among patients with T2DM and MetSyn. The efficacy might be more remarkable in those with liver, lung, colorectal, and prostate cancers. The potential benefit of metformin in patients with these risk factors should be further investigated.

1. Introduction

Metabolic syndrome (MetSyn) is a cluster of risk factors predisposing cardiovascular disease development. In addition to cardiovascular disease and type 2 diabetes mellitus (T2DM), recent studies have reported a relationship between MetSyn and different types of cancer(Gyamfi et al., 2022). Notably, MetSyn may play an important role in the etiology of some cancers, including liver (Borena et al., 2012), colorectal (Jin et al., 2022), and bladder cancers in men; and endometrial (Rosato et al., 2011), pancreatic, postmenopausal breast (Agnoli et al., 2010, Osaki et al., 2012), and colorectal cancers (Aleksandrova et al., 2011) in women. In the Korean population, the metabolic risk profile was reported to be related to a high risk of earlier-onset colorectal cancer (Jin et al., 2022), and colon cancer in men and gallbladder and biliary tract cancer in women (Ko et al., 2016).

As MetSyn is considered to increase cardiovascular morbidity and mortality, there has been much effort to modify the risk factors of MetSyn (Lim et al., 2011). However, due to a high-fat and/or high-

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calorie diet and physical inactivity, the prevalence of MetSyn in Korea has increased up to 27.9% in men, and 17.9% in women in 2018 (Huh et al., 2021). In addition to lifestyle modifications, metformin, an oral antidiabetic drug belonging to the biguanide class of drugs, was found to reduce the MetSyn incidence by 17% compared to placebo in a previous large randomized clinical trial (Orchard et al., 2005). Metformin has pharmacological activities which act to improve hyperglycemia and insulin resistance, and also control AMPK and mTOR signaling (Dowling et al., 2012, Hua et al., 2023, Quinn et al., 2013). Recent studies reported that metformin use was related to the survival outcome of the lung, breast, colorectal, prostate, or pancreatic cancer patients with T2DM (Brancher et al., 2021, Scarton et al., 2022, Tarhini et al., 2022), whereas metformin did not improved an invasive disease-free survival of the patients with early breast cancer without T2DM (Goodwin et al., 2022).

In addition, according to the diagnostic criteria for MetSyn (Alberti et al., 2009, Alberti et al., 2006, Grundy et al., 2005), diabetic patients are required to meet at least two criteria other than dysglycemia for a diagnosis of MetSyn. As a result, there are T2DM patients with MetSyn and T2DM patients without MetSyn, according to whether they exhibit obesity, dyslipidemia, and raised blood pressure. In a study performed by Kim *et al.*, T2DM patients with MetSyn showed higher insulin resistance compared to T2DM patients without MetSyn (Kim et al., 2008). Considering that hyperinsulinemia and insulin resistance are the possible main mechanisms of metabolic syndrome-induced cancer as well as for inducing disease progression (Quinn et al., 2013), metformin effect on survival may be distinct in the cancer patients with T2DM and MetSyn. In this study, we hypothesized that metformin is useful for improving survival, especially in cancer patients with T2DM and MetSyn. We aimed to find the association between regular intake of metformin and all-cause mortality among patients with T2DM and MetSyn using a large population-based health survey and screening database in Korea. In addition, we also analyzed the difference in metformin efficacy according to the presence of various types of cancer.

2. Materials and methods

2.1. Study population from a national cohort database (NHIS-HEALS) in South Korea

In this study, we analyzed a large national cohort database, known as the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) (Kim et al., 2015), which was established by the National Health Insurance Service (NHIS). Under the national health insurance system, which is compulsory for all Korean citizens to participate in, the NHIS manages and maintains the national health examination programs recommended for all insured employees or self-employed persons over 40 years of age. These health examinations must be taken at least once biennially. The cohort data which the NHIS-HEALS released in 2015 represents roughly a 10% random sample of the population who underwent a health examination in 2002 and 2003. The cohort provides information for each participant, including the basic demographic information (i.e., age, sex, death, region, income quantiles, etc.), medical records, health examination records (i.e., waist, body mass index [BMI], systolic blood pressure [SBP], diastolic blood pressure [DBP], fasting glucose, total cholesterol, triglyceride, high-density lipoprotein [HDL], low-density lipoprotein [LDL], medication, etc.), and lifestyle information (exercise time, smoking, drinking, etc.). The variables (waist circumference, HDL and LDL cholesterol) necessary for defining a metabolic syndrome and lifestyle-related variables were mostly available from 2009 (Seong et al., 2017). The presence of diabetes mellitus was defined as a subject with either a prescription record of diabetes medication within the health insurance claim data, which were routinely collected for payment of health services in Korea or a fasting blood glucose $\geq$ 126 mg/dL during a health examination.

The schema plot (Fig. 1) depicts the overall steps taken to retrieve our study population from the NHIS-HEALS database. The NHIS-HEALS database is a public database, which is available with appropriate request on the official website (https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do). Briefly, we first obtained a dataset of 514,866 patients in NHIS-HEALS. Next, we excluded the patients without health screening information between 2009 and 2010. Additionally, we also excluded

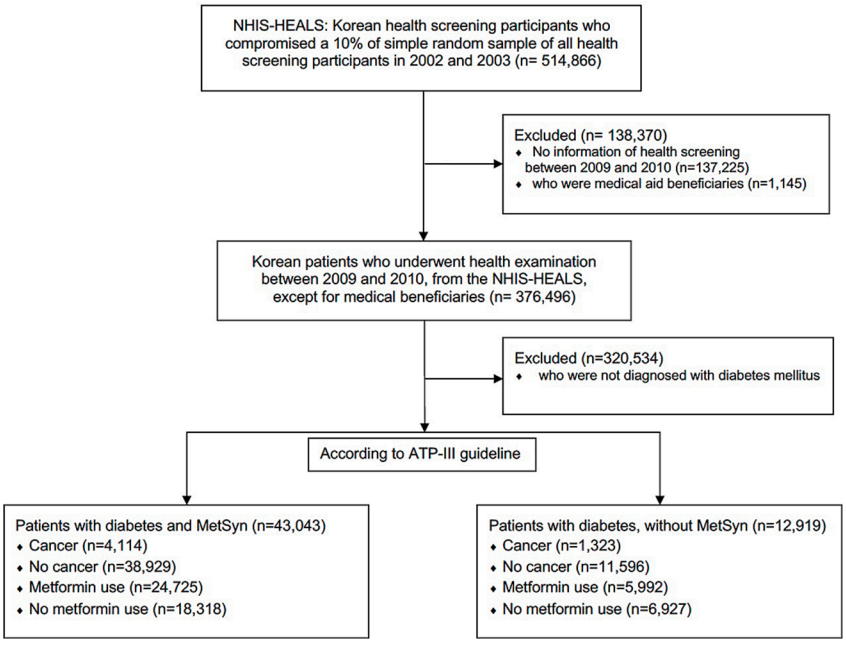

Fig. 1. Flow diagram depicting the overall steps of extracting the study population from the health-screening adult participants in 2002 and 2003 from Korean NHIS-HEALS cohort. *Note:* Patient with T2DM and MetSyn (n = 43,043) and without MetSyn (n = 12,919) were enrolled among the health-screening adult participants in 2002 and 2003 from Korean NHIS-HEALS cohort, and followed until the end of 2013. NHIS-HEALS, National Health Insurance Service-National Health Screening Cohort.

data of medical aid beneficiaries who may complicate our analyses; they had a different health screening system in the NHIS, and thus it was not possible to gain all of the required information (Seong et al., 2017). As a result, we were able to include 376,496 participants who completed their health examinations over two consecutive years, 2009 and 2010. If any participant underwent more than one examination, we used the results from the last examination. Then, we identified 55,962 (14.86%) subjects with T2DM and classified them according to the presence of MetSyn according to the modified ATP-III definition. Finally, to constitute our baseline study population, we selected 43,043 subjects (11.4%) who had both MetSyn and diabetes. Follow-up was conducted until the end of 2013, unless a participant was disqualified from the health services. The primary outcome of this study was death from all causes, out of which information was provided by the National Statistical Office and available in the NHIS-HEALS.

According to the 10th revision of the International Classification of Diseases (ICD-10), we selected participants with cancer using medical diagnostic codes starting with C and D0–D4 and participants with diabetes using codes starting with E10–E14, respectively. Based on the maximum insurance premium by income quantiles for insurance subscribers at workplaces, we categorized the participants into three income levels: low income (<30%), middle income (≥30%, <70%), and high income (≥70%).

2.2. Definition of metabolic syndrome

In this study, we defined MetSyn using the modified ATP-III guideline, as suggested by the American Heart Association and the National Heart, Lung, and Blood Institute (NHLBI) (Grundy et al., 2005) with the incorporation of the ethnic-specific values for waist circumference for the Asia-Pacific region: (WHO (World Health Organization), 2000).

1. Elevated waist circumference, ≥90 cm in men/≥80 cm in women
2. Elevated triglyceride, ≥150 mg/dL or drug treatment for hypertriglyceridemia
3. Reduced HDL-C, <40 mg/dL in men/<50 mg/dL in women, or drug treatment for reduced HDL-C
4. Elevated blood pressure, ≥130 mmHg SBP or ≥85 mmHg DBP or drug treatment for hypertension
5. Elevated fasting glucose, ≥100 mg/dL or drug treatment for elevated glucose

Confirmation of any three of the five criteria above constituted a diagnosis of MetSyn.

2.3. Statistical analysis

Differences in baseline characteristics between metformin and non-metformin use groups were tested using t-statistics for continuous variables and chi-square statistics for categorical variables. During the initial data exploration, the functional shape of each variable was marginally investigated using a nonparametric method (Meira-Machado et al., 2013). Cox proportional hazards (PH) regression models were used to investigate the metformin effects adjusted for potential confounding effects of other variables. For assessing the heterogeneous metformin effects on patients with different types of cancer, we tested the interaction terms between metformin and cancer groups. Avoiding over-parameterization, we performed model selection based on the Akaike information criterion with three different algorithms: stepwise selection, forward selection, and backward selection (Hastie, 2005). The underlying proportional hazards assumptions of the Cox PH regression models were validated through Schoenfeld residual tests. For propensity score matching, we used the nearest neighbor matching method with a caliper size of 0.01 and evaluated the matching quality according to the covariate balances between two groups in the matched set. For measuring covariate balances, we used standardized differences in the means between the two groups, and considered the covariate balance achieved as long as the absolute standardized difference was less than 0.2. All standardized differences in the covariates were less than 0.05. To account for the matched pairs, we used the Cox regression model with the sandwich standard errors for time to all-cause mortality. All statistical analyses were performed using the R software 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria; www.r-project.org) (Team, 2019). A p-value <0.05 was considered statistically significant for all two-sided tests.

2.4. Ethics statement

The protocol was approved by the Institutional Review Board (IRB) of Yonsei University Health System, Seoul, Republic of Korea (4-2019-0464). Informed consent was waived by the decision of IRB. All methods were performed in accordance with the relevant guidelines and regulations by including a statement in the methods section.

3. Results

3.1. Patient characteristics

Baseline characteristics of the study population are summarized in Table 1. Among a total of 43,043 patients with both MetSyn and diabetes, 33,814 (78.56%) were prescribed diabetes medication; 24,725 (57.44%) and 18,318 (42.56%) patients were assigned to the metformin and non-metformin groups, respectively. Regarding basic demographic variables, there were more males in the metformin group. In terms of bio-clinical laboratory results, individuals in the metformin group had lower levels of SBP, DBP, total cholesterol, triglyceride, and LDL cholesterol compared to those in the non-metformin group. Furthermore, the patients in the metformin group tended to take more medication (excluding metformin) for dyslipidemia, hypertension, and diabetes mellitus compared to those in the non-metformin group. As for lifestyle variables, current and ex-smokers were more common in the non-metformin group, whereas exercise time showed no significant difference between the two groups. The prevalence of cancer was 9.82% for the metformin group and 9.20% for the non-metformin group.

3.2. Overall effect of metformin when adjusted for possible confounding variables

The application of different model selection criteria led to an identical final multivariable Cox regression model. All of the covariates included in the model are listed in Table 2, in which an estimated hazard ratio for each variable, with its 95% confidence interval (CI), is present. The estimated hazards ratio for metformin was 0.68 (CI, 0.63 – 0.75; p <0.001), which supports a statistically significant effect of metformin on survival after appropriately adjusting for potential confounding variables listed in Table 2 (sex, age, BMI, SBP, gamma-gtp, creatinine, current medication, income classes, exercise time, smoking status, and cancer status). Fig. 2 shows the statistically significant separation (p <0.001) between the adjusted survival curves of non-metformin and metformin groups.

3.3. Heterogeneous metformin effects on different cancer types

Upon verifying the overall effect of metformin, we further explored the effects of metformin on different types of cancer. Our study population consisted of eight major cancer types (colorectal, breast, prostate, stomach, liver, uterine cervix, lung, and thyroid) and other minor cancers (Supplementary Table 1) classified by the cancer prevalence in the Korean general population. First, we performed a search for assessing metformin effects on patients with major cancer types using interaction terms between metformin and cancer types (Supplementary Table 2). We found that four cancer types, including colorectal, prostate, lung,

Table 1
Baseline characteristics of the study population according to metformin intake among patients with T2DM and MetSyn in the Korean NHIS-HEALS cohort in 2022 and 2003.

Variables	Metformin		*p*-value
	Use (%) (n = 24,725)	Non-use (%) (n = 18,318)	
Sex, male	13,318 (53.86)	11,245(61.39)	<0.001
Age, years (mean ± SD)	62.93 ± 8.64	62.04 ± 8.99	<0.001
BMI, kg/m^2 (mean ± SD)	25.31 ± 3.09	25.38 ± 2.98	0.024
Waist circumference, cm (mean ± SD)	86.82 ± 8.06	87.01 ± 7.76	0.016
SBP, mmHg (mean ± SD)	129.84 ± 15.11	131.70 ± 15.64	<0.001
DBP, mmHg (mean ± SD)	78.77 ± 9.78	80.22 ± 10.30	<0.001
Fasting glucose, mg/dL (mean ± SD)	138.27 ± 46.69	138.7 ± 40.35	0.319
Total cholesterol, mg/dL (mean ± SD)	190.26 ± 42.61	199.85 ± 43.85	<0.001
Triglyceride, mg/dL (mean ± SD)	179.13 ± 112.94	191.89 ± 120.55	<0.001
HDL, mg/dL (mean ± SD)	50.32 ± 28.37	51.12 ± 29.56	0.005
LDL, mg/dL (mean ± SD)	106.25 ± 41.41	112.78 ± 42.66	<0.001
Gamma-gtp, U/L (mean ± SD)	48.61 ± 72.02	59.04 ± 86.27	<0.001
Creatinine, mg/dL (mean ± SD)	1.06 ± 1.07	1.14 ± 1.32	<0.001
Chronic diseases and medication			
Dyslipidemia	15,279 (61.80)	8,296 (45.29)	<0.001
Hypertension	19,687 (79.62)	13,056 (71.27)	<0.001
Diabetes medication except metformin	20,530 (83.03)	9,089 (49.62)	<0.001
Income classes			0.692
Low income	4,092 (16.55)	2,975 (16.24)	
Middle income	6,892 (27.87)	5,129 (28.00)	
High income	13,741 (55.58)	10,214 (55.76)	
Exercise time (more than 30 min)			0.695
0–1 times per week	10,349 (41.86)	7,612 (41.55)	
2–4 times per week	7,081 (28.64)	5,314 (29.01)	
5–7 times per week	7,102 (28.72)	5,273 (28.79)	
Smoking (100 cigarettes in lifetime)			<0.001
Non-smoker	15,554 (62.91)	10,647 (58.12)	
Ex-smoker	4,697 (19.00)	3,815 (20.83)	
Current smoker	4,078 (16.49)	3,551 (19.39)	
Cancer status, cancer	2,429 (9.82)	1,685 (9.20)	0.030
Stomach	266 (1.08)	197 (1.08)	1.000
Liver	356 (1.44)	274 (1.50)	0.662
Colorectal	345 (1.40)	222 (1.21)	0.108
Breast	98 (0.40)	56 (0.31)	0.140
Cervical	28 (0.11)	24 (0.13)	0.701
Lung	168 (0.68)	118 (0.64)	0.700
Prostate	443 (1.79)	321 (1.75)	0.788
Thyroid	172 (0.70)	117 (0.64)	0.512
Other cancers	553 (2.24)	356 (1.94)	0.040

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein cholesterol;
LDL, low density lipoprotein cholesterol; Gamma-gtp, gamma-glutamyl transpeptidase, NHIS-HEALS, National Health Insurance Service-National Health Screening Cohort; SD, standard deviation
Note: data presented as the mean ± SD or %. *p-values* comparing between metformin use and non-use patients, continuous variables between two groups were tested by using the t-statistics, categorical variables between two groups were tested by using the chi-square statistics.

and liver cancers, act in a similar way from the perspective of metformin effect. As such, we aggregated patients with these four cancer types together and classified them as cancer group 1 (CG1). We classified the other four major cancer types, including stomach, thyroid, breast, and cervical cancers as cancer group 2 (CG2), all the other minor cancers as cancer group 3 (CG3) and patients without cancer as no cancer group (no CG). All of the minor cancers belonging to CG3 are listed in Supplementary Table 3.

For each cancer group as well as the no CG group, we estimated the hazard ratios between non-metformin (referent) and metformin groups; these are summarized in Fig. 3 (No CG: HR, 0.72; CI, 0.64 – 0.80; p <0.001; CG1: HR, 0.57; CI, 0.46 – 0.70; p < 0.001; CG2: HR, 0.82; CI, 0.55 – 1.23; p = 0.329; CG3, HR, 0.59; CI, 0.44 – 0.80; p < 0.001). Our results suggest the heterogeneous effects of metformin. Our hypothesis was formally tested using an interaction term between metformin and cancer group variables (Supplementary Tables 4–7). Fig. 4 compares the adjusted survival curves of the non-metformin with those of the metformin group in no cancer group and three different cancer groups, where no CG (A), CG1 (B) and CG3 (D) indicate significant separation (p < 0.001).

Table 2
Adjusted hazard ratio for the association of metformin with all-cause mortality among patients with T2DM and MetSyn in the Korean NHIS-HEALS cohort in 2002 and 2003.

Variables	HR[a]	95 % CI	*p*-value
Metformin	0.68	0.63–0.75	<0.001

Abbreviations: HR[a], adjusted hazard ratio; CI, confidence interval; NHIS-HEALS, National Health Insurance Service-National Health Screening Cohort.
Note: Multivariable Cox regression model was adjusted for sex, age, body mass index, systolic blood pressure, gamma-glutamyl transpeptidase., creatinine, hypertension, diabetes medication except metformin, income classes, exercise time, smoking, cancer status.

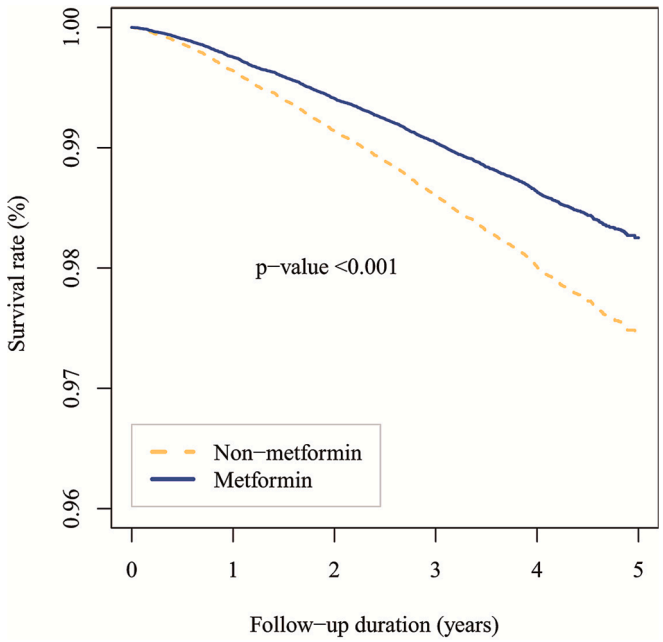

Fig. 2. Comparison of adjusted survival curves between the metformin and non-metformin groups in patients with T2DM and MetSyn among Korean NHIS-HEALS cohort in 2002 and 2003. *Note:* After adjusting for potential confounding variables (sex, age, BMI, SBP, gamma-gtP, creatinine, current medication, income classes, exercise time, smoking status, and cancer status) using Cox proportional hazards (PH) regression models, the adjusted survival curves of non-metformin and metformin group showed a statistically significant separation (p < 0.001). NHIS-HEALS, National Health Insurance Service-National Health Screening Cohort.

4. Discussion

The current study suggests that the use of metformin may be beneficial for the survival of patients with T2DM and MetSyn using a nationwide population-based health survey and screening database. Our results also showed that metformin significantly reduced all-cause

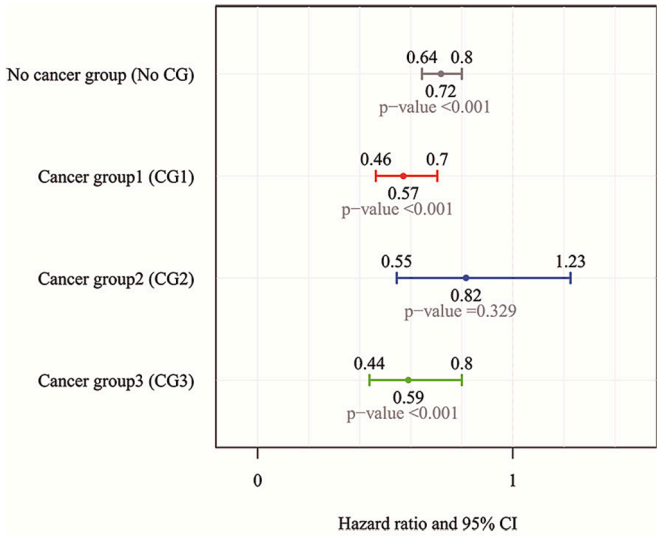

Fig. 3. Comparison of metformin effects according to cancer groups in patients with T2DM and MetSyn among Korean NHIS-HEALS cohort in 2002 and 2003. *Note*: Adjusted hazard ratios for all-cause mortality are marked by solid circles. Horizontal bars with vertical line segments indicate 95 % confidence intervals. The models were selected based on the Akaike information criterion with three different algorithms: stepwise selection, forward selection, and backward selection. The underlying proportional hazards assumptions of the Cox PH regression models were validated through Schoenfeld residual tests. Cancer group 1 includes liver, colorectal, lung, and prostate cancers; cancer group 2 includes stomach, thyroid, breast, and cervical cancers; cancer group 3 includes all other cancers excluded from cancer groups 1 and 2. Significant metformin effects were shown in no cancer group ($p < 0.001$), cancer group 1 ($p < 0.001$) and cancer group 3 ($p < 0.001$), respectively. NHIS-HEALS, National Health Insurance Service-National Health Screening Cohort.

mortality in patients diagnosed with T2DM, and that its efficacy might be related to a group composed of individuals with certain types of cancer (CG1: including liver, colorectal, lung, and prostate cancers).

Previous studies showed that metformin (dimethyl-biguanide) lowered cancer-related mortality in diabetic patients more compared to insulin or sulfonylurea (Bowker et al., 2006, Landman et al., 2010). These findings were thought to be due to metformin involving several drug mechanisms capable of preventing cancer progression. Hyperinsulinemia allows insulin-like growth factor (IGF)-1 and its receptor, IGF-1R, to stimulate cancer cell proliferation and metastasis (Pollak, 2008). The binding of insulin to the relevant receptors also triggers the activation of multiple cellular signaling cascades, including PI3K/Akt/mTOR and MEK/ERK pathways (Arcidiacono et al., 2012, Hua et al., 2023). Hypoxia of adipose tissue can activate the production of inflammatory cytokines and mediators are known to play certain roles in regulating malignant transformation or cancer progression (Giovannucci et al., 2010). Metformin is also known to play a major role in improving hyperglycemia and insulin resistance, as well as normalizing hyperactivation of cell proliferative pathways, all of which are important underlying mechanisms.

Metformin improved the survival after curative resection of pancreatic (Jang et al., 2017), rectal (Ki et al., 2017), and gastric cancers (Lee et al., 2016), or induced complete response to neoadjuvant chemotherapy for breast cancer (Jiralerspong et al., 2009) in T2DM patients. However, there has been a discordance regarding the efficacy of metformin according to the type of cancer (Gandini et al., 2014), study outcome (incidence or mortality), the difference in confounders (Gandini et al., 2014), and sex (Park et al., 2017).

In the present study, we hypothesized that metformin is effective for T2DM patients with MetSyn in terms of improving survival, especially in patients with certain types of cancer. Consistent with previous reports, metformin improved the overall survival among all of the 55,962 diabetic patients in the current study. However, metformin efficacy was more evident in patients with diabetes mellitus and MetSyn (HR, 0.79; 95% CI, 0.73–0.86; $p < 0.001$) than in diabetic patients without MetSyn (HR, 0.86; 95% CI, 0.74–1.01; $p = 0.0595$). Therefore, we focused on patients with T2DM and MetSyn.

Diabetes medications, except for metformin, were related to higher patient mortality, which was consistent with previous reports (Bowker et al., 2006, Landman et al., 2010, Libby et al., 2009). Among the diabetic medications other than metformin prescribed in this study, insulin secretagogues (sulfonylurea and meglitinide) and insulin accounted for 72.05% of all cases. Since these agents did not play a role in relieving insulin resistance or hyperinsulinemia, they might not prevent cancer progression of the patients compared to those with metformin. Moreover, these medications were generally prescribed to treat more advanced diabetic patients than those who were treated with metformin or lifestyle modification only. Therefore, the poor survival outcome was probably influenced by the poorly controlled diabetes mellitus.

Unlike other diabetes medications, metformin reduced the all-cause mortality in all of the patients with T2DM and MetSyn after adjustment for possible confounding variables (Table 2). Considering the significant differences between metformin use and non-use groups, we also derived the propensity scores nonparametrically using clinical variables. After propensity score matching, we observed no significant differences in terms of covariates between the metformin use and non-use groups (Supplementary Table 8). As shown in Supplementary Table 9, we found no major differences in the analysis results obtained by statistical methods after adjusting for potential confounding effects between using multivariable regression analysis and using propensity score matching. Moreover, we did not observe any strong indication of time-dependent patterns in the metformin variable that necessitates the consideration of time-dependent regression models.

In this study, the presence of hypertension was generally verified by hypertension medication intake. Since the Korean hypertension treatment rate is similar to the hypertension detection/awareness rate (Collaboration, 2021), the patients who are aware of hypertension are likely to take hypertension medication. Although we suggest that the deleterious effect of hypertension was mostly influenced by the hypertension itself, the possible influences by the unawareness of hypertension and hypertension medication type were not fully investigated in this study. As BMI showed a quadratic functional association with patients' time to mortality, the term was incorporated into our models. In previous studies, all-cause mortality was the lowest in the BMI 20.0–25.0 kg/m^2 group; the correlation was influenced by sex, ethnicity, age, smoking history, and cancer type (Jee et al., 2006).

In addition, the efficacy of metformin might be favorable in patients with certain types of cancer (CG1, including liver, colorectal, lung, and prostate cancers) in this study. In previous studies and meta analyses, colorectal, prostate, pancreas, liver, lung, and postmenopausal breast cancers showed significant correlations with metabolic syndrome and metformin intake (Esposito et al., 2012, Gandini et al., 2014, Park et al., 2017), which was consistent with the result of the present study. Several cancers in CG1 were reported to have tumorigenesis mechanisms possibly modified by metformin treatment. A two-fold or higher risk of liver cancer was reported in patients with T2DM than in those without T2DM (Giovannucci et al., 2010). Circulating IGF-1 and IGF-2 levels were positively associated with the risk of colorectal and prostate cancers (Allen et al., 2007, Renehan et al., 2004). However, the prevalence rates of certain cancer types were too low to be analyzed as an independent cancer group.

This study had several limitations. First, since this study lacked information on several lifestyle factors, including the duration of T2DM or MetSyn and the stage and treatment of cancer, which could influence the mortality of study participants. In addition, the definition of diabetes mellitus was based on the values available from the NHIS-HEALS cohort; therefore, some diabetic patients with normal fasting glucose and

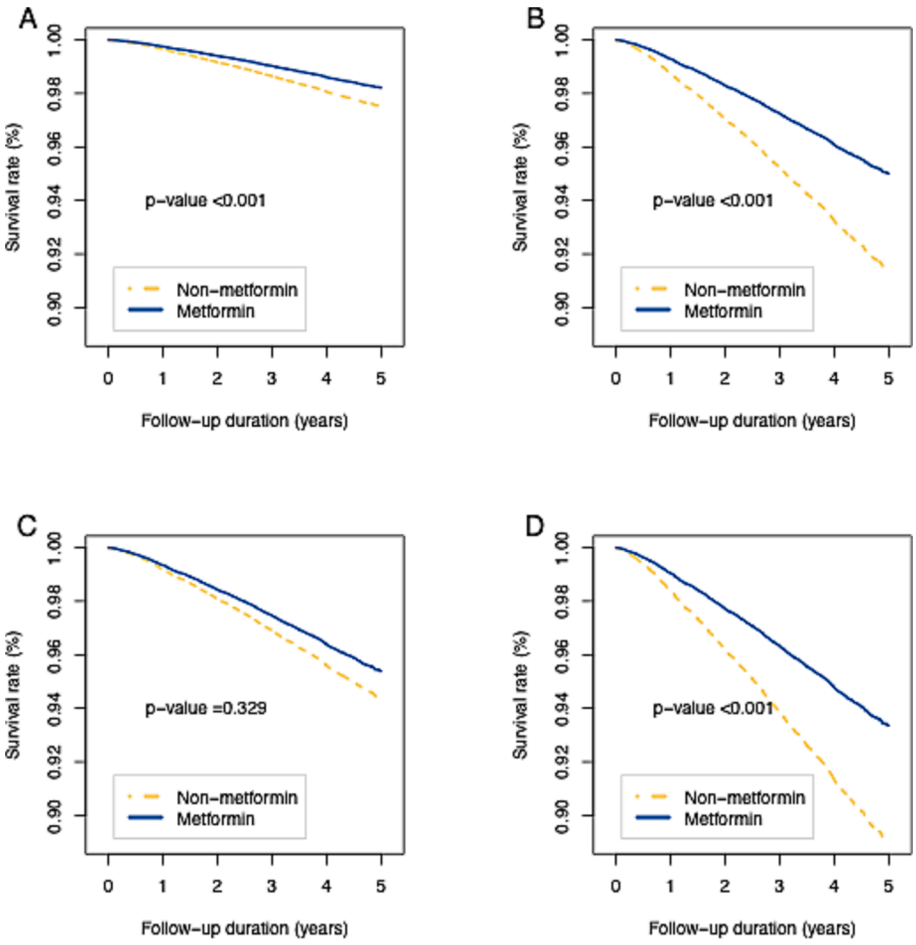

Fig. 4. Adjusted survival curves of the metformin and non-metformin groups in no cancer group and three different cancer groups with T2DM and MetSyn among Korean NHIS-HEALS cohort in 2002 and 2003. Note: (A) No cancer group; (B) Cancer group 1 includes liver, colorectal, lung, and prostate cancers; (C) Cancer group 2 includes stomach, thyroid, breast, and cervical cancers; (D) Cancer group 3 includes all other cancers excluded from cancer groups 1 and 2. After adjusting for potential confounding variables (sex, age, BMI, SBP, gamma-gtP, creatinine, current medication, income classes, exercise time, smoking status, and cancer status) using Cox proportional hazards (PH) regression models, the separations of adjusted survival curves of non-metformin and metformin groups in (A) cancer group 1 and (C) cancer group 3 were significant ($p < 0.001$). NHIS-HEALS, National Health Insurance Service-National Health Screening Cohort.

without awareness of diabetes mellitus may not have been analyzed in this study. Second, we tried to adjust for potential confounding variables as much as possible; however, the different baseline clinical characteristics between groups using and not using metformin could not be completely compensated. Third, information regarding the regular healthcare, diagnosis, duration and control of diabetes, dose levels, and the exact duration of metformin use were not included in the database. Fourth, this study only used 5 year-information from the database for the cohort, due to the variables essential for the diagnosis of MetSyn. The cancer-specific survival was not analyzed. Fifth, since we used the general populational cohort, metformin showed insufficient efficacy due to low prevalence in several types of cancer. Therefore, we combined different types of cancer with similar trends into a group to analyze metformin efficacy. As a result, the grouping of cancer types was somewhat arbitrary, and the efficacy in each cancer type was not clearly explained.

Despite some limitations, this study has clinical implications as it suggests the potential role of metformin in patients with T2DM and MetSyn using a large nationwide database. Metformin efficacy in MetSyn and the specific cancer type should be confirmed in a well-designed prospective clinical study.

CRediT authorship contribution statement

Ji Soo Park: Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Soo Jin Moon:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation. **Hyung Seok Park:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Sang-Hoon Cho:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation.

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Declaration of competing interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pmedr.2024.102928.

Data availability

Data will be made available on request.

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