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Original Article

Impact of metformin on survival outcome in ovarian cancer: a nationwide population-based cohort study

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ABSTRACT

Objective: Investigation of new drugs (INDs) is a tremendously inefficient process in terms of time and cost. Drug repositioning is another method used to investigate potential new agents in well-known drugs. This study assessed the survival impact of metformin medication on ovarian cancer.

Methods: A national sample cohort of the Korean National Health Insurance Service Data was analyzed. Cox proportional hazards regression was used to analyzing hazard ratios (HRs) and 95% confidence intervals (CIs) after adjusting for underlying diseases and medications as confounding factors for overall survival (OS) and cancer-specific survival (CSS).

Results: A total of 866 eligible patients were included from among 1,025,340 cohort participants. Among them, 101 (11.7%) were metformin users. No difference in OS was observed between non-users and users. No difference in OS was observed according to age and Charlson Comorbidity Index. Long-term metformin use (≥720 days) was associated with better OS (adjusted HR=0.244; 95% CI=0.090–0.664; p=0.006). A multivariate Cox proportional hazards model showed that long-term metformin use was an independent favorable prognostic factor for OS (HR=0.193; 95% CI=0.070–0.528; p=0.001) but not for CSS (HR=0.599; 95% CI=0.178–2.017; p=0.408).

Conclusion: Long-term metformin use reduced all-cause mortality, but not CSS in ovarian cancer. Whether metformin itself reduces deaths because of ovarian cancer requires further investigation.

Keywords: Ovarian Neoplasms; Metformin; Survival; Treatment Outcome

INTRODUCTION

Ovarian cancer is one of the 10 most common cancers in women, with an estimated 295,414 new cases and 184,799 deaths worldwide in 2018 [1]. Ovarian cancer is also one of the most

Author Contributions

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common gynecologic malignancies, with an estimated 21,750 new diagnoses and 13,940 deaths in 2020 in the United States [2]. The standard treatment for ovarian cancer is primary debulking surgery followed by taxane and platinum-based adjuvant chemotherapy. Advances in treatment and incorporation of new targeted agents such as bevacizumab have gradually improved the prognosis of ovarian cancer in recent decades [3]. However, 80% of patients still experience recurrence and less than half of ovarian cancer patients will survive longer than 5 years due to aggressive disease and the development of platinum resistance [4]. Thus, studies are required to improve the current status.

Investigation of new drugs (INDs) to add or replace current adjuvant treatment is a tremendously inefficient process in terms of time and cost, requiring approximately 10–17 years and 800 million US dollars per drug, with only a few INDs eventually available as new expensive agents [5]. Moreover, new potential drugs must also consider low and non-overlapping toxicity to current treatments. Thus, IND requires more variable and wider aspects. The notion of drug repositioning is another way of investigating potential new agents by rediscovering anti-tumor actions in well-known drugs [6].

Metformin is an anti-diabetic medicine that has been used as an herb since the Medieval era. It is currently one of the most commonly prescribed medicines for managing diabetes mellitus (DM) worldwide and is a promising medicine in oncology due to its inexpensive cost, well-established pre-clinical anti-cancer evidence, and universally accepted safety profile with a long history of use.

Its pharmaco-dynamic anti-cancer pathway was elucidated in 2005, less than 15 years ago. More recently, its mechanism has been studied at the molecular level [7]. The results of pre-clinical studies on the anti-cancer mechanisms of metformin can be summarized into 3 representative mechanisms [8,9]. First, metformin lowers high systemic glucose, insulin, and insulin-like growth factor levels, which are positive factors of tumorigenesis. Metformin also activates the adenosine monophosphate-activated protein kinase pathway via liver kinase B1, which is a key gate pathway related to inhibition of subsequent tumor growth biomarkers, insulin signaling cascade, and cell cycle regulatory pathways such as phosphatidylinositol 3-kinases, protein kinase B, mammalian target of rapamycin, Ki-67, and mitogen-activated protein kinase. Finally, metformin inhibits the energy-producing processes of tumor cell mitochondria.

Numerous clinical trials are ongoing on various types of solid tumors to confirm the anti-cancer effects of metformin [10]. However, the few studies assessing the prognostic impact of metformin on ovarian cancer have not reached a consensus [11-15].

Furthermore, the World Health Organization reported that approximately 171 million people have been diagnosed with DM, a number expected to double in 10 years [16]. The world will also face an aging society and metformin prescription is likely to increase with the higher future prevalence of DM. Therefore, it is also important to investigate how metformin will affect the prognosis of ovarian cancer in a nationally representative dataset as the population pattern and proportion of chronic medical diseases will change soon.

This nationwide population-based cohort study was performed to analyze the impact of metformin on survival outcomes of ovarian cancer.

MATERIALS AND METHODS

1. Data

This study used data from the South Korean National Health Insurance Service-National Sample Cohort (NHIS-NSC) from 2002 to 2013. This encrypted representative cohort comprises 2.2% (n=1,025,340) of the South Korean population (n=46,605,433) without significant differences on entire background variables.

This database included information from random stratified 5-year age groups, including sex, diagnosis, mortality, prescriptions, income status, and health insurance status, and is updated annually with the random addition of newborns and deletion of emigrated or dead participants [17].

2. Cohort

The tenth version of the International Statistical Classification of Diseases (ICD-10) and the Korean Classification of Disease, the Korean version of the ICD, was used to identify patients with ovarian cancer (C56) aged ≥20 years. Eligible patients were identified by applying inclusion criteria for more accurate data and analyses. This study included only ovarian cancer patients with a hospital admission record, a medical record ≥1 year before the time of diagnosis, and follow-up for ≥3 years after diagnosis (**Fig. 1**). The information on metformin use, duration of metformin use, age at diagnosis, median years of follow-up, the Charlson Comorbidity Index (CCI) score, and mortality rate of eligible cohort data set were categorized and analyzed.

3. Definition of metformin use

The Anatomical Therapeutic Chemical (ATC) and Korean Health Insurance Review and Assessment service drug codes were used to identify metformin use from the prescription data. Data on generic and brand names, routes of administration, the number of supplied days, and the date of prescription were collected. Patients with at least one prescription within 90 days of ovarian cancer diagnosis were defined as metformin users according to worldwide conventions to prescribe for 30–90 days for long-term users [18].
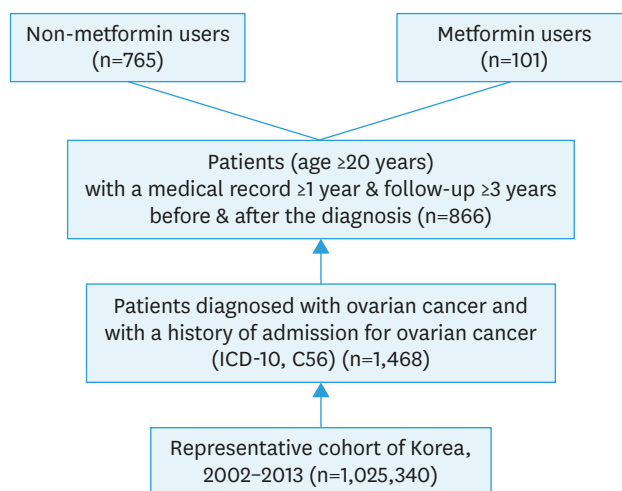
Fig. 1. Flow diagram.
ICD-10, International Classification of Disease, 10th Revision.

4. Mortality

Follow-up data over 11 years until 2013 were available from the NHIS-NSC. The follow-up period was defined at that from the date from ovarian cancer diagnosis to death, last hospital visit, or emigration, whichever came first. Data on cause-specific and all-cause mortality for all patients were also identified and investigated.

5. Confounder adjustment

Underlying diseases and medications, which are major potential confounding factors, were identified in the database from ICD-10 and ATC codes. The year of diagnosis and history of cerebrovascular disease, dementia, congestive heart failure, myocardial infarction, chronic pulmonary disease, liver disease, gastric ulcer, kidney disease, peripheral vascular disease, connective tissue disease, hemiparesis, DM with or without related complications, hematological malignancies, other co-existing malignancies, and acquired immune deficiency syndrome were obtained. The history of medications (aspirin, statins, and diuretics) was also investigated. Based on these data, the CCI was calculated and the severity of the underlying diseases was assessed, adjusted, and categorized [19].

6. Statistical analysis

The frequencies and proportions of accumulated person-time, covariates, and death events were assessed. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by Cox proportional hazard regression analysis. A multivariate model including age, year of diagnosis, CCI, and medication history was constructed using the risk factor modeling method. Independent prognostic factors were analyzed by multivariate Cox proportional hazard models. The p-values <0.05 were considered statistically significant. The statistical analyses were performed in SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

7. Ethical consideration

This study fulfilled the ethical principles of the Declaration of Helsinki, reporting guideline of STROBE, and was approved by the Institutional Review Board of Hallym University Sacred Heart Hospital (No. 2016-I084).

RESULTS

The mortality HRs of ovarian cancer patients according to metformin use were analyzed and subgroup analyses were performed in various settings.

1. Age at diagnosis

Among the 866 ovarian cancer patients were 101 (11.7%) metformin users (**Fig. 1**). Metformin users and non-users had median follow-up periods of 6.10 and 5.74 years, respectively. Overall, no significant survival differences were observed between the 2 groups (HR=0.821; 95% CI=0.559–1.205; p=0.314).

Ovarian cancer patients categorized based on their age at diagnosis showed no survival differences among subgroups (**Table 1**).

2. CCI

Ovarian cancer patients were categorized according to CCI. No survival differences were observed in subgroups of ovarian cancer patients using metformin medication according

Table 1. Mortality HRs of ovarian cancer patients using metformin according to age at diagnosis

Characteristics	No.	No. of deaths	Median years of follow-up	Crude HR (95% CI)	p	Adjusted HR* (95% CI)	p
Total							
No	765	252	6.10	1 (reference)		1 (reference)	
Yes	101	29	5.74	0.821 (0.559–1.205)	0.314	-	
20–39 years (n=216)							
No	208	22	6.54	1		1	
Yes	8	0	5.64	-		-	
40–59 years (n=350)							
No	314	95	6.08	1		1	
Yes	36	4	6.21	0.329 (0.121–0.894)	0.029	0.431 (0.154–1.207)	0.109
60–79 years (n=237)							
No	189	94	5.99	1		1	
Yes	48	20	5.53	0.719 (0.444–1.166)	0.181	0.880 (0.533–1.455)	0.619
≥80 years (n=63)							
No	54	41	4.59	1		1	
Yes	9	5	6.45	0.492 (0.193–1.257)	0.139	0.722 (0.254–2.048)	0.540
20–59 years (n=566)							
No	522	117	6.19	1		1	
Yes	44	4	5.78	0.380 (0.140–1.028)	0.057	0.399 (0.142–1.120)	0.081
≥60 years (n=300)							
No	243	135	5.97	1		1	
Yes	57	25	5.72	0.651 (0.425–0.998)	0.049	0.818 (0.524–1.276)	0.376

CI, confidence interval; HR, hazard ratio.
*Adjusted for comorbidity level, prior use of diuretics (yes/no), year of diagnosis, aspirin (yes/no), and statins (yes/no). Comorbidity was computed using the Charlson Comorbidity Index score categorized as low (0), medium (1–2), or high (3+).

Table 2. Mortality HRs of ovarian cancer patients according to CCI and diabetes mellitus

Characteristics	No.	No. of deaths (%)	Median years of follow-up	Crude HR (95% CI)	p	Adjusted HR* (95% CI)	p
CCI 0–2 (n=350)							
No metformin use	325	45 (13.85)		1 (reference)		1 (reference)	
Metformin use	25	1 (4.00)		0.255 (0.035–1.853)	0.177	0.295 (0.039–2.209)	0.234
CCI ≥3 (n=516)							
No metformin use	440	207 (47.05)	5.78	1 (reference)		1 (reference)	
Metformin use	76	28 (36.84)	5.78	0.697 (0.469–1.034)	0.073	0.835 (0.548–1.271)	0.400

CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio.
*Adjusted for age (20–39, 40–59, 60–79, ≥80 years), comorbidity level (0–2, 3+), prior use of diuretics (yes/no), year of diagnosis, aspirin (yes/no), and statins (yes/no). Comorbidity was computed using the Charlson Comorbidity Index score categorized as low (0), medium (1–2), or high (3+).

to CCI (CCI 0–2 [adjusted HR=0.295; 95% CI=0.039–2.209; p=0.234] and ≥3 [adjusted HR=0.835; 95% CI=0.548–1.271; p=0.400]) (**Table 2**).

3. Long-term metformin use

The duration of metformin use in ovarian cancer patients was categorized according to days of use. Longer duration of use (≥720 days) was associated with better survival outcomes in patients with ovarian cancer (adjusted HR=0.244; 95% CI=0.090–0.664; p=0.006) (**Table 3**).

4. Multivariate Cox proportional hazards analysis of cancer-specific survival (CSS)

Multivariate Cox proportional hazards model was used to analyze whether long-term metformin use was independently associated with better overall survival (OS) and CSS in ovarian cancer patients. Long-term metformin use (≥720 days) was an independent favorable prognostic factor for OS (HR=0.193; 95% CI=0.070–0.528; p=0.001) but not for CSS (HR=0.599; 95% CI=0.178–2.017; p=0.408) (**Table 4**).

Table 3. Mortality HRs of ovarian cancer patients using metformin according to duration of use

Characteristics	No.	No. of deaths	Median years of follow-up	Crude HR (95% CI)	p	Adjusted HR* (95% CI)	p
Duration of use (unit: year)							
Non-users	765	252	6.10	1 (reference)		1 (reference)	
Current users of metformin							
<1	39	20	5.34	1.808 (1.146–2.852)	0.011	1.314 (0.822–2.101)	0.254
≥1	62	9	6.03	0.371 (0.191–0.721)	0.003	0.375 (0.189–0.741)	0.005
Duration of use (unit: day)							
Non-users	765	252	6.10	1 (reference)		1 (reference)	
Current users of metformin							
<180	29	17	5.53	2.165 (1.324–3.541)	0.002	1.371 (0.824–2.280)	0.224
180–720	27	8	6.04	0.828 (0.410–1.675)	0.600	0.774 (0.378–1.582)	0.482
≥720	45	4	5.62	0.224 (0.084–0.602)	0.003	0.244 (0.090–0.664)	0.006

CI, confidence interval; HR, hazard ratio.
*Adjusted for age (20–39, 40–59, 60–79, ≥80 years), comorbidity level, prior use of diuretics (yes/no), year of diagnosis, aspirin (yes/no), and statins (yes/no). Comorbidity was computed using the Charlson Comorbidity Index score categorized as low (0), medium (1–2), or high (3+).

Table 4. Multivariate Cox proportional hazards model in ovarian cancer patients using metformin

Characteristics	HR (95% CI)	p
Overall survival (281 events)		
Metformin use (day)		
No	1 (reference)	0.006
<720	0.930 (0.607–1.425)	0.740
≥720	0.193 (0.070–0.528)	0.001
Age		
≥60	2.244 (1.733–2.905)	<0.001
CCI		
0	1 (reference)	<0.001
1–2	3.699 (1.567–8.735)	0.003
≥3	8.949 (3.940–20.327)	<0.001
Diabetes mellitus		
Yes	1.139 (0.866–1.498)	0.352
Prior use of diuretics		
Yes	2.313 (1.789–2.990)	<0.001
Prior use of statins		
Yes	0.371 (0.270–0.510)	<0.001
Cancer-specific survival (100 events)		
Metformin use (day)		
No	1 (reference)	0.703
<720	1.017 (0.458–2.263)	0.966
≥720	0.599 (0.178–2.017)	0.408
Age		
≥60	1.547 (1.005–2.380)	0.047
CCI		
0	1 (reference)	0.001
1–2	2.932 (1.000–8.596)	0.050
≥3	5.489 (1.975–15.253)	0.001
Diabetes mellitus		
Yes	0.657 (0.383–1.127)	0.127
Prior use of diuretics		
Yes	3.594 (2.305–5.603)	<0.001
Prior use of statins		
Yes	0.307 (0.173–0.543)	<0.001

CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio.

DISCUSSION

In this study, 22.5% of ovarian cancer patients were diagnosed with DM and 11.7% of the eligible cohort used metformin. Overall, no difference in all-cause mortality was observed

between metformin users and non-users among patients with ovarian cancer. However, analysis of patients according to the duration of metformin use showed an association between long-term use (≥720 days) and improved OS. However, long-term metformin use was not associated with improved CSS.

There was statistical significance with 1year cut-off, but we performed a further analysis according to 'days' of medication with a longer period (>720 days) to truly know the impact of long-term use of metformin. As it is customary to prescribe a 30 to 90 days (1 to 3 months) period for long-term users worldwide, long-term use was determined based on this prescription pattern. We defined long-term users in days when 30 days of use continues over 24 months as the mean duration, effect of prolonged use, and statistical significances were observed when metformin use was overall over 2 years in the previous series [11,13,20].

Based on these promising findings, previous studies investigated the role of metformin in the treatment of ovarian cancer; however, the results are conflicting, with no consensus. As previous retrospective chart review studies were limited by small sample sizes from single institutions with the possibility of selection bias [13-15], population-based cohort studies from large nationally representative databases may better inform the impact of metformin in ovarian cancer. Urpilainen et al. [12] reported no survival benefit of metformin use in an analysis of the Diabetes in Finland (FinDM) database. However, the lack of confounder adjustment due to the lack of detailed information on the demographic background of the cohort, especially underlying co-morbidities, was a major limitation of this series. Moreover, the median follow-up of 2.2 years was insufficient to observe the long-term effect of metformin use in ovarian cancer. Finally, the inclusion of only ovarian cancer patients with DM may have led to selection bias, in contrast with previous and our series [11]. Hyper-insulinemia and hyper-glycemia, conditions of DM itself, are important causes of carcinogenesis and its unfavorable prognosis in human malignancies including ovarian cancer [21]. These factors may ameliorate the anti-cancer effect of metformin in ovarian cancer. The absence of a non-DM control group makes it difficult to assess the impact of metformin regardless of DM status.

Garcia et al. [11] investigated the survival impact of metformin in ovarian cancer by analyzing the Surveillance, Epidemiology, and End Results Medicare database and reported no significant prognostic improvement. However, a late survival benefit was reported in a subgroup of ovarian cancer patients who survived ≥30 months with metformin, consistent with the findings of our series.

The development of ovarian cancer and its progression is a chronic process resulting from the accumulation and interaction of various genetic and environmental factors such as immune-suppression, stress, and gene mutations. Pre-clinical studies in ovarian cancer cells showing that metformin activated the anti-tumor pathway in time- and dose-dependent manners support this theory [9]. Thus, we believe that the anti-cancer and prophylactic effect of metformin was observed in previous studies in which metformin use was maintained long-term, which is consistent with the current series and the clinic-pathophysiologic characteristics of ovarian cancer [11,20].

It is difficult to claim that metformin has a comparable immediate anti-tumor response to that of taxane and platinum-based conventional chemotherapy. Previous in vivo and in vitro studies identified the synergistic effect of metformin when added to traditional

chemotherapeutic agents [9]. Therefore, most of the ongoing clinical trials in other types of solid tumors are investigating the anti-cancer role of metformin as a chemo/radio-sensitizer and in combination with targeted agents, with an anticipated synergistic effect [10]. Although metformin may not show positive results in the short-term, we speculate that metformin shows its synergistic anti-tumor mechanism when certain conditions are met and when used long-term.

The most important question remains whether the anti-cancer mechanism of metformin will improve mortality due to ovarian cancer itself regardless of diabetes. Well-designed multicenter prospective open-label or randomized controlled trials are ongoing in primary and recurrent settings in ovarian cancer (NCT02312661, NCT02437812, NCT03378297, NCT02050009, and NCT02122185). Metformin will be combined or compared to standard chemotherapeutic agents, hormone therapies, and poly ADP ribose polymerase inhibitors. These studies may answer whether metformin will prolong tumor progression, improve survival outcomes, and change related biomarker expression.

The retrospective study design may limit our ability to determine the relationship between metformin use and the prognosis of ovarian cancer. Because the number of patients using metformin increases with time as well as an advance of ovarian cancer treatment, it is difficult to establish the contributing proportion of the metformin on OS improvement compared to the standard management. Also, the possible weak statistical power because of the small proportion of the metformin user group (11.7%) in accordance with the previous series (4.7%–7.9%) as the prevalence of diabetes is low may have limited robust data analyses including subgroup analysis [11,14]. Furthermore, like the previous cohort series [11,12], the current NHIS-NSC lacks data on ovarian cancer recurrence. The lack of data on the clinic-pathologic background (residual disease, FIGO stage, histology, tumor grade, and primary treatment) as found in the FinDM database may be another limitation of this study [12]. Finally, it would have been a better study if all available data were used in the analysis. But difficulties putting all variables in multivariate analyses, only the factors including related medicines with clinical importance and statistical significance to the objective of this study were adopted. Even, authors' effort on adjusting confounders using CCI score and multivariate analysis on national data with epidemiologic perspective, these important variables still remain as a possible bias.

The strength of this study is the generally applicable national representative cohort with minimal selection bias. The NHIS-NSC offers accurate data not only on death but also on its cause with no overlap bias, which analyzes the effect of metformin on CSS feasible compared to other population-based cohort series. This is because the NHIS is a single-payer health insurance program that covers the entire population in Korea. All Koreans must be enrolled in the NHIS with their resident registration identification number which is maintained from birth to death. This identification number is used for registration and treatment in all Korean medical institutions and is tracked by the government without exception. The date and cause of death have to be reported to the government under Korean law with physician-issued death certificates.

Most previous series had no clear definition of metformin use, further analysis of its impact according to the duration of use, and lacked long-term follow-up, which are important factors to determine the anti-cancer effect of metformin on ovarian cancer. Moreover, these studies lacked detailed analyses to identify the subgroup of patients with increased sensitivity to metformin [11-15]. The present study defined metformin use as the presence of

at least one prescription within 90 days of ovarian cancer diagnosis and analyzed the anti-cancer effect according to the duration of medication. Furthermore, subgroup analyses were performed according to age, CCI, and DM with long median follow-up durations of 6.1 years in metformin users and 5.74 years in non-users.

Previous studies reported that patients with more underlying diseases had a higher tendency for other combined co-morbidities including DM and metformin use. Therefore, the burden of medical demographic background is a major confounder in nationwide cohort studies. Detailed information on underlying co-morbidities and related medications was used to systemically adjust according to the CCI score in this series [19]. Finally, the effect of metformin on OS and CSS was further confirmed by multivariate Cox proportional hazards analysis.

In conclusion, long-term metformin use was associated with improved all-cause mortality in patients with ovarian cancer. But the core value of metformin as improving the cancer-specific prognosis of ovarian cancer still remains as a theory. Whether metformin itself reduces death due to ovarian cancer requires further study. Ongoing prospective clinical trials will elucidate the anti-tumoral activity and role of metformin in near future. Metformin is a safe, inexpensive, and ethically sound medicine supported by solid pre-clinical evidence and long history. Thus, it is easily introduced in treatment. If effective, metformin may be re-positioned as a potential synergistic adjunctive agent to relieve the financial burden to both nations and individuals in managing ovarian cancer.

Presentation

This study was presented on 1) March 15, 2019, in the International Session at the Annual Meeting of the. Society of Gynecologic Oncology in Honolulu, Hawaii, USA; 2) July 19, 2019, in the 24th Korean Gynecologic Oncology Group Meeting at the NRG Oncology Semi-Annual Meeting in Philadelphia, Pennsylvania, USA.

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