

RESEARCH ARTICLE

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# Therapeutic Use of Metformin in Diabetes and Survival Outcomes in Endometrial Cancer Patients with Diabetes

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## Abstract

**Objectives:** To compare survival outcomes between endometrial cancer (EC) patients with diabetes who used metformin to those who did not use metformin. **Materials and Methods:** A retrospective cohort study was conducted of EC patients who were diabetes at the time of their cancer diagnosis and had been scheduled for elective surgery at Rajavithi Hospital between 1 January 2003 and 31 December 2013. The patients were excluded if they had type I diabetes mellitus and a history of other cancers. **Results:** Of 1,262 EC patients in the study period, there was 212 (16.8%) patients who met the inclusion criteria. Among them, 90 (42.5%) were non-metformin users and 122 (57.5%) were metformin users. With a median follow-up of 47 months, the 5-year overall survivals (76.4% vs 77.9%,  $p=0.959$ ) and the 5-year progression-free survivals (92.6% vs 84.7%,  $p=0.091$ ) did not significantly differ between the both groups. On Cox proportional-hazards regression analysis, independent prognostic factors for overall survival (OS) were FIGO stage, depth of myometrial invasion, and cervical involvement. Patients with non-endometrioid histology and advanced stage were found to have a significant effect on progression-free survival (PFS). However, metformin used did not predict either OS (HR, 0.99; 95%CI, 0.56-1.73;  $p=0.959$ ) or PFS (HR, 2.19; 95%CI, 0.86-5.55;  $p=0.099$ ). **Conclusion:** Overall, a significant effect of metformin on survival outcomes in EC patients with diabetes was not found in the current study. Larger studies with a prospective randomized control design are needed to clarify the benefit of metformin as a strategy for endometrial cancer prevention and treatment.

**Keywords:** Endometrial cancer- diabetes- metformin- overall survival- progression- free survival

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## Introduction

Endometrial cancer (EC) is the second most common gynecologic malignancy in worldwide and the third most common after cervical and ovarian cancer in Thailand (Jemal et al., 2008; Cancer of Thailand, 2010). The age standardized incidence rate (ASR) is 8.3 per 100,000 women and there were an estimated 76,160 deaths from EC worldwide in 2012 (Ferlay et al., 2013). Although, EC is often diagnosed at an early stage with a good prognosis, but the number of new cases and deaths appear to be on a rising trend in recent years (Trovik et al., 2012; Galaal et al., 2014). Many evidence suggested that insulin resistance and diseases associated with insulin resistance such as obesity, type II diabetes mellitus and polycystic ovary syndrome (PCOS), are the strong risk factor for developing type I EC (Wild et al., 2000; Saltzman et al., 2008). For those women who do develop endometrial cancer with diabetes and obesity have a decreased life expectancy when compared to non-diabetes and non-obese with the same malignancy (Abu-Abid et al., 2002; Kaaks et al., 2002). Therefore, more effective and acceptable chemotherapeutic strategies in a role of treatment and

prevention of EC are necessary for these patients.

Metformin, a synthetic biguanide derivative which has been used extensively in the treatment of type II diabetes mellitus, is recommended as first-line therapy by American Diabetes Association (Standards of medical care in diabetes, 2009). Metformin therapy is associated with favorable outcomes in cancer through its ability to lower cancer risk and reduce cancer deaths among diabetic patients suffering from various cancer such as breast cancer, prostate cancer, colon cancer, pancreatic cancer and other solid malignancies, including those with EC (Pollak et al., 2008; Pollak et al., 2012; Emami et al., 2013). Metformin has an anti-tumorigenic benefit via both indirect and direct actions on tumor growth (Pollak et al., 2012; Viollet et al., 2012; Emami et al., 2013). Its direct effects are mediated via adenosine monophosphate-activated protein kinase (AMPK) activation and reduction of the mammalian target of the rapamycin (mTOR) signaling pathway which leads to inhibition of hepatic gluconeogenesis, protein synthesis and cell proliferation in the cancer cells. The indirect effects are mediated through its blood glucose lowering ability and subsequent reduction of the circulating insulin level.

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Metformin's potential role in the prevention of EC has been evaluated in several studies (Ko et al., 2014; Nevadunsky et al., 2014). One study, a retrospective analysis of 1,495 EC patients which conducted at the University of North Carolina, reported that metformin used was associated with significant improved recurrence-free and overall survival. Non-metformin users were 2.3 times more likely to die than metformin users (95%CI, 1.3-4.2;  $p=0.005$ ) and 1.8 times worsen recurrence-free survival (95% CI, 1.1-2.9;  $p=0.02$ ) (Ko et al., 2014). Another study reported by Nevadunsky et al. that metformin could improve overall survival but only among diabetic patients with non-endometrioid histologic subtypes (HR, 0.57; 95% CI, 0.31-0.97;  $p=0.04$ ) when compared to non-diabetic patients (Nevadunsky et al., 2014). Moreover, a recent study found that non-diabetic patients with EC reduced levels of a cell proliferation marker (Ki67) in endometrial tumor specimens and decreased in insulin and IGF-1 levels in serum after metformin treatment (Laskov et al., 2014).

Nowadays, diabetes and obesity are increasing at alarming rates and have been linked to an increased risk of mortality from EC (Calle et al., 2003). The role of metformin as a chemotherapeutic strategy to treat EC and improve outcomes for these high-risk patients by impacting insulin resistance is challenging. Therefore, we plan to investigate the association between metformin used and EC outcomes in Rajavithi Hospital.

The primary objective of this study was to compare overall survival (OS) between EC patients with diabetes who used metformin and those who did not use metformin. The secondary objective was to compare progression-free survival (PFS) between both groups and evaluated prognostic factors in EC patients with diabetes, in order to predict the survival outcomes and plan for offering adjuvant therapy to these patients.

## Materials and Methods

The present study was a retrospective cohort study and was approved by the Institutional Review Board (IRB) of Rajavithi Hospital. We included all EC patients who were diabetes and they had been scheduled for elective surgery at Rajavithi Hospital between 1 January 2003 and 31 December 2013. We designed the cohort to compare EC patients who were diabetes and using metformin at the time of their cancer diagnosis to those who were diabetes and not using metformin. The patients were excluded if they were type I diabetes mellitus, had a history of other cancers, had received neoadjuvant chemotherapy, had undergone surgery in other hospitals or had an incomplete data.

The clinical data were obtained from the medical records including age, body mass index in  $\text{kg}/\text{m}^2$  (BMI), diagnosis of diabetes, other comorbidities, metformin use, pre-operative fasting blood sugar, date of diagnosis EC, histologic subtypes, grade, stage, nodal status, a surgical and an adjuvant treatment, date of each treatment, date of recurrence, recurrent data, date of last follow-up period, date of death, and cause of death.

All patients in this study had undergone primary

surgery, including total abdominal hysterectomy and bilateral salpingo-oophorectomy, with additional lymph node dissection and omentectomy in selected high-risk patients. Tumor staging was determined according to the revised 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system (Pecorelli et al., 2009). Adjuvant treatment (radiotherapy and/or chemotherapy) was given to patients with intermediate to high-risk groups according to NCCN guidelines and depending on patient preference and physician determination. The follow-up data were obtained from medical records. The date of death was obtained by review of medical record and the civil registration. For the recurrences that were diagnosed by histologic exams, the date of recurrence was defined as the date of the histopathological proved. Additionally, the recurrences that were diagnosed by imaging study and isolated rising tumor marker (serum Cancer Antigen 125 (CA125) levels  $\geq 35$  U/mL), the failure date of the treatment was set as the date when the computed tomography (CT) was taken or the sample of blood for serum CA125 was obtained.

### Statistical analysis

The calculated sample size of each group was 72 patients by using "log-rank test" formula (Freedman et al., 1982) with a reference number is the hazard ratios (HRs) for OS from KO et al (Ko et al., 2014). When combined with dropout 10%, a total of at least 79 subjects were required per group.

Frequency distributions of categorical variables among the groups were compared using the Chi-square test and the Fisher's exact test. The survival curves, OS and PFS curves, were estimated using the Kaplan-Meier method for metformin users and non-metformin users. OS was measured from the date of surgery until the death of any cause or the date of last follow-up for the patients who were still alive. PFS was defined as the period between the surgery date and the date of disease recurrence or death from any cause. Disease recurrence was histologically confirmed relapse or clinically assumed when the imaging study highly suggested recurrence and elevated tumor markers from the basal level. The log-rank test was used to statistically compare OS and PFS between two groups. The multivariable Cox proportional hazards regression analysis was used to assess the association between metformin use and survival outcomes of interest. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated on the entire cohort. All analyzes were carried out using IBM SPSS Statistics version 23.0 (IBM Cooperation, New York, USA) and a level of  $p$ -value less than 0.05 was accepted as being statistically significant.

## Results

From 1 January 2003 to 31 December 2013, a total of 1,262 EC patients who had been scheduled for elective surgery at Rajavithi Hospital were identified. Two hundred and twelve (16.8%) EC patients who had been diagnosed with diabetes and met the inclusion criteria were enrolled for analysis, 90 (42.5%) patients were non-metformin users and 122 (57.5%) patients were

Table 1. Demographic Data and Clinico-Pathological Characteristics of Endometrial Cancer Patients with Diabetes

Endometrial cancer patients with diabetes	Non-metformin users n = 90 (42.5%)	Metformin users n = 122 (57.5%)	P Value
Mean age, year ±SD	62.2 ± 9.8	58.8 ± 9.1	0.012
BMI, kg/m <sup>2</sup>			
≤25	35 (38.9%)	23 (18.9%)	0.002
>25	55 (61.1%)	99 (81.1%)	
Parity			
Nulliparous	15 (16.7%)	22 (18.0%)	0.856
Multiparous	75 (83.3%)	100 (82.0%)	
Menopause			
Pre-	11 (12.2%)	22 (18.0%)	0.338
Post-	79 (87.8%)	100 (82.0%)	
Pre-op FBS, mg/dl			
≤130	51 (56.7%)	63 (51.6%)	0.489
>130	39 (43.3%)	59 (48.4%)	
Histology			
Endometrioid	74 (82.2%)	99 (81.1%)	0.842
Non-endometrioid	16 (17.8%)	23 (18.9%)	
Papillary serous	5 (5.6%)	8 (6.6%)	
Clear cell	6 (6.7%)	9 (7.4%)	
Carcinosarcoma	5 (5.6%)	6 (4.9%)	
2009 FIGO stage			
I	60 (66.7%)	73 (59.8%)	0.626
II	10 (11.1%)	15 (12.3%)	
III	19 (21.1%)	30 (24.6%)	
IV	1 (1.1%)	4 (3.3%)	
Grade			
1	33 (36.7%)	42 (34.4%)	0.37
2	19 (21.1%)	36 (29.5%)	
3	38 (42.2%)	44 (36.1%)	
Type of surgery			
With lymphadenectomy	83 (92.2%)	99 (81.1%)	0.373
Positive lymph node	9 (10.0%)	15 (12.3%)	0.602
Without lymphadenectomy	7 (7.8%)	14 (11.5%)	
Residual disease after surgery			
No	90 (100%)	118 (96.7%)	0.139
Yes	0 (0%)	4 (3.3%)	
Primary tumor size, mean±SD	4.8±3.0	4.8±2.6	0.955
≤2 cm.	9 (10.0%)	15 (12.3%)	0.666
>2 cm.	81 (90%)	107 (87.7%)	
Myometrial invasion			
≤50 %	43 (47.8%)	66 (54.1%)	0.405
>50 %	47 (52.2%)	56 (45.9%)	
Positive LVSI	28 (31.1%)	33 (27.0%)	0.542
Extra-uterine disease	28 (31.1%)	46 (38.0%)	0.311
Adjuvant treatment			
None	40 (44.4%)	57 (46.7%)	0.425
Chemotherapy alone	15 (16.7%)	16 (13.1%)	
Radiation alone	27 (30.0%)	32 (26.2%)	
Combine CMT and RT	7 (7.8%)	17 (13.9%)	
Hormonal therapy	1 (1.1%)	0 (0%)	

BMI, body mass index; FBS, fasting blood sugar; LVSI, lymphovascular space invasion; CMT, chemotherapy; RT, radiotherapy

Table 2. Patterns of Recurrence and Death Based on Metformin Use in Endometrial Cancer Patients with Diabetes

Endometrial cancer patients with diabetes	Non-metformin users n = 90 (42.5%)	Metformin users n = 122 (57.5%)	p Value
Recurrence, no. (%)	6 (6.7%)	17 (13.9%)	0.119
Site of recurrence, no. (%)			
Locoregional	2 (33.3%)	6 (35.3%)	1
Distant	4 (66.7%)	11 (64.7%)	
Treatment of recurrence			
None	0 (0%)	6 (35.3%)	0.084
Surgery	0 (0%)	0 (0%)	
Chemotherapy	1 (16.7%)	1 (5.9%)	
Radiation	3 (50.0%)	1 (5.9%)	
Hormonal therapy	0 (0%)	1 (5.9%)	
Combination	2 (33.3%)	8 (47.1%)	
Death, no. (%)	23 (25.6%)	27 (22.1%)	0.624
Cause of death, no. (%)			
Cancer	12 (52.2%)	17 (63.0%)	0.567
Non-cancer	11 (47.8%)	10 (37.0%)	

no, number of patients

metformin users. 67.2% (82/122) of the metformin users were using an effective dose of metformin (greater than 850 mg per day) (American Diabetes Association et al., 2009). Of the non-metformin users, 26 (28.9%) used sulfonylureas, 12 (13.3%) used insulin-based regimens and 52 (57.8%) had lifestyle modification with dietary strategies. The distribution of demographic data and clinicopathological characteristics according to metformin used are summarized in Table 1. The mean age of the non-metformin users was significantly older than the metformin users (62.2±9.8 vs 58.8±9.1 years; p=0.012). Almost three fourth patients (72.6%) were considered to be overweight or obese (BMI ≥ 25 kg/m<sup>2</sup>); the number of the metformin users with BMI ≥ 25 kg/m<sup>2</sup> was significantly higher than the non-metformin users approximately 20% (81.1% vs 61.1%, p=0.002). Nevertheless, the other demographic data and clinicopathological characteristics of the two groups were similar (Table 1).

According to the histologic subtypes; 173 (81.6%) were endometrioid tumors and 39 (18.4%) were non-endometrioid tumors. The non-endometrioid tumors were: clear cell carcinoma 15 (7.1%), papillary serous 13 (6.1%), and carcinosarcoma 11 (5.2%). By stage distributions, stage I was present in approximately 60% of both groups and there was no significant difference between the non-metformin users and the metformin users (stage I: 66.7% vs 59.8%, stage II: 11.1% vs 12.3%, stage III: 21.1% vs 24.6%, stage IV: 1.1% vs 3.3%, p= 0.626), respectively). A similar proportion of patients who had histologic grade 1 tumors (36.7% vs 34.4%), grade 2 tumors (21.1% vs 29.5%), and grade 3 tumors (42.2% vs 36.1%) between the non-metformin users and the metformin users (p=0.370). The vast majority of patients received standard surgery with lymphadenectomy (92.2% of non-metformin users and 81.1% of the metformin users, p= 0.373) and no residual disease after surgery (100% of non-metformin

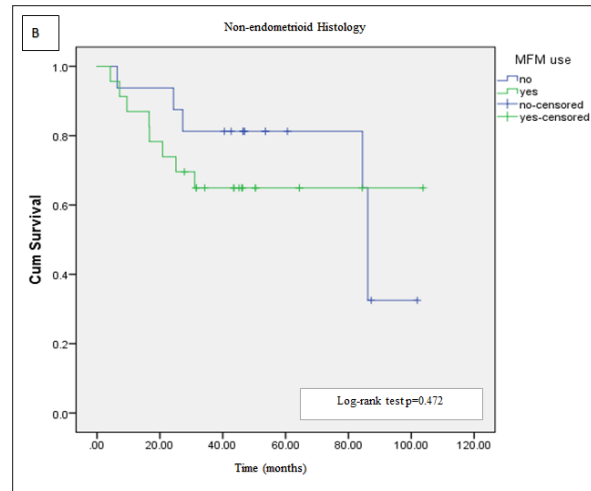
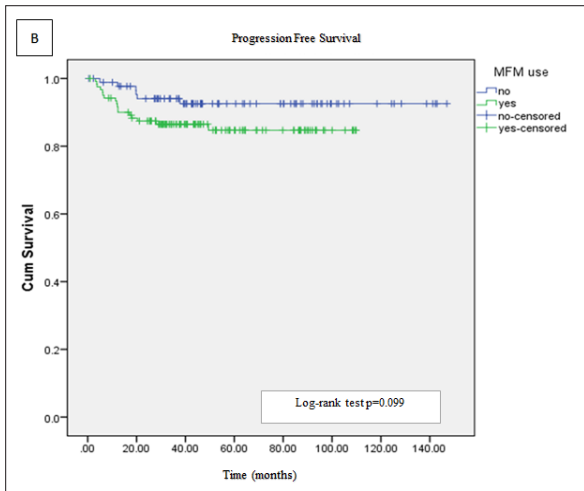
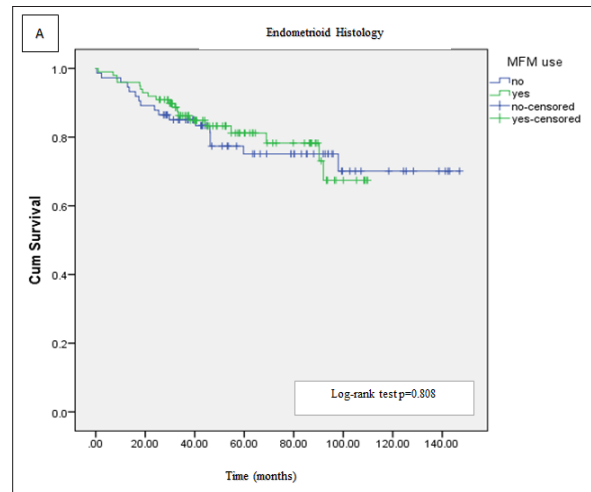
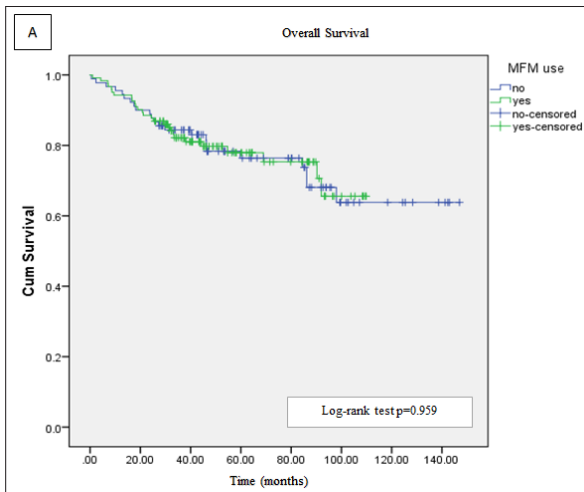


Figure 1. Kaplan-Meier Curves for Patients with Diabetes Who Used Metformin to Those Who Did not Use Metformin: (A), Overall survival; (B), Progression free-survival

Figure 2. Kaplan-Meier Curves for Overall Survival in EC Patients with Diabetes Who Used Metformin to Those Who Did not Use Metformin with : (A) Endometrioid histology; (B), Non-endometrioid histology.

users and 96.7% of metformin users,  $p = 0.139$ ). All patients who had residual disease were in the metformin users group and one patients have died due to omental metastasis with a very short survival time (only 1 months after surgery). No recurrence in the patients who had residual disease was observed. Nearly 50% of both group

were received adjuvant treatment after primary surgery as shown in Table 1.

At the time of the study end (December 31, 2015), 50 (23.6%) of 212 patients were known to have died: 23 in the non-metformin users and 27 in the metformin users. The median follow-up duration for the entire

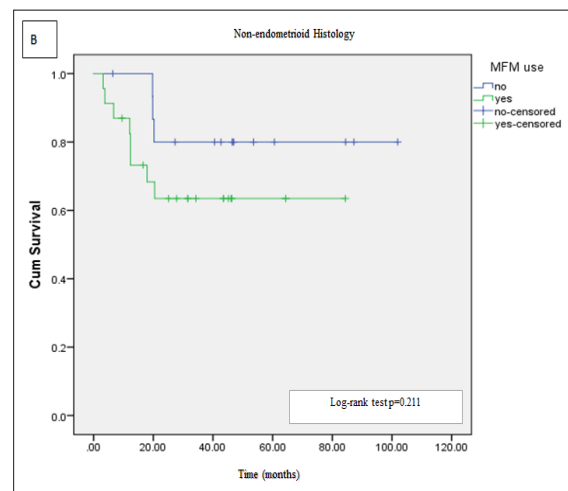
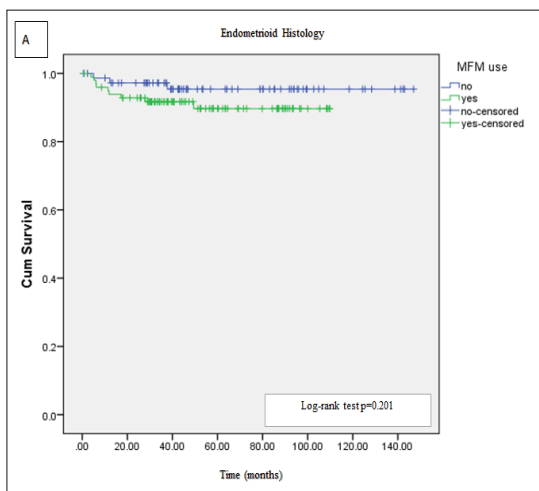


Figure 3. Kaplan-Meier Curves for Progression-Free Survival in EC Patients with Diabetes Who Used Metformin to Those who did not Use Metformin with, (A), Endometrioid histology; (B), Non-endometrioid histology.

Table 3. Univariate and Multivariate Analyses for Survival Outcomes According to Individual Parameters

Parameter	Progression-free survival		Overall survival	
	HR (95%CI)	p-Value	HR (95%CI)	p-Value
Univariate analysis				
Metformin use (no vs yes)	2.19 (0.86-5.55)	0.099	0.99 (0.56-1.73)	0.959
Age (≤60 years vs >60 years)	2.04 (0.87-4.82)	0.103	1.71 (0.97-3.02)	0.063
Menopause (pre- vs post-)	2.12 (0.50-9.03)	0.311	2.52 (0.91-7.02)	0.076
BMI (≤25 kg/m <sup>2</sup> vs >25 kg/m <sup>2</sup> )	0.55 (0.24-1.28)	0.165	0.73 (0.40-1.32)	0.298
FBS (≤130 mg/dl vs >130 mg/dl)	0.71 (0.31-1.64)	0.421	0.89 (0.51-1.55)	0.67
Endometrioid histology (yes vs no)	4.68 (2.06-10.63)	0.001	2.08 (1.12-3.88)	0.021
2009 FIGO stage (I-II vs III-IV)	4.18 (1.84-9.50)	0.001	3.52 (1.99-6.22)	0.001
Tumor size (≤2 cm. vs >2 cm.)	1.34 (0.31-5.71)	0.693	1.64 (0.59-4.56)	0.347
MI (≤50% vs >50%)	2.73 (1.12-6.64)	0.027	2.98 (1.63-5.46)	0.001
Cervical involvement (no vs yes)	1.04 (0.39-2.81)	0.935	1.06 (1.03-1.09)	0.001
LVSI (absent vs present)	1.91 (0.82-4.43)	0.132	3.48 (1.93-6.30)	0.001
Peritoneal cytology (neg vs pos)	1.25 (0.17-9.28)	0.827	1.39 (0.43-4.51)	0.579
LND (no vs yes)	1.24 (0.30-16.65)	0.429	0.87 (0.35-2.20)	0.872
Adjuvant treatment (no vs yes)	1.50 (1.06-2.11)	0.022	1.21 (0.95-1.56)	0.125
Multivariate analysis				
Endometrioid histology (yes vs no)	3.91 (1.54-9.96)	0.004	1.15 (0.74-2.71)	0.294
2009 FIGO stage (I-II vs III-IV)	3.18 (1.16-8.73)	0.025	2.02 (1.06-3.83)	0.032
MI (≤50% vs >50%)	1.83 (0.69-4.85)	0.223	2.14 (1.09-4.20)	0.026
Cervical involvement (no vs yes)	-	-	1.05 (1.02-1.08)	0.001
LVSI (absent vs present)	-	-	1.79 (0.91-3.52)	0.093
Adjuvant treatment (no vs yes)	0.81 (0.51-1.28)	0.365	-	-

BMI, body mass index; FBS, fasting blood sugar; MI, myometrial invasion; LVSI, lymphovascular space invasion; neg, negative; pos, positive; LND, lymphadenectomy

cohort was 47 months (IQR: 33-85 months). The median time to death was 26 months (IQR: 14-47 months) in the non-metformin users and 22 months (IQR: 10-34 months) in the metformin users. Most deaths were caused by endometrial cancer (29 patients, 58%); 12 (52.2%) in the non-metformin users and 17 (63%) in the metformin users. Other causes of death were diabetes-specific complications, sepsis, cardiovascular disease, renal failure, cirrhosis, and senility. Table 2 showed the patterns of recurrence and death based on the metformin use in endometrial cancer patients with diabetes and we observed that there was not different between the two groups (p-value > 0.05).

One hundred sixty-two patients (76.4%) were alive without disease at the end of the follow-up. The recurrent rate was 6.7% (6/90) for the non-metformin users and 13.9% (17/122) for the metformin users. The median time to recurrence was 20 months (IQR: 11-25 months) in the non-metformin users and 12 months (IQR: 6-18 months) in the metformin users. The two groups had a more distant recurrence than locoregional recurrence (the non-metformin users, 4/6 [66.7%] and the metformin users, 11/17 [64.7%]). The majority modality of treatment in recurrence disease was radiotherapy (50%) in the non-metformin users and combination therapy (47.1%) in the metformin users.

Among all patients in our study, Kaplan–Meier analysis demonstrated that no statistically significant

difference in the survival outcomes was observed between the non-metformin users and the metformin users. The 5-year overall survivals were 76.4% and 77.9% for the non-metformin users and the metformin users, respectively (log-rank test p=0.959) (Figure 1A). The 5-year progression-free survivals were 92.6% and 84.7% for the non-metformin users and the metformin users, respectively (log-rank test p=0.091) (Figure 1B).

We performed subgroup analysis regarding subtypes (endometrioid and non-endometrioid tumors) and found comparable survival (Figure 2,3). Therefore, metformin has similar effect to either endometrioid or non-endometrioid endometrial cancer.

Table 3 showed the univariate and multivariate analyzes for OS and PFS in EC patients with diabetes. Univariate analysis revealed endometrioid histology, FIGO stage, depth of myometrial invasion, cervical involvement, and lymphovascular invasion as significant prognostic factors for OS. Those significant variables were submitted for Cox proportional hazard multivariate regression model. In the final analysis, FIGO stage, depth of myometrial invasion, and cervical involvement remained independently associated with decreased OS.

PFS and OS were influenced by similar prognostic factors. On univariate analysis, patients with non-endometrioid histology, advanced stage cancer (2009 FIGO stage III-IV), depth of myometrial invasion greater than 50%, and adjuvant treatment received after

primary surgery were found to have a significant effect on PFS. Cox proportional-hazards model analysis revealed that in multivariate models the independent prognostic factors of poorer PFS were non-endometrioid histology and advanced stage cancer. However, the statistical result indicated that metformin used had no prognostic value in univariate and multivariate analysis for OS (HR, 0.99; 95%CI, 0.56-1.73;  $p=0.959$ ) and PFS (HR, 2.19; 95%CI, 0.86-5.55;  $p=0.099$ ).

## Discussion

We should acknowledge that diabetes and obesity have been associated with increased risk of developing EC and these factors also influenced the severity of disease and the EC mortality (Calle et al., 2003). EC patients with diabetes may have increased proliferation of tumor cells due to hyperinsulinemia in the same way as hyperestrogenemia and insulin resistance in obese women (Naomi et al., 2008). Thus, the pharmacologic agent that modulates insulin sensitivity or normalizes insulin levels, such as metformin, is likely to inhibit tumor cells growth and become a valuable target in the adjuvant treatment of these high-risk EC patients.

Currently, the association of metformin with EC survival outcomes has not been summarized and remains unclear. Although metformin has been shown to improve recurrence-free and overall survival in some previous studies, but there was a small number of clinical researches which carried out in Asian populations (Ko et al., 2014; Nevadunsky et al., 2014; Laskov et al., 2014; Chin-Hsiao et al., 2015). The present study is the first to establish a survival outcome between EC patients with diabetes who use metformin and who do not use metformin in our institution and we hypothesize that metformin therapy may be associated with better survival outcomes.

Our findings in this study revealed that no statistically significant difference in the survival outcomes was observed between the non-metformin users and the metformin users. With regards to OS, the 5-year overall survivals for the non-metformin users was better than the study by Ko et al., (2014) (76.4% vs 53.0%). The possible reason may be that the vast majority of patients in our study had an early stage at initial diagnosis (stage I: 66.7% of non-metformin users and 59.8% of metformin users). Because the FIGO stage was an independent prognostic factors for OS and PFS.

Considered to the PFS analysis, it was unexpected that in the current study reflected a trend of increasing PFS in diabetic EC patients with non-metformin users. Furthermore, regarding a greater proportion of the overweight or obese patients ( $BMI \geq 25 \text{ kg/m}^2$ ), which was associated with tumor aggressiveness, in the metformin users (81.1% vs 61.1%) might be related to a higher recurrent rate in the metformin users (13.9% vs 6.7%) and may also lead to a poorer PFS in this group (Mauland et al., 2011). However, in the present study, we also observed that there were some patients who had referred to follow-up at the peripheral centers, the under-estimate detection rate of recurrence may have occurred and could affect PFS results.

Ko et al., (2014) reported that the metformin users had significantly improved in recurrence-free and overall survival after adjusting for age, stage, grade, histology, and treatment. However, no statistically significant difference in time to recurrence (TTR) was observed between the non-metformin users and the metformin users, so the authors suggested that metformin offered a benefit primarily to all-cause mortality (including death due to non-cancerous causes) rather than cancer-specific progression. In our opinions, if the primary outcome was all-cause mortality, not death for EC. The conclusion on the effect of metformin on improving survival must be considered because it probably decreases other cause of death regardless endometrial cancer.

Nevadunsky et al., (2014) found that metformin could improve overall survival but only among diabetic patients with non-endometrioid subtypes when compared to non-diabetic patients. In contrast to the present study, we had performed a subgroup analyzed for the two histologic subtypes (endometrioid tumors vs non-endometrioid tumors) and showed no difference in survival according to histology in EC patients with diabetes treated with metformin. Although insulin resistance is associated with a risk of developing endometrioid EC and we expected that metformin may provide a benefit in these histologic subtypes, the other confounding variables may also have an impact on the survival and recurrence of those tumors (Laskov et al., 2014).

Chin-Hsiao et al., (2015) has evaluated the association between metformin use and endometrial cancer risk in Chinese women with type II diabetes mellitus in Taiwan. The study showed the protective effect of metformin that was associated with an overall significantly lower risk of endometrial cancer with dose-response relationship. Similar to our study, the study populations were homogeneous in the ethnicity because Taiwanese and Thai were Asian populations. But it would be some explanation for the lack of a protective effect of metformin in our study. The study by Chin-Hsiao has a very large sample size ( $n= 478,921$ ) and followed the patients with newly diagnosed type II diabetes mellitus and without EC until they developed EC. It seems to be reflected the true incidence of EC in this group and revealed metformin as a significant prognostic factor for lowering EC risk.

We observed that the most patients in this study had an early stage EC (approximately 70%), which associated with a favorable prognosis. The minimal number of events have occurred so the long-term follows up of the study period will be recommended providing a possibility to include sufficient number of events. Furthermore, in the multivariate analyzes for OS and PFS, an advanced stage was only an independent prognostic factor. Therefore, in the further study, the effect of metformin therapy in advanced stage EC may be considered.

Dong et al., (2012) reported metformin reversed resistance to progestin therapy by inhibiting the expression of glyoxalase I, an enzyme related to glucose metabolism and normally overexpressed in tumor tissue, and associated with resistance to chemotherapy in EC. In our study, there was a small proportion (25.9%) of the patients who had received adjuvant chemotherapy after primary

surgery. Thus, the role of metformin on chemotherapeutic sensitivity could not be clearly summarized. The combined therapy with metformin and chemotherapeutic agents would be an interesting issue for future studies.

The strengths of the present study include the use of a homogeneous group of patients' clinical and baseline characteristics as shown in Table 1 and the inclusion of the patients who were treated at the single institution that could be minimized the variation of operative techniques and treatment protocols. It can be seen that the most patients had received standard surgery with lymphadenectomy and the complete tumor resection was achieved nearly 100% of all patients.

A limitation of the current study is the retrospective study design, therefore it could be prone to a recall bias especially the only information available in the medical records could be collected. Detailed information on anti-diabetic medication, i.e. duration of drug use, doses, toxicity, and HbA1C values were not always reported, even though the glycemic control and the timing of anti-diabetic drug use prior to and post-cancer diagnosis might influence severity and survival outcome of EC (Suissa et al., 2012). Another limitation was a small sample size and it may be a reason for not showing a significant difference in our study.

The clinical usefulness of metformin in gynecology is obviously seen in the patients with PCOS. Metformin has the benefits by an improvement of ovulation and reduction of long-term metabolic complications (Nestler et al., 2008; Mathur et al., 2008). Although in the current study did not show a protective effect of metformin on the treatment of EC, metformin may be offered as an effective chemotherapeutic agent in the treatment and long-term management of EC, with the additional benefits of low cost, oral route of administration, proven safety and very little toxicity (Mathur et al., 2008).

Recommendation for future clinical researches to confirm a protective effect of metformin on survival outcome in EC patients include many patients with a prospective randomized control design. We also found that the present study has analyzed specifically patients who were using metformin for diabetes, the question of metformin's ability to against cancer in patients without diabetic was unanswered. A study of metformin as a cancer treatment in non-diabetics patients is needed to provide the best answer to this challenge. Additionally, the majority of patients was type I EC with early stage at the time of diagnosis, the OS is usually more than 5 years after diagnosis. Another important issue that would be concerned is the quality of life care for EC survivors.

In conclusion, a significant effect of metformin on survival outcomes in EC patients with diabetes was not found. Although the study was not clearly conclusive due to some limitations, metformin still has the additional benefits of cost saving and safety. Thus, larger studies with a prospective randomized control design are needed to clarify the benefit of metformin as a strategy for endometrial cancer prevention and treatment.

#### Conflict of interest

The authors declared no conflict of interest.

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