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Outcomes after surgery in patients with diabetes who used metformin: a retrospective cohort study based on a real-world database

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ABSTRACT

Introduction Limited information was available regarding the perioperative outcomes in patients with and without use of metformin. This study aims to evaluate the complications and mortality after major surgery in patients with diabetes who use metformin.

Research design and methods Using a real-world database of Taiwan's National Health Insurance from 2008 to 2013, we conducted a matched cohort study of 91 356 patients with diabetes aged >20 years who used metformin and later underwent major surgery. Using a propensity score-matching technique adjusted for sociodemographic characteristics, medical condition, surgery type, and anesthesia type, 91 356 controls who underwent surgery but did not use metformin were selected. Logistic regression was used to calculate the ORs with 95% CIs for postoperative complications and 30-day mortality associated with metformin use.

Results Patients who used metformin had a lower risk of postoperative septicemia (OR 0.94, 95% CI 0.90 to 0.98), acute renal failure (OR 0.87, 95% CI 0.79 to 0.96), and 30-day mortality (OR 0.79, 95% CI 0.71 to 0.88) compared with patients who did not use metformin, in both sexes and in every age group. Metformin users who underwent surgery also had a decreased risk of postoperative intensive care unit admission (OR 0.60, 95% CI 0.59 to 0.62) and lower medical expenditures (p<0.0001) than non-use controls.

Conclusions Among patients with diabetes, those who used metformin and underwent major surgery had a lower risk of complications and mortality compared with non-users. Further randomized clinical trials are needed to show direct evidence of how metformin improves perioperative outcomes.

Significance of this study

What is already known about this subject?

- Patients with diabetes had more postoperative complications and higher mortality than people without diabetes.

What are the new findings?

- Metformin use was associated with a reduced risk of 30-day in-hospital mortality and postoperative complications in patients with diabetes.
- The use of metformin was strongly associated with reduced use of intensive care and less medical expenditure.
- There was a dose–response relationship between use of metformin and reduced postoperative adverse events.

How might these results change the focus of research or clinical practice?

- Whether the association between metformin use and reduced risk is causal remains to be explored in future studies.

INTRODUCTION

The disease burden related to diabetes is rising,[1] and it was estimated in 2017 that there are 451 million people with diabetes worldwide.[2] Diabetes causes multisystem complications, including retinopathy, nephropathy, neuropathy, ischemic heart disease, stroke and peripheral vascular disease. Diabetes and its complications, associated mortality, reduced life expectancy, and financial costs have become an important public health concern.

Metformin, a first-line therapeutic agent among newly diagnosed patients with diabetes, is attracting attention as a new supportive therapy against a variety of diseases, such as cancer,[3 4] stroke,[5 6] and infectious diseases.[7 8] In the UK Prospective Diabetes Study, metformin use was associated with significant risk reductions for myocardial infarction and death at long-term follow-up.[9] The use of metformin was also associated with a significant 24.0% reduction in all-cause mortality when used as a means of secondary prevention.[10] Other studies have shown that metformin treatment improves poststroke angiogenesis and recovery and may have practical clinical use for stroke prevention.[5 6]

It was known that people with diabetes had more complications, higher mortality, and consumed more medical resources after surgery than people without diabetes.[11 12] The effects of metformin use on perioperative outcomes were not completely understood because there were several limitations in previous studies, such as small sample size,[13 14] a focus on specific surgical procedures,[13–15] inadequate control for confounding factors,[15] and a lack of global assessment.[13 15] Using the real-world data of Taiwan's National Health Insurance, we conducted a retrospective cohort study to evaluate complications and in-hospital mortality after major surgical procedures in patients with diabetes who did and did not use metformin.

METHODS

Source of data

In this study, we used the real-world database of Taiwan's National Health Insurance program that was implemented in March 1995; this insurance program covers more than 99% of the population in Taiwan. The available information included all beneficiaries' medical services, including inpatient and outpatient demographic characteristics, physicians' primary and secondary diagnoses, treatment procedures, prescriptions, and medical expenditures. This database has been validated previously.[16–23] According to regulations of Taiwan's Ministry of Health and Welfare, informed consent is not required because patient identifications were decoded and scrambled.

Study design

Among 3.6 million surgical patients who underwent major inpatient surgeries in Taiwan from 2008 to 2013, we identified 476 938 surgical patients with diabetes aged 20 years and 153 943 of them had used metformin within 24 months prior to the index surgery. Among surgical patients with diabetes, each patient who used metformin was randomly matched to a surgical patient who did not use metformin, using a propensity score-matched pair procedure (case–control ratio, 1:1) to adjust for sociodemographics, volume of the hospital, types of surgery, types of anesthesia, medical conditions, and Charlson comorbidity index.

Definition and criteria

For appropriately identifying metformin users in this study, we defined people who visited medical care and received a physician's prescription for metformin under the coverage of Taiwan's Health Insurance Program. In this study, we defined major inpatient surgery as surgical procedures requiring general, epidural or spinal anesthesia and index surgery with hospitalization for >1 day. Low-income status was defined as having a low income within 2 years before surgery. According to the regulations from the Ministry of Health and Welfare in Taiwan, people with low-income status were qualified to have the registration fee and medical copayment waived when visiting outpatient, emergency, and inpatient medical care. The criterion of low income was defined by local city or county governments. For example, a person living in Taipei (the capital of Taiwan) with a monthly income of less than US$500 (1 Taiwanese dollar is equal to US$30.324) and immovable possessions with a value of less than US$244 031 per household was considered to have a low income. In Taiwan, there were 144 863 low-income households and 304 470 low-income people in 2019. The definition of low income varies with urban and rural areas because of the local living conditions.

The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) administration codes and physicians' primary diagnoses were used to identify diabetes (ICD-9-CM 250), coexisting medical conditions (within the preoperative 24 months) and postoperative complications (that occurred during the index admission) for surgical patients.[11 24] These medical conditions were determined from medical claims for the 24-month preoperative period and included hypertension (ICD-9-CM 401–405), mental disorders (ICD-9-CM 290–319), ischemic heart disease (ICD-9-CM 410–414), chronic obstructive pulmonary disease (ICD-9-CM 491, 492 and 496), hyperlipidemia (ICD-9-CM 272.0, 272.1 and 272.2), liver cirrhosis (ICD-9-CM 571.2, 571.5 and 571.6), heart failure (ICD-9-CM 428), alcohol-related illness, renal dialysis (administration codes D8 and D9), and Parkinson's disease (ICD-9-CM 332). We defined alcohol-related illnesses, including alcoholic psychoses (ICD-9-CM 291), alcohol dependence syndrome (ICD-9-CM 303), alcohol abuse (ICD-9-CM 305), alcoholic fatty liver (ICD-9-CM 571.0), acute alcoholic hepatitis (ICD-9-CM 571.1), alcoholic cirrhosis of the liver (ICD-9-CM 571.2), and alcoholic liver damage (ICD-9-CM 571.3). Postoperative complications included postoperative bleeding (ICD-9-CM 998.0, 998.1 and 998.2), pneumonia (ICD-9-CM 480–486), septicemia (ICD-9-CM 038 and 998.5), urinary tract infection (ICD-9-CM 599.0), deep wound infection (ICD-9-CM 958.3), stroke (ICD-9-CM 430–437), acute myocardial infarction (ICD-9-CM 410), acute renal failure (ICD-9-CM 584) and pulmonary embolism (ICD-9-CM 415).

In this study, we examine the number of surgical procedures in every hospital in 2008–2013 and then categorized the surgical volume of hospital into three groups: low (the lowest tertile of surgical volume), moderate (the second tertile of surgical volume), and high (the highest tertile of surgical volume). In the National Health Insurance Program, the coverage of payment included all physician specialties of outpatient care, inpatient care, and emergency care. During the 24-month period before the index surgery, diabetes and coexisting medical conditions were defined as patients had at least two visits of medical care with physician's primary diagnosis. The 30-day postoperative mortality was calculated as death occurred within 30 days after the time point of surgical procedure included the period of during and discharge of index surgical admission. The complications after surgery during the index surgical admission

Table 1 Preoperative characteristics of diabetic patients with and without use of metformin after matching by propensity score

	No metformin (n=91 356)	Metformin (n=91 356)	P value
Sex	n (%)	n (%)	1.0000
Female	47 461 (52.0)	47 461 (52.0)	
Male	43 895 (48.0)	43 895 (48.0)	
Age, years			1.0000
20–29	1326 (1.5)	1326 (1.5)	
30–39	4133 (4.5)	4133 (4.5)	
40–49	8871 (9.7)	8871 (9.7)	
50–59	21 197 (23.2)	21 197 (23.2)	
60–69	26 132 (28.6)	26 132 (28.6)	
70–79	21 667 (23.7)	21 667 (23.7)	
≥80	8030 (8.8)	8030 (8.8)	
Low income			1.0000
No	90 538 (99.1)	90 538 (99.1)	
Yes	818 (0.9)	818 (0.9)	
Volume of hospital			1.0000
Low	31 044 (34.0)	31 044 (34.0)	
Moderate	30 652 (33.6)	30 652 (33.6)	
High	29 660 (32.5)	29 660 (32.5)	
Medical conditions			
Hypertension	28 901 (31.6)	28 901 (31.6)	1.0000
Mental disorders	12 861 (14.1)	12 861 (14.1)	1.0000
Ischemic heart disease	8098 (8.9)	8098 (8.9)	1.0000
COPD	3194 (3.5)	3194 (3.5)	1.0000
Hyperlipidemia	3929 (4.3)	3929 (4.3)	1.0000
Liver cirrhosis	2082 (2.3)	2082 (2.3)	1.0000
Heart failure	929 (1.0)	929 (1.0)	1.0000
Alcohol-related illness	1125 (1.2)	1125 (1.2)	1.0000
Renal dialysis	448 (0.5)	448 (0.5)	1.0000
Parkinson's disease	619 (0.7)	619 (0.7)	1.0000
CCI scores			1.0000
1	51 380 (56.2)	51 380 (56.2)	
2	16 406 (18.0)	16 406 (18.0)	
3	13 109 (14.4)	13 109 (14.4)	
≥4	10 461 (11.5)	10 461 (11.5)	
Types of surgery			1.0000
Skin	1040 (1.1)	1040 (1.1)	
Breast	1046 (1.1)	1046 (1.1)	
Musculoskeletal	32 296 (35.4)	32 296 (35.4)	
Respiratory	2919 (3.2)	2919 (3.2)	
Cardiovascular	2181 (2.4)	2181 (2.4)	
Digestive	20 435 (22.4)	20 435 (22.4)	
Kidney, ureter, bladder	8354 (9.1)	8354 (9.1)	
Obstetric surgery	1792 (2.0)	1792 (2.0)	
Neurosurgery	11 949 (13.1)	11 949 (13.1)	
Eye	1161 (1.3)	1161 (1.3)	
Others	8183 (9.0)	8183 (9.0)	
Types of anesthesia			1.0000
General	68 144 (74.6)	68 144 (74.6)	
Epidural or spinal	23 212 (25.4)	23 212 (25.4)	
Chronic kidney disease	1421 (1.6)	1421 (1.6)	1.0000
Prior diabetes hospitalization	1062 (1.2)	1062 (1.2)	1.0000
Inadequate control for diabetes	10 487 (11.5)	10 487 (11.5)	1.0000
Diabetes-related ketoacidosis	100 (0.1)	100 (0.1)	1.0000
Diabetes-related coma	123 (0.1)	123 (0.1)	1.0000
Diabetes-related renal manifestations	6509 (7.1)	6509 (7.1)	1.0000
Diabetes-related eye involvement	8570 (9.4)	8570 (9.4)	1.0000
Diabetes-related PCD	1464 (1.6)	1464 (1.6)	1.0000
Type I diabetes	309 (0.3)	309 (0.3)	1.0000
Preoperative use of insulin	6773 (7.4)	6773 (7.4)	1.0000

CCI, Charlson comorbidity index; COPD, chronic obstructive pulmonary disease; PCD, peripheral circulatory disorder.

were considered as secondary outcomes. The length of hospital stay (more than 1 day), medical expenditures (US dollars), and intensive care during the index surgical admission were also compared between patients who did and did not use metformin preoperatively.

Statistical analysis

We used a propensity score-matched pair design combined with frequency matching to balance the distribution of the covariates including age, sex, low income, volume of the hospital, types of surgery, types of anesthesia, hypertension, mental disorders, ischemic heart disease, chronic obstructive pulmonary disease, hyperlipidemia, liver cirrhosis, heart failure, alcohol-related illness, renal dialysis, Parkinson's disease, and Charlson comorbidity index between surgical patients who did and did not use metformin. For achieving a balance of covariates within matched pairs, we performed a structured iterative approach to refine this logistic regression model using 1:1 case–control match on the propensity score. We then matched (without replacement) patients who had metformin with those who did not by using a greedy matching algorithm. The algorithm proceeds

sequentially to the lowest digit match on propensity score (one digit). This will be referred to as the 8–1 digit match.

Categorical variables were summarized using frequencies (percentages) and were compared between patients with diabetes who did and did not use metformin using the χ^2 test. Continuous variables were summarized using means±SD and were compared using t-tests. Adjusted ORs and 95% CIs of postoperative complications, intensive care, and mortality associated with metformin use were calculated by multiple logistic regressions. Additional subgroup analyses stratified by age, sex, and number of medical conditions were also performed to examine the surgical outcomes among metformin recipients within these strata.

RESULTS

Under the propensity score-matching procedure, table 1 shows the balance in age, sex, low income, volume of the hospital, types of surgery, types of anesthesia, hypertension, mental disorders, ischemic heart disease, chronic obstructive pulmonary disease, hyperlipidemia, liver cirrhosis, heart failure, alcohol-related illness, renal dialysis, Parkinson's disease, and Charlson comorbidity index between surgical patients who did and did not use metformin. The characteristics of surgical patients with diabetes before matching procedure were shown in online supplemental table S1.

After adjustment in multiple logistic regression (table 2), patients with diabetes who used metformin had a lower risk of septicemia (OR 0.94, 95% CI 0.90 to 0.98), acute renal failure (OR 0.87, 95% CI 0.79 to 0.96), and 30-day mortality (OR 0.79, 95% CI 0.71 to 0.88) than did the control group. The use of metformin was associated with a decreased risk of intensive care use after surgery (OR 0.60, 95% CI 0.59 to 0.62). Lower medical expenditures (1974±3887 vs 2737±4200 US$, p<0.0001) were also noted for patients with diabetes who used metformin than for those who did not use metformin.

In the stratified analysis (table 3), a reduced risk of postoperative adverse events (including postoperative pneumonia, septicemia, acute renal failure, stroke, intensive care and mortality) was associated with metformin use in subgroups of females (OR 0.68, 95% CI 0.65 to 0.70), males (OR 0.65, 95% CI 0.63 to 0.67) and patients with every age group. The association between metformin and reduced risk of postoperative adverse events was significant in patients with medical conditions (0, 1, 2, and ≥3), Charlson comorbidity index (1, 2, 3, and ≥4 scores), various types of surgeries and those received general anesthesia or epidural/spinal anesthesia.

In table 4, metformin users with chronic kidney disease (OR 0.85, 95% CI 0.74 to 0.97), prior diabetes hospitalization (OR 0.66, 95% CI 0.57 to 0.77), inadequate control for diabetes (OR 0.63, 95% CI 0.60 to 0.67), diabetes-related ketoacidosis (OR 0.80, 95% CI 0.49 to 1.29), renal manifestations (OR 0.60, 95% CI 0.56 to 0.64), eye involvement (OR 0.56, 95% CI 0.53 to 0.59), and peripheral circulatory disorder (OR 0.58, 95% CI 0.50 to 0.67) had lower risks of postoperative adverse events compared with non-metformin control group. Patients with type 1 diabetes who used metformin also had reduced risk of postoperative adverse events (OR 0.62, 95% CI 0.46 to 0.82). Compared with patients without use of metformin, the decreased risk of postoperative adverse events

Table 2 Use of metformin and postoperative outcomes in patients with diabetes

	No metformin (N=91356)		Metformin (N=91356)		Risk of outcomes	
	Events	%	Event	%	OR	(95% CI)*
30-day in-hospital mortality	779	0.9	616	0.7	0.79	(0.71 to 0.88)
Postoperative complications						
Pneumonia	2422	2.7	2307	2.5	0.95	(0.90 to 1.01)
Septicemia	4487	4.9	4224	4.6	0.94	(0.90 to 0.98)
Pulmonary embolism	97	0.1	111	0.1	1.15	(0.87 to 1.50)
Acute renal failure	988	1.1	864	1	0.87	(0.79 to 0.96)
Stroke	3399	3.7	3328	3.6	0.98	(0.93 to 1.03)
Urinary tract infection	5519	6	5656	6.2	1.03	(0.99 to 1.07)
Deep wound infection	468	0.5	443	0.5	0.95	(0.83 to 1.08)
Acute myocardial infarction	423	0.5	378	0.4	0.89	(0.77 to 1.02)
Postoperative bleeding	507	0.6	483	0.5	0.95	(0.84 to 1.08)
ICU stay	27255	29.8	19720	21.6	0.6	(0.59 to 0.62)
Medical expenditure, US$†	2737±4200		1974±3887		p<0.0001	
Length of hospital stay, days†	8.6±13.3		8.5±14.2		p=0.1449	

*Adjusted for all covariates listed in table 1.
†Mean±SD.
ICU, intensive care unit.

Table 3 The stratified analysis for postoperative adverse events associated with metformin use in patients with diabetes

			Adverse events*			
		n	Events	Rate, %	OR	(95% CI)†
Female	No metformin	47461	13398	28.2	1	(reference)
	Metformin	47461	10356	21.8	0.68	(0.65 to 0.70)
Male	No metformin	43895	15979	36.4	1	(reference)
	Metformin	43895	12432	28.3	0.65	(0.63 to 0.67)
Age 20–39 years	No metformin	5459	1270	23.3	1	(reference)
	Metformin	5459	1172	21.5	0.89	(0.81 to 0.98)
Age 40–49 years	No metformin	8871	2497	28.2	1	(reference)
	Metformin	8871	2286	25.8	0.87	(0.81 to 0.94)
Age 50–59 years	No metformin	21197	6527	30.8	1	(reference)
	Metformin	21197	5333	25.2	0.73	(0.70 to 0.76)
Age 60–69 years	No metformin	26132	8391	32.1	1	(reference)
	Metformin	26132	6195	23.7	0.61	(0.59 to 0.64)
Age 70–79 years	No metformin	21667	7462	34.4	1	(reference)
	Metformin	21667	5388	24.9	0.58	(0.55 to 0.61)
Age ≥80 years	No metformin	8030	3230	40.2	1	(reference)
	Metformin	8030	2414	30.1	0.58	(0.54 to 0.63)
0 medical condition	No metformin	44113	13488	30.6	1	(reference)
	Metformin	44113	10596	24	0.69	(0.66 to 0.71)
1 medical condition	No metformin	34599	11311	32.7	1	(reference)
	Metformin	34599	8619	24.9	0.64	(0.62 to 0.67)
2 medical conditions	No metformin	10556	3775	35.8	1	(reference)
	Metformin	10556	2943	27.9	0.64	(0.60 to 0.69)
≥3 medical conditions	No metformin	2088	803	38.5	1	(reference)
	Metformin	2088	630	30.2	0.63	(0.55 to 0.73)
1 CCI score	No metformin	51380	14236	27.7	1	(reference)
	Metformin	51380	10745	20.9	0.65	(0.63 to 0.67)
2 CCI scores	No metformin	16406	5530	33.7	1	(reference)
	Metformin	16406	4538	27.7	0.72	(0.69 to 0.76)
3 CCI scores	No metformin	13109	4770	36.4	1	(reference)
	Metformin	13109	3459	26.4	0.59	(0.56 to 0.62)
≥4 CCI scores	No metformin	10461	4841	46.3	1	(reference)
	Metformin	10461	4046	38.7	0.71	(0.67 to 0.75)
Skin surgery	No metformin	1040	402	38.7	1	(reference)
	Metformin	1040	334	32.1	0.74	(0.61 to 0.89)
Breast surgery	No metformin	1046	327	31.3	1	(reference)
	Metformin	1046	269	25.7	0.75	(0.61 to 0.91)
Musculoskeletal surgery	No metformin	32296	6128	19	1	(reference)
	Metformin	32296	4696	14.5	0.71	(0.68 to 0.74)
Respiratory surgery	No metformin	2919	1180	40.4	1	(reference)
	Metformin	2919	907	31.1	0.65	(0.58 to 0.72)
Cardiovascular surgery	No metformin	2181	1809	82.9	1	(reference)
	Metformin	2181	1384	63.5	0.33	(0.28 to 0.38)
Digestive surgery	No metformin	20435	8771	42.9	1	(reference)
	Metformin	20435	6881	33.7	0.65	(0.63 to 0.68)

Continued

Table 3 Continued

			Adverse events*			
		n	Events	Rate, %	OR	(95% CI)†
Kidney, ureter, bladder surgery	No metformin	8354	2411	28.9	1	(reference)
	Metformin	8354	2015	24.1	0.78	(0.72 to 0.83)
Obstetric surgery	No metformin	1792	176	9.8	1	(reference)
	Metformin	1792	206	11.5	1.21	(0.97 to 1.50)
Neurosurgery surgery	No metformin	11949	5954	49.8	1	(reference)
	Metformin	11949	4217	35.3	0.52	(0.49 to 0.55)
Eye surgery	No metformin	1161	271	23.3	1	(reference)
	Metformin	1161	204	17.6	0.69	(0.57 to 0.85)
Others surgery	No metformin	8183	1948	23.8	1	(reference)
	Metformin	8183	1675	20.5	0.81	(0.75 to 0.88)
Epidural or spinal anesthesia	No metformin	23212	3726	16.1	1	(reference)
	Metformin	23212	2979	12.8	0.76	(0.72 to 0.80)
General anesthesia	No metformin	68144	25651	37.6	1	(reference)
	Metformin	68144	19809	29.1	0.64	(0.63 to 0.66)

*Adverse events included with 30-day in-hospital mortality, pneumonia, septicemia, acute renal failure, stroke, and intensive care.
†Adjusted for all covariates listed in table 1.
CCI, Charlson comorbidity index.

was also found in preoperative metformin users with (OR 0.75, 95% CI 0.72 to 0.77) and without (OR 0.61, 95% CI 0.59 to 0.62) used metformin during the index surgical admission. Metformin users who had no preoperative insulin had lower risk of postoperative adverse events than the non-metformin control group (OR 0.63, 95% CI 0.62 to 0.65). However, the risk of postoperative adverse event was higher in metformin users who had preoperative insulin than in the non-metformin control group. There is a significant dose–response relationship between cumulative use of metformin and postoperative adverse event.

DISCUSSION

This is the first study to comprehensively evaluate the risks of complications and mortality after major surgery in patients who use metformin. Under a matching procedure by propensity score, we found that patients with diabetes who used metformin were more likely to have lower rates of postoperative stroke, pneumonia, sepsis, acute renal failure, and 30-day mortality compared with those who did not use metformin. Reduced use of the intensive care unit, length of hospital stay, and medical expenditure were also found more often in the metformin group compared with the non-metformin group.

Prior research has shown that metformin treatment was associated with a 15% decrease in all-cause mortality compared with insulin treatment in patients with diabetes undergoing colorectal surgery.[25] Some studies also found that patients who used metformin had decreased 30-day mortality compared with non-users after ICU admission.[26] However, the association between metformin use and mortality in patients with diabetes remains controversial. Various studies have found that the outcomes of septic patients who use metformin were not significantly different from those who did not use metformin.[27 28] The possible cause for metformin reducing the mortality of patients with diabetes remains unclear. Earlier experimental studies showed that metformin might ameliorate sepsis or endotoxemia-associated lung injuries in many inflammatory diseases.[29] It was suggested that metformin inhibits mitochondrial complex I, which plays an important role in modulating Toll-like receptor 4-mediated neutrophil activation, thus preventing acute inflammatory processes.[30]

In this study, we failed to investigate the association between metformin use and reduced risk of postoperative stroke. Previous studies have shown that metformin use in patients with diabetes might have a neuroprotective effect and was associated with a reduced incidence of stroke and neurological severity.[5 31] The mechanisms underlying reductions in stroke severity in patients treated with metformin remain speculative and are likely multifactorial. Metformin is known to be a glucose-lowering agent with actions mediated by the activation of adenosine 5′-monophosphate-activated protein kinase.[32] Metformin possesses a direct scavenging effect against oxygenated free radicals generated in vitro[33] and decreases intracellular production of reactive oxygen species in aortic endothelial cells.[34] Various studies have reported that adenosine 5′-monophosphate-activated protein kinase signaling is associated with stimulation of vascular endothelial growth factor expression, angiogenesis in response to hypoxic stress, inhibition of the

Table 4 Postoperative adverse events in association with the severity of patients with diabetes who used metformin

	Adverse event*				
	n	Events	Rate, %	OR	(95% CI)†
Non-metformin control group	91 356	29 377	32.2	1	(reference)
Preoperative metformin users had					
Chronic kidney disease	1421	555	39.1	0.85	(0.74 to 0.97)
Prior diabetes hospitalization	1062	292	27.5	0.66	(0.57 to 0.77)
Inadequate control for diabetes	10 487	2477	23.6	0.63	(0.60 to 0.67)
Diabetes-related ketoacidosis	100	26	26	0.8	(0.49 to 1.29)
Diabetes-related coma	123	43	35	1.12	(0.74 to 1.69)
Diabetes-related renal manifestations	6509	1508	23.2	0.6	(0.56 to 0.64)
Diabetes-related eye involvement	8570	1714	20	0.56	(0.53 to 0.59)
Diabetes-related PCD	1464	289	19.7	0.58	(0.50 to 0.67)
Type I diabetes	309	65	21	0.62	(0.46 to 0.82)
No use of metformin in index admission	54 959	11 602	21.1	0.61	(0.59 to 0.62)
Used metformin in index admission	36 397	11 186	30.7	0.75	(0.72 to 0.77)
No preoperative use of insulin	84 583	19 859	23.5	0.63	(0.62 to 0.65)
Preoperative use of insulin	6773	2929	43.3	1.12	(1.06 to 1.18)
Cumulative use of metformin, DDD					
<50	50 360	15 464	30.7	0.82	(0.80 to 0.85)
50–99	13 636	2718	19.9	0.53	(0.50 to 0.55)
100–149	8199	1577	19.2	0.51	(0.48 to 0.54)
150–199	6015	1041	17.3	0.47	(0.43 to 0.50)
200–249	3426	616	18	0.49	(0.45 to 0.54)
≥250	9720	1372	14.1	0.39	(0.37 to 0.41)

*Adverse events included with 30 day in-hospital mortality, pneumonia, septicemia, acute renal failure, stroke, and intensive care.
†Adjusted for all covariates listed in table 1.
DDD, daily defined dose; PCD, peripheral circulatory disorder.

inflammatory response, and protective effects against endothelial cell injury.[35 36] These various mechanisms may lead to reductions in cellular stress under hypoxia, thus protecting brain tissue from ischemic injury. As a result, future prospective studies may explore the association between metformin use and reduced risk of postoperative stroke.

The increased risk of infection after surgeries has been investigated in patients with diabetes.[24 37] Recent studies have demonstrated that metformin use may reduce the infectious risk in patients with diabetes.[7 8 38] Metformin has several actions that cause it to mimic an antibiotic. Metformin is known to alter folate metabolism in certain bacteria by inhibiting the bacterial folate cycle. Its action was found to be similar to the antibiotic trimethoprim, which inhibits the enzyme dihydrofolate reductase.[39] Previous research has shown that metformin inhibits complex 1 of the electron transport chain in mitochondria,[40] which is structurally similar to the proton translocating unit of the bacterial respiratory chain complex. Hence, metformin has the potential to inhibit the energy-generating process in bacteria, which will result in inhibition of growth in bacteria. Metformin is also known to inhibit the bacterial mitochondrial enzyme glycerophosphate dehydrogenase,[41] which will further prevent the utilization of glycerol and subsequent generation of ATP. This is expected to inhibit the growth of bacteria dependent on glycerol for their growth and virulence, such as *Streptococcus pneumoniae* and *Mycoplasma pneumoniae*.[42] In the present study, we found that metformin use in patients with diabetes was associated with a reduced risk of postoperative pneumonia. However, the biomedical mechanism of the association between metformin and decreased risk of postoperative pneumonia requires further experimental research.

In the present study, we found that metformin use was associated with a significantly reduced risk of postoperative acute renal failure. Previous experimental studies have demonstrated the nephroprotective effect of metformin.[43 44] The authors suggested that metformin activates adenosine 5′-monophosphate-activated protein kinase signaling and modulates other signaling pathways, including inhibition of mitochondrial reactive oxygen species generation, inhibition of mitochondrial respiratory chain complex I, reduction of renal lipotoxicity, and reduction of hypoxia inducible

factor, thus protecting renal cells from damage.[45] The therapeutic use of metformin in kidney disease was restricted by the US Food and Drug Administration due to the risk of patients developing lactic acidosis after its administration. However, more studies have indicated a relatively low incidence of lactic acidosis and revealed the additional benefits of metformin therapy.[46] Hence, the US Food and Drug Administration has recently approved the use of metformin in patients with underlying kidney disease based on their estimated glomerular filtration rate. Its nephroprotective properties warrant additional studies to evaluate its effect as a nephroprotectant in patients with and without chronic kidney disease.

Although our study had several strengths, such as a large sample size, comprehensive matching by propensity score, global assessment of postoperative outcomes, including various types of surgery, and multivariate adjustment, some limitations need to be considered when interpreting our findings. First, we used administrative claims data that lacked detailed information on sociodemographic factors and lifestyle. Unmeasured confounding due to a combination of various factors, such as those related to unhealthy lifestyle and less social support, might have influenced the risk of outcomes. Second, we had no clinical data on various organ systems. The severity of disease and comorbid medical conditions could not be validated. The severity of kidney disease could have an impact on the prescription of metformin, as most metformin users could have mild kidney disease. The beneficial effect of metformin on postoperative acute renal failure could have been biased. The information of stage of chronic kidney disease and estimated glomerular filtration rate is not available in this database. Third, although the accuracy of the diagnosis codes from the research database in studies based on these codes has been accepted by peer reviewers for prominent scientific journals worldwide, the validity of diabetes, other comorbidities and complication codes might still be a limitation of this study. Fourth, we have to emphasize that a physician's prescription is not equal to a patient's intake because patient non-compliance commonly occurs in non-clinical settings. We also could not exclude the possibility that the results of this study were confounded by indication of metformin. In addition, the impact of characteristics of physician and hospital could not be controlled, although we adjusted the volume of hospital in this study. Finally, although we used multivariate adjustment to control for confounders, residual confounding is always possible.

In conclusion, metformin use was associated with a reduced risk of 30-day in-hospital mortality and postoperative complications, including pneumonia, septicemia, acute renal failure, and stroke. However, the beneficial effects of metformin on postoperative outcome should be validated in future randomized clinical trials to provide more evidence.

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