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ORIGINAL ARTICLE

Metformin's impact on delirium in diabetic cardio surgery patients

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Abstract

Purpose The effect of metformin on postoperative delirium (POD) in patients with type 2 diabetes mellitus (T2DM) undergoing cardiovascular surgery remains unclear. This study aimed to evaluate whether metformin use reduces POD risk in this high-risk population by analyzing data from Taiwan's National Health Insurance Research Database using propensity score matching (PSM).

Methods We included T2DM patients who underwent coronary artery bypass grafting (CABG) or valve replacement between 2015 and 2018. PSM was used to balance covariates between metformin users and non-users. Logistic regression and Kaplan–Meier analyses were performed to assess POD risk and its cumulative incidence.

Results Metformin use was associated with a significantly reduced risk of POD (adjusted odds ratio [aOR], 0.52; 95% confidence interval [CI], 0.40–0.67). A dose–response trend was observed, with decreasing aORs for higher cumulative metformin exposure. Protective factors included higher income, urban residency, and statin use; risk factors included older age, prolonged anesthesia, higher aDCSI, CCI scores, and depression.

Conclusion Metformin significantly lowers the risk of POD in T2DM patients undergoing cardiovascular surgery, showing a clear dose-dependent protective effect. These findings highlight metformin's potential as a chemopreventive agent against post-surgical complications in this population.

Keywords Metformin · Postoperative delirium · Type 2 diabetes mellitus · Cardiovascular surgery · Prognostic factors

Zhongyuan Lu, Mingyang Sun, Szu-Yuan Wu and Jiaqiang Zhang have contributed equally to this study.

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Abbreviations

aOR	Adjusted odds
CI	Confidence interval
aDCSI	Adapted diabetes complications severity index
DDD	Defined daily dose
cDDD	Cumulative defined daily dose
DM	Diabetes mellitus
T2DM	Type 2 diabetes mellitus
POD	Postoperative delirium
NHIRD	National Health Insurance Research Database
cDDD	Cumulative defined daily dose
RCT	Randomized controlled trials
PSM	Propensity score matching
CABG	Coronary artery bypass grafting
ASA	American Society of Anesthesiologists

Introduction

Annually, over a million patients in the United States and Europe undergo cardiovascular surgery, a procedure known for its potential to enhance life quality and extend lifespan [1, 2]. Despite advancements, cardiovascular surgery is not without risks, including complications [3, 4]. However, postoperative delirium (POD) continues to be a significant concern [5, 6], affecting 27.2–53.3% of the patients [7, 8]. This condition, a common yet severe clinical issue, often signals negative outcomes such as delayed cognitive recovery, a decline in independence, extended hospital stays, increased likelihood of nursing home placement, and even mortality [5, 9]. A concerning observation is that only 4% of the patients experience complete delirium resolution upon hospital discharge after cardiovascular surgery [10]. Moreover, elderly patients developing delirium are at a nearly fivefold increased risk of new dementia compared to their counterparts without delirium [11]. The financial impact is significant in the United States, where annual healthcare costs related to POD are estimated at $32.9 billion [12].

The etiology of POD following cardiovascular surgery remains elusive, likely stemming from a complex interplay of multiple pathologies and inherent patient characteristics that manifest as clinical symptoms [13]. Generally, individuals with a greater burden of pre-existing conditions have an increased number of risk factors, making them more susceptible to delirium. Recent studies highlight a heightened vulnerability to POD among patients with diabetes mellitus (DM) [14–17]. The global prevalence of DM is on the rise, currently affecting an estimated 285 million people, or 6.6% of the global population aged between 20 and 79 years [18]. Type 2 diabetes mellitus (T2DM) is associated with alterations in key cardiovascular risk factors, including increased levels of glycated hemoglobin, LDL cholesterol, proteinuria, smoking habits, and blood pressure [19]. These changes contribute significantly to the number of T2DM patients requiring cardiovascular surgery. Consequently, identifying effective prevention and treatment strategies for POD in this patient demographic is imperative.

Metformin, a staple in glucose management, is hypothesized to enhance cognitive function [20, 21]. Our previous research indicated its dose-dependent protective role against diabetes-related dementia [22]. However, studies on metformin's impact on delirium risk are limited. Delirium also independently predicts future dementia development [23]. These conditions likely share common mechanisms and risk factors, such as age, diabetes mellitus, phosphorylated tau protein levels, and educational attainment [23]. In this context, understanding the prognostic factors of POD post-surgery is vital, prompting our investigation using a logistic regression model. While a randomized controlled trial (RCT) could provide insights, ethical considerations make this challenging [24]. Therefore, a well-structured real-world propensity score matching (PSM) study is essential. Our study aims to thoroughly examine how metformin usage and other clinical factors affect the POD risk in T2DM patients undergoing cardiovascular surgery, offering valuable insights for clinical decision-making.

Methods

Study population

In this cohort investigation, we conducted an extensive study employing the Taiwan National Health Insurance (NHI) Research Database (NHIRD) spanning the timeframe from 2015 to 2018. Our study cohort comprised individuals diagnosed with type 2 diabetes mellitus (T2DM) in 2008, ensuring the selection of a representative sample from the T2DM population for meticulous analysis. The NHIRD provides a wealth of comprehensive medical claims data encompassing diagnoses, surgical and anesthetic procedures, drug prescriptions, as well as encrypted demographic and enrollment profiles, all linked to unique patient identifiers [25–30]. This invaluable database is further linked to the death registry, enabling precise determination of vital status and cause of death for each participant. Notably, the NHIRD stands as a cornerstone for population-based research, offering an exhaustive coverage of the entire NHI-insured population of Taiwan, encompassing over 99% of the Taiwanese populace [25–30]. This data source serves as a linchpin for our exploration, providing a foundation for comprehensive insights into the studied cohort.

Criteria for inclusion and exclusion

Our study focused on individuals aged 18 or older with T2DM undergoing elective coronary artery bypass grafting (CABG) or valve replacement. Exclusion criteria comprised patients with missing age data and those undergoing a second cardiovascular surgery. Metformin use was defined as a minimum of 28 cumulative defined daily doses (cDDDs) within 3 months before the index date, set as the date of cardiovascular surgery. The observation period started on the index date and continued until discharge, death, or the occurrence of the primary endpoint, postoperative delirium (POD), whichever came first. The case group, representing metformin users, met the criteria of receiving at least 28 cDDDs of metformin within 3 months before the index date. The control group, consisting of non-metformin users, included patients with no metformin use during the entire follow-up period. Follow-up duration was defined from the diagnosis of T2DM to the admission period for cardiovascular surgery. We further analyzed the association between cumulative metformin dosage before cardiovascular surgery and POD risk. Our study, the first to investigate the link between metformin use and POD risk undergoing cardiovascular surgery in T2DM patients, aims to provide valuable insights into this association.

Exclusion criteria from our T2DM cohort encompassed patients meeting any of the following: (1) pre-existing diagnosis of delirium or dementia before the index date, (2) missing sex or age data or being younger than 18 years old, or (3) undergoing previous cardiovascular surgery. In addition, individuals with severe renal impairment, hepatic dysfunction, or pre-existing cognitive impairment were excluded. In addition, patients undergoing a second cardiovascular surgery were excluded to ensure a more homogeneous study population in terms of disease severity. Patients requiring a second surgery typically have more severe underlying cardiac conditions, leading to greater intraoperative hypoxia and an increased risk of POD. Since disease severity is a crucial confounding factor, we aimed to minimize variability by including only patients undergoing their first cardiovascular surgery. This approach allowed us to assess the association between metformin use and POD risk more accurately, without the additional confounding effects of prior surgeries. The study protocols received approval from the Institutional Review Board of Tzu-Chi Medical Foundation (IRB number: IRB109-015-B).

Metformin exposure

The cumulative metformin dose was determined by multiplying the number of dispensed pills by the prescribed dose and then dividing this value by the recorded days' supply. Dosage was expressed using the defined daily dose (DDD) of metformin, a measure established by the World Health Organization representing the average maintenance dose per day for a drug used for its main indication in adults. The cumulative defined daily doses (cDDDs) were calculated as the sum of the daily defined doses.

In pharmacoepidemiological research, long-term use of medications for chronic diseases is typically defined as exceeding 28 cDDDs [22, 31–33]. In this study, we classified metformin users as those who had taken at least 28 cDDDs within the 3 months preceding cardiovascular surgery. This threshold ensures that patients classified as metformin users have a consistent history of metformin use, reflecting its long-term impact rather than incidental or sporadic exposure. Conversely, non-metformin users were defined as those who had never taken metformin, either before surgery or during the follow-up period. Patients with cDDD < 28 were not included in the analysis, as their metformin exposure was deemed insufficient to exert a clinically meaningful effect and could introduce misclassification bias by including patients with inconsistent or transient metformin use. This approach was adopted to establish a clear distinction between metformin users and non-users, ensuring a meaningful difference in metformin exposure at the time of cardiovascular surgery. The follow-up period for metformin users was defined as the interval from T2DM diagnosis to cardiovascular surgery, allowing for the comprehensive assessment of long-term patient characteristics and comorbidities. However, for defining metformin exposure, a 3-month window prior to surgery was selected to ensure that only recent and sustained metformin users were classified as metformin users. This approach aligns with perioperative pharmacoepidemiological principles, ensuring that the observed effects on POD reflect the influence of metformin use immediately before surgery rather than prior, potentially discontinued usage.

Metformin nonuse was defined as the absence of metformin use throughout the entire follow-up period, excluding occasional users. Patients were then stratified into four subgroups based on quartiles of cDDDs.

PSM and covariates

To address potential confounding factors, our analysis included various covariates. Study participants were categorized into four age groups based on their age at the index date: 18–50, 51–60, 61–70, and 71 or older. For matched metformin non-users, variables collected at the index date were employed.

We employed a logistic regression model to explore the relationship between metformin use and the risk of POD, while controlling for potential confounders. To enhance comparability between metformin users and non-users, patients were matched based on their propensity scores.

Matching variables encompassed age, sex, income levels, urbanization, American Society of Anesthesiologists (ASA) physical status, anesthesia duration hours, combination therapies in antidiabetic medications (individual therapy, dual therapy, triple combination, quadruple combination, and more than four combinations), specific antidiabetic medications (insulin, sulfonylurea, sodium-glucose co-transporter 2 [SGLT2] inhibitor, alpha-glucosidase inhibitor, thiazolidinedione, and dipeptidyl peptidase-4 [DPP-4] inhibitor), the adapted Diabetes Complications Severity Index (aDCSI) Score (indicating the severity of diabetes), Charlson Comorbidity Index (CCI) scores, coexisting comorbidities, and medication use (statin). To avoid repeated adjustment in multivariate analysis, we excluded repeat comorbidities from the CCI calculations. Comorbidity onset within 1 year of the index date was identified using International Classification of Diseases codes from either the Ninth Revision, Clinical Modification (ICD-9-CM) or the Tenth Revision, Clinical Modification (ICD-10-CM), obtained from either the main inpatient diagnosis or at least two outpatient visits within 1 year.

Continuous variables are presented as means with standard deviations or medians with first and third quartiles, as appropriate. To minimize intergroup differences, a greedy matching technique was employed: propensity score matching (PSM) with a caliper width of 0.1, matching patients at a ratio of 1:1 [34]. This method entails selecting controls with identical background covariates deemed essential for control by the investigator.

Primary endpoints

The principal outcome investigated in this study was the incidence of POD following the initial cardiovascular surgery in patients diagnosed with type 2 diabetes mellitus (T2DM), with a focus on those with or without metformin use.

Statistical analysis

We gathered patient characteristics as covariates, detailed in Table 1, employing the Chi-squared test for categorical variables, t-test for continuous variables, and Wilcoxon rank-sum test for median values. The baseline was set as the cohort entry date. To evaluate the association between metformin use and the risk of POD, we calculated odds ratios (ORs) with 95% confidence intervals (CIs) using logistic regression models. The adjustments included age, sex, income levels, urbanization, ASA physical status, anesthesia duration hours, combination therapies in antidiabetic medications, specific antidiabetic medications, aDCSI Score, CCI scores, coexisting comorbidities, and medication use. In addition, logistic regression analysis was conducted for POD in T2DM patients undergoing cardiovascular surgery, comparing different metformin doses (cDDD). The logistic regression model aimed to identify independent prognostic factors for POD in T2DM undergoing cardiovascular surgery (pre-propensity score matching). The cumulative incidence of POD was estimated using the Kaplan–Meier method and compared using the log-rank test. All statistical analyses were executed in SAS for Windows (version 9.4; SAS Institute, Cary, NC), with a two-sided P value of < 0.05 considered statistically significant.

Results

Baseline characteristics of the study population

In this investigation, we analyzed data from 4,319 patients with T2DM undergoing CABG or valve replacement, enrolled between 2015 and 2018 (Table 1). Before implementing PSM, the metformin use group demonstrated a higher proportion of younger individuals, more male patients, lower income levels, higher ASA scores, shorter anesthesia duration hours, more combination therapies in antidiabetic medications (an alternative for severe diabetes severity), increased antidiabetic medication use, higher aDCSI scores, and more coexisting comorbidities compared to the non-metformin use group. For comparison between metformin user and nonuser groups, individual 1:1 matching was performed, resulting in each group comprising 416 patients. Post-PSM, we observed that variables such as age, sex, income levels, urbanization, ASA physical status, anesthesia duration hours, combination therapies in antidiabetic medications, specific antidiabetic medications, aDCSI Score, CCI scores, coexisting comorbidities, and medication use were comparable between the metformin user and nonuser groups, with no significant differences observed. Following PSM application, the crude incidence of POD was 25.96% in the metformin use group and 40.38% in the non-metformin use group ($P < 0.0001$).

POD risk odds between metformin use and non-metformin use groups

Table 2 depicts the association of POD risk with metformin use in our study cohort. Before PSM, the adjusted odds ratio (aOR) for POD was 0.58 (95% CI 0.47–0.71, $P < 0.0001$) in the metformin use group compared to the non-metformin use group. Following well-matched confounding factors through PSM, no covariates were significantly associated with POD risk. The independent significant predictor remained metformin use, with aOR (95% CI) of 0.52 (0.40–0.67, $P < 0.0001$) after PSM. In addition, Fig. 1 illustrates the Kaplan–Meier cumulative incidence of POD in

Table 1 Comparison of patient characteristics before and after propensity score matching among those undergoing cardiovascular surgery with or without metformin treatment

	Before propensity score matching					After propensity score matching				
	Non-metformin		Metformin		*P* value	Non-metformin		Metformin		*P* value
	N = 2940		*N* = 1379			*N* = 416		*N* = 416		
	N	%	*N*	%		*N*	%	*N*	%	
Age (mean ± SD), years old	63.44 ± 14.65		62.10 ± 11.29		0.0028	64.32 ± 12.90		63.58 ± 11.89		0.3850
Age, median (IQR)	65.00 (54.00,75.00)		62.00 (54.00,70.00)		< 0.0001	65.00 (56.00,74.00)		63.00 (54.00,73.00)		0.2638
Age group, years					< 0.0001					0.5844
≤ 50	872	29.66%	390	28.28%		102	24.52%	111	26.68%	
51–60	274	9.32%	258	18.71%		59	14.18%	69	16.59%	
61–70	712	24.22%	398	28.86%		111	26.68%	105	25.24%	
≥ 71	1082	36.80%	333	24.15%		144	34.62%	131	31.49%	
Sex					0.0423					0.9404
Female	978	33.27%	416	30.17%		131	31.49%	130	31.25%	
Male	1962	66.73%	963	69.83%		285	68.51%	286	68.75%	
Income levels (NTD)					< 0.0001					0.4090
Low income	55	1.87%	28	2.03%		10	2.40%	7	1.68%	
Financial dependent	944	32.11%	497	36.04%		154	37.02%	145	34.86%	
< 20,000	1,528	51.97%	617	44.74%		196	47.12%	195	46.88%	
2001–30000	180	6.12%	134	9.72%		22	5.29%	31	7.45%	
30,001–45000	160	5.44%	65	4.71%		18	4.33%	27	6.49%	
> 45,000	73	2.48%	38	2.76%		16	3.85%	11	2.64%	
Urbanization					0.2245					0.5625
Rural	741	25.20%	324	23.50%		98	23.56%	91	21.88%	
Urban	2199	74.80%	1055	76.50%		318	76.44%	325	78.13%	
ASA physical status					< 0.0001					0.5222
1	90	3.06%	0	0.00%						
2	456	15.51%	36	2.61%		24	5.77%	20	4.81%	
3	814	27.69%	521	37.78%		161	38.70%	176	42.31%	
4	1580	53.74%	822	59.61%		231	55.53%	220	52.88%	
Anesthesia duration hours					< 0.0001					0.8697
≤ 4	2524	85.85%	1350	97.90%		396	95.19%	397	95.43%	
> 4	416	14.15%	29	2.10%		20	4.81%	19	4.57%	
Combination therapies in antidiabetic					< 0.0001					0.7481
Individual therapy	1127	38.33%	26	1.89%		30	7.21%	26	6.25%	
Dual therapy	1440	48.98%	117	8.48%		117	28.13%	117	28.13%	
Triple combination	189	6.43%	242	17.55%		141	33.89%	142	34.13%	

Table 1 (continued)

	Before propensity score matching					After propensity score matching				
	Non-metformin		Metformin		*P* value	Non-metformin		Metformin		*P* value
	N = 2940		*N* = 1379			*N* = 416		*N* = 416		
	N	%	*N*	%		*N*	%	*N*	%	
Quadruple combination	107	3.64%	388	28.14%		70	16.83%	71	17.07%	
More than four combinations	77	2.62%	606	43.94%		58	13.94%	60	14.42%	
Antidiabetic medications										
Insulin	1784	60.68%	1004	72.81%	< 0.0001	220	52.88%	221	53.13%	0.8830
Sulfonylurea	269	9.15%	1071	77.66%	< 0.0001	223	53.60%	225	54.09%	0.8265
SGLT2i	319	10.85%	228	16.53%	< 0.0001	29	6.97%	28	6.73%	0.7414
AGI	59	2.01%	361	26.18%	< 0.0001	52	12.50%	46	11.06%	0.5187
TZD	32	1.09%	240	17.40%	< 0.0001	27	6.49%	26	6.25%	0.8871
DPP4i	320	10.88%	258	18.71%	< 0.0001	33	7.93%	35	8.41%	0.7243
Others	603	20.51%	365	26.47%	< 0.0001	47	11.30%	51	12.26%	0.3680
aDCSI score (mean ± SD)	2.44 ± 1.81		3.31 ± 2.19		< 0.0001	2.90 ± 1.97		3.09 ± 2.13		0.1994
	2.00 (1.00,4.00)		3.00 (2.00,5.00)		< 0.0001	2.00 (2.00,4.00)		3.00 (2.00,4.00)		0.2892
aDCSI score					< 0.0001					0.8477
0	530	18.03%	128	9.28%		48	11.54%	50	12.02%	
1	282	9.59%	156	11.31%		53	12.74%	45	10.82%	
2	992	33.74%	298	21.61%		108	25.96%	101	24.28%	
3	277	9.42%	185	13.42%		46	11.06%	51	12.26%	
≥ 4	859	29.22%	612	44.38%		161	38.70%	169	40.63%	
aDCSI scores										
Retinopathy	236	8.03%	337	24.44%	< 0.0001	79	18.99%	86	20.67%	0.6391
Nephropathy	987	33.57%	568	41.19%	< 0.0001	169	40.63%	169	40.63%	1.0000
Neuropathy	210	7.14%	284	20.59%	< 0.0001	62	14.90%	65	15.63%	0.4204
Cerebrovascular	527	17.93%	303	21.97%	0.0016	93	22.36%	84	20.19%	0.4458
Cardiovascular	1,917	65.20%	1,001	72.59%	< 0.0001	300	72.12%	283	68.03%	0.1981
Peripheral vascular disease	293	9.97%	266	19.29%	< 0.0001	74	17.79%	78	18.75%	0.4228
Metabolic	21	0.71%	48	3.48%	< 0.0001	10	2.40%	15	3.61%	0.3099
CCI scores										
Mean (SD)	2.81 ± 2.35		2.79 ± 2.26		0.7451	2.85 ± 2.36		2.76 ± 2.28		0.5905
Median (Q1–Q3)	2.00 (1.00,4.00)		2.00 (1.00,4.00)		0.8631	2.00 (1.00,4.00)		2.00 (1.00,4.00)		0.6351
CCI scores					0.2335					0.8603
0	567	19.29%	245	17.77%		81	19.47%	79	18.99%	
≥ 1	2373	80.71%	1134	82.23%		335	80.53%	337	81.01%	

Table 1 (continued)

	Before propensity score matching					After propensity score matching				
	Non-metformin		Metformin		*P* value	Non-metformin		Metformin		*P* value
	N = 2940		*N* = 1379			*N* = 416		*N* = 416		
	N	%	*N*	%		*N*	%	*N*	%	
CCI										
Congestive heart failure	944	32.11%	455	32.99%	0.5618	133	31.97%	125	30.05%	0.5488
Dementia	76	2.59%	22	1.60%	0.0417	11	2.64%	5	1.20%	0.1299
Chronic pulmonary disease	883	30.03%	283	20.52%	< 0.0001	107	25.72%	97	23.32%	0.4203
Rheumatic disease	90	3.06%	31	2.25%	0.1311	7	1.68%	11	2.64%	0.3405
Liver disease	645	21.94%	283	20.52%	0.2906	96	23.08%	90	21.63%	0.6176
Hemiplegia and paraplegia	91	3.10%	35	2.54%	0.3104	16	3.85%	7	1.68%	0.0570
Renal disease	785	26.70%	375	27.19%	0.7333	128	30.77%	122	29.33%	0.6500
AIDS	0	0.00%	1	0.07%	0.1442	0	0.00%	0	0.00%	0.9999
Cancer	726	24.69%	266	19.29%	< 0.0001	87	20.91%	84	20.19%	0.7969
Coexisting comorbidities										
Hypertension	1934	65.78%	1201	87.09%	< 0.0001	349	83.89%	352	84.62%	0.7752
Hyperlipidemia	1000	34.01%	980	71.07%	< 0.0001	235	56.49%	248	59.62%	0.3611
Coronary artery disease	1466	49.86%	885	64.18%	< 0.0001	242	58.17%	243	58.41%	0.9439
Stroke	658	22.38%	370	26.83%	0.0014	113	27.16%	112	26.92%	0.9378
Depression	148	5.03%	71	5.15%	0.8728	25	6.01%	23	5.53%	0.7662
Anxiety	379	12.89%	185	13.42%	0.6335	64	15.38%	64	15.38%	1.0000
Heart failure	812	27.62%	409	29.66%	0.1651	121	29.09%	116	27.88%	0.7009
Peripheral vascular disease	267	9.08%	193	14.00%	< 0.0001	49	11.78%	48	11.54%	0.9140
COPD	801	27.24%	336	24.37%	0.0452	114	27.40%	111	26.68%	0.8149
Atrial fibrillation	342	11.63%	104	7.54%	< 0.0001	44	10.58%	35	8.41%	0.2872
Traumatic head injury	170	5.78%	76	5.51%	0.7201	25	6.01%	29	6.97%	0.5735
Hearing loss	102	3.47%	61	4.42%	0.1250	24	5.77%	20	4.81%	0.5355
Sleep apnea	21	0.71%	17	1.23%	0.0889	7	1.68%	5	1.20%	0.5609
Liver cirrhosis	761	25.88%	431	31.25%	0.0002	134	32.21%	130	31.25%	0.7657
SLE	71	2.41%	20	1.45%	0.0396	10	2.40%	9	2.16%	0.8165
Medication use										
Statin	772	26.26%	848	61.49%	< 0.0001	190	45.67%	202	48.56%	0.4046
Metformin					< 0.0001					< 0.0001
Non-use	0	0.00%	0	0.00%		416	100.00%	0	0.00%	
Q1(109 cDDD)	0	0.00%	343	24.87%		0	0.00%	105	25.24%	
Q2 (300 cDDD)	0	0.00%	347	25.16%		0	0.00%	103	24.76%	

Table 1 (continued)

	Before propensity score matching					After propensity score matching				
	Non-metformin		Metformin		*P* value	Non-metformin		Metformin		*P* value
	N = 2940		*N* = 1379			*N* = 416		*N* = 416		
	N	%	*N*	%		*N*	%	*N*	%	
Q3 (690 cDDD)	0	0.00%	345	25.02%		0	0.00%	104	25.00%	
Q4 (> 690 cDDD)	0	0.00%	344	24.95%		0	0.00%	104	25.00%	
Daily intensity (DDD)					< 0.0001					0.0026
< 1	0	0.00%	1,330	96.45%		416	100.00%	407	97.84%	
≥ 1	0	0.00%	49	3.55%		0	0.00%	9	2.16%	
Primary outcome										
Postoperative delirium	1,168	39.73%	420	30.46%	< 0.0001	168	40.38%	108	25.96%	< 0.0001

N number; *SD* standard deviation; *DDD* defined daily dose; *cDDD* cumulative defined daily dose; *IQR* interquartile range; *NTD* New Taiwan Dollar; *ASA* American Society of Anesthesiologists; *SGLT2i* sodium-glucose co-transporter-2 inhibitor; *AGI* alpha-glucosidase inhibitor; *TZD* thiazolidinedione; *DPP4i* dipeptidyl peptidase-4 inhibitor; *Q* quartile; *CCI* Charlson comorbidity index; *AIDS* acquired immune deficiency syndrome; *COPD* chronic obstructive pulmonary disease; *SLE* systemic lupus erythematosus

T2DM patients undergoing cardiovascular surgery, stratified by metformin treatment status, showing a significantly higher incidence of POD in non-metformin users compared with metformin users (log-rank test $P = 0.0001$ for PSM patients with or without metformin use).

Association of dose-dependent metformin uses with POD risk

To examine the dose-dependent relationship between metformin use and POD risk, we categorized the cDDD of metformin before surgery into four quartiles (Q1, Q2, Q3, and Q4) (Table 3). Before PSM, the aORs for POD risk in each quartile were as follows: Q1, 0.66 (95% CI 0.51–0.84); Q2, 0.57 (95% CI 0.40–0.68); Q3, 0.53 (95% CI 0.40–0.69); and Q4, 0.44 (95% CI 0.39–0.55), all compared to the non-metformin use group. A significant trend (P for trend < 0.0001) indicated a dose-dependent effect of cDDD on reducing POD risk with increasing metformin use. After PSM, the aORs for POD risk in each quartile were as follows: Q1, 0.67 (95% CI 0.45–0.97); Q2, 0.54 (95% CI 0.28–0.69); Q3, 0.45 (95% CI 0.27–0.63); and Q4, 0.40 (95% CI 0.35–0.88), all compared to the non-metformin use group. The significant trend (P for trend < 0.0001) persisted, indicating a dose-dependent effect of cDDD on reducing POD risk with increasing metformin use.

Identifying prognostic factors for POD in cardiovascular surgery

Table 4 presents the logistic regression model identifying independent prognostic factors for postoperative delirium (POD) in patients undergoing cardiovascular surgery before propensity score matching. The results indicate that metformin use was associated with a significantly lower risk of POD (adjusted OR, 0.58; 95% CI 0.47–0.71; $P < 0.0001$), suggesting potential neuroprotective effects beyond glycemic control. Other protective factors included higher income levels (> 45,000 NTD) (adjusted OR, 0.61; 95% CI 0.38–0.98; $P = 0.0410$), urban residence (adjusted OR, 0.83; 95% CI 0.74–0.93; $P = 0.0010$), and statin use (adjusted OR, 0.75; 95% CI 0.56–0.86; $P = 0.0009$), all of which were associated with a reduced risk of POD.

Conversely, several factors were identified as adverse prognostic indicators, contributing to an increased risk of POD. Advanced age (≥ 71 years) was associated with a significantly higher risk (adjusted OR, 1.29; 95% CI 1.11–1.49; $P = 0.0007$), consistent with prior studies linking aging to neurocognitive vulnerability. A prolonged anesthesia duration of more than 4 h was also associated with an increased risk (adjusted OR, 1.13; 95% CI 1.03–1.21; $P = 0.0392$), likely reflecting the cumulative physiological stress of extended surgical procedures. A higher aDCSI score (≥ 4)

Table 2 Logistic regression analysis of postoperative delirium in patients undergoing cardiovascular surgery, comparing those with and without metformin treatment

	Crude OR (95% CI)		*P* value	Adjusted OR* (95% CI)		*P* value
Before propensity score matching						
Non-metformin users (Ref.)	1.00	–	–	1.00	–	–
Metformin users	0.81	(0.72, 0.91)	0.0002	0.58	(0.47, 0.71)	< 0.0001
After propensity score matching						
Non-metformin users (Ref.)	1.00	–	–	1.00	–	–
Metformin users	0.58	(0.45, 0.73)	< 0.0001	0.52	(0.40, 0.67)	< 0.0001

N number; *Ref.* reference group; *CI* confidence interval; *OR* odds ratio

*Adjustment of age, sex, income levels, urbanization, ASA physical status, anesthesia duration hours, combination therapies in antidiabetic medications, antidiabetic medications, aDCSI Score, CCI scores, coexisting comorbidities, and medications use

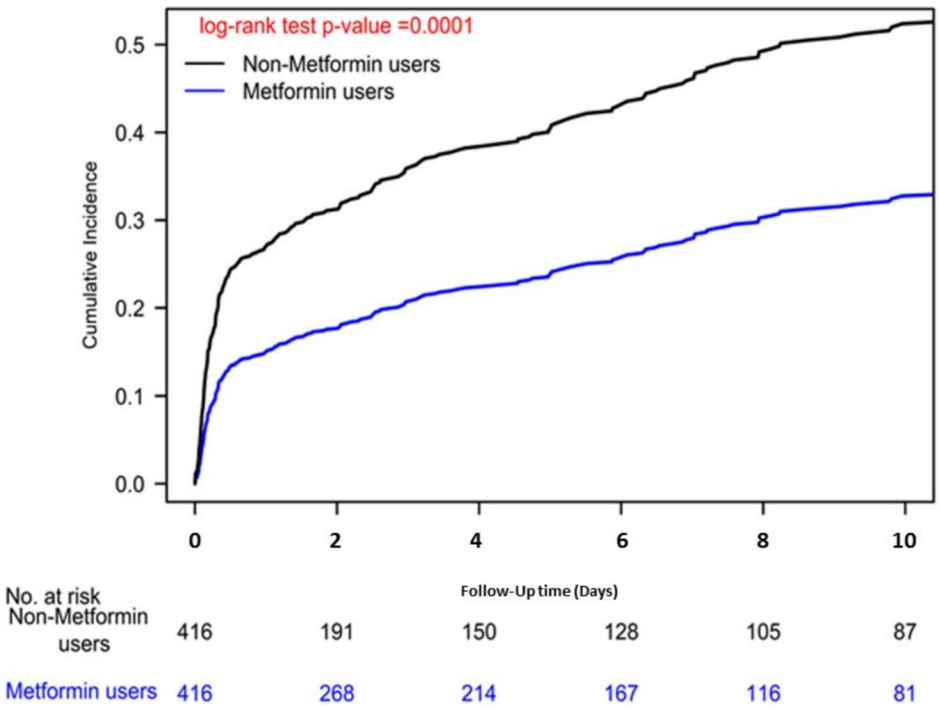

Fig. 1 Kaplan–Meier cumulative incidence of postoperative delirium in patients undergoing cardiovascular surgery, stratified by metformin treatment status

was another significant risk factor (adjusted OR, 1.16; 95% CI 1.06–1.41; $P = 0.0224$), underscoring the role of diabetes-related complications in cognitive outcomes. In addition, a Charlson Comorbidity Index (CCI) of 1 or greater (adjusted OR, 1.47; 95% CI 1.25–1.72; $P < 0.0001$) and a pre-existing diagnosis of depression (adjusted OR, 1.27; 95% CI 1.02–1.59; $P = 0.0338$) were both independently associated with an elevated risk of POD.

Among antidiabetic medications, insulin use was associated with an increased risk of POD (adjusted OR, 1.45; 95% CI 1.08–1.94; $P = 0.0120$), potentially due to its role in exacerbating glycemic fluctuations and metabolic stress. In contrast, other antidiabetic agents, including sulfonylureas, SGLT2 inhibitors, AGIs, TZDs, and DPP-4 inhibitors, did not show statistically significant associations with POD risk. These findings highlight the multifactorial nature of POD in patients with T2DM undergoing cardiovascular surgery and suggest a potential neuroprotective role for metformin while identifying high-risk populations that may benefit from enhanced perioperative delirium prevention strategies.

Discussion

In our cohort study, we investigated the risk of POD in T2DM patients undergoing cardiovascular surgery, comparing metformin users with non-users. The results reveal that preoperative metformin administration notably reduces POD risk in a dose-dependent manner. PSM showed that metformin users had a significantly lower POD risk, with an aOR of 0.52 (Table 2). This association remained strong even after adjusting for multiple variables, including age,

Table 3 Logistic regression analysis of postoperative delirium in patients undergoing cardiovascular surgery, comparing those depending on different metformin dose

	Crude OR (95% CI)		*P* value	Adjusted OR* (95% CI)		*P* value
Before propensity score matching						
Non-metformin users (Ref.)	1.00	–	–	1.00	–	–
Q1(109 cDDD)	0.86	(0.71, 1.04)	0.1233	0.66	(0.51, 0.84)	0.0009
Q2 (300 cDDD)	0.75	(0.60, 0.89)	0.0022	0.57	(0.40, 0.68)	< 0.0001
Q3 (690 cDDD)	0.73	(0.62, 0.92)	0.0060	0.53	(0.40, 0.69)	< 0.0001
Q4 (> 690 cDDD)	0.63	(0.55, 0.94)	0.0386	0.44	(0.39, 0.55)	< 0.0001
P for trend			< 0.0001			< 0.0001
After propensity score matching						
Non-metformin users (Ref.)	1.00	–	–	1.00	–	–
Q1(109 cDDD)	0.73	(0.51, 1.05)	0.0873	0.67	(0.45, 0.97)	0.0364
Q2 (300 cDDD)	0.53	(0.32, 0.76)	0.0015	0.54	(0.28, 0.69)	0.0003
Q3 (690 cDDD)	0.48	(0.31, 0.73)	0.0006	0.45	(0.27, 0.63)	< 0.0001
Q4 (> 690 cDDD)	0.43	(0.32, 0.87)	0.0337	0.40	(0.35, 0.88)	0.0101
P for trend			< 0.0001			< 0.0001

N number; *Ref* reference group; *Q* quartile; *CI* confidence interval; *OR* odds ratio

*Adjustment of age, sex, income levels, urbanization, ASA physical status, anesthesia duration hours, combination therapies in antidiabetic medications, antidiabetic medications, aDCSI Score, CCI scores, coexisting comorbidities, and medications use

income, urbanization, anesthesia duration, depression, and statin use, with an aOR of 0.58 for metformin users undergoing cardiovascular surgery. Furthermore, a dose–response relationship was evident in our analysis of cDDD of metformin (Table 3), with lower POD risks at higher doses, highlighting metformin's potential as a protective agent against POD.

We acknowledge the potential influence of other glucose-lowering medications on POD risk [35]. To address this concern, various antidiabetic medications were included as covariates in Table 1, and their confounding effects were adjusted for in our statistical models. Even after accounting for these medications, a significant difference in POD risk persisted between metformin users and non-users, suggesting that metformin's protective effect extends beyond its glucose-lowering properties. Metformin exerts neuroprotective effects through multiple mechanisms, including anti-inflammatory and antioxidative pathways, improved insulin sensitivity, and the activation of key molecular regulators such as AMP-activated protein kinase (AMPK), which is associated with cognitive function [22, 31]. These pleiotropic effects may explain its potential role in reducing the risk of POD, independent of glycemic control. While other antidiabetic agents, such as GLP-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter 2 inhibitors (SGLT2is), have also been suggested to have neuroprotective properties [36], their use in Taiwan is restricted by National Health Insurance (NHI) indications. Specifically, these second-line therapies are only prescribed when first-line metformin therapy fails. As a result, our study population primarily consisted of patients using metformin as their standard treatment, with limited exposure to these newer agents. Although all effective glucose-lowering drugs may theoretically mitigate inflammation by reducing advanced glycation end-products (AGEs) [37, 38], their impact on cognitive outcomes and POD prevention likely differs due to their distinct pharmacological mechanisms [22, 31, 36]. Therefore, it is inappropriate to assume that all antidiabetic medications confer the same protective effect against POD. Metformin, in particular, has garnered special attention due to its broad neuroprotective mechanisms [31]. Future research is warranted to further elucidate the specific cognitive benefits of different glucose-lowering agents and their underlying mechanisms.

The influence of metformin on POD remains unclear, with existing studies presenting conflicting findings. Prior research, including a retrospective population-based cohort study [39] suggested a negative correlation between metformin use and POD. However, limitations such as diverse surgical procedures, small sample sizes, short follow-up periods, and insufficient control for key covariates have hindered these studies' reliability [39]. Another investigation using the U.S. Food and Drug Administration Adverse Event Reporting System (FAERS) identified metformin as a potential delirium inducer, but the FAERS data's primary focus was not on metformin-delirium associations, raising concerns about bias [40]. Ethical challenges prevent the withholding of metformin in patients with T2DM, leading to a lack of RCTs exploring its impact on POD risk in this demographic. Addressing these gaps, our study, using a rigorously designed PSM approach, targets a specific vulnerable group—patients with T2DM undergoing major

Table 4 Logistic regression model identifying independent prognostic factors for postoperative delirium in patients undergoing cardiovascular surgery (pre-propensity score matching)

	Crude OR (95% CI)		*P* value	Adjusted OR* (95% CI)		*P* value
Metformin (ref. non-metformin users)						
Metformin users	0.81	(0.72, 0.91)	0.0002	0.58	(0.47, 0.71)	< 0.0001
Age group, years old (Ref. [18–49])						
51–60	0.88	(0.74, 1.06)	0.1746	0.92	(0.77, 1.11)	0.4003
61–70	1.00	(0.87, 1.14)	0.9676	0.96	(0.82, 1.11)	0.5671
≥ 71	1.46	(1.29, 1.65)	< 0.0001	1.29	(1.11, 1.49)	0.0007
Sex (ref. female)						
Male	1.03	(0.93, 1.14)	0.5836	1.06	(0.95, 1.18)	0.3107
Income levels (ref. low income)						
Financial dependent	0.69	(0.5, 0.95)	0.0232	0.78	(0.56, 1.08)	0.1328
< 20,000	0.74	(0.54, 1.02)	0.0677	0.77	(0.56, 1.07)	0.1216
2001–30000	0.54	(0.38, 0.79)	0.0013	0.66	(0.45, 1.16)	0.0598
30,001–45000	0.57	(0.38, 0.83)	0.0037	0.72	(0.48, 1.06)	0.0932
> 45,000	0.47	(0.29, 0.75)	0.0016	0.61	(0.38, 0.98)	0.0410
Urbanization (ref. rural)						
Urban	0.78	(0.7, 0.87)	< 0.0001	0.83	(0.74, 0.93)	0.0010
ASA physical status (ref. [1])						
2	1.10	(0.77, 1.56)	0.6094	0.83	(0.57, 1.22)	0.3437
3	1.09	(0.78, 1.51)	0.6207	0.80	(0.54, 1.17)	0.2433
4	1.22	(0.88, 1.68)	0.2381	0.90	(0.61, 1.31)	0.5743
Anesthesia duration (ref ≤ 4 h)						
> 4	1.09	(1.01, 1.17)	0.0411	1.13	(1.03, 1.21)	0.0392
Combination therapies in antidiabetic (ref = individual therapy)						
Dual therapy	1.07	(0.95, 1.21)	0.2805	1.13	(0.99, 1.28)	0.0749
Triple combination	1.01	(0.68, 1.02)	0.0730	1.12	(0.9, 1.4)	0.3154
Quadruple combination	1.04	(0.78, 1.14)	0.5276	1.13	(0.89, 1.97)	0.3010
More than four combinations	1.13	(0.96, 1.33)	0.1412	1.15	(0.91, 2.52)	0.2201
aDCSI score (ref = 0)						
1	1.08	(0.54, 1.24)	0.0905	1.02	(0.56, 1.11)	0.3054
2	1.16	(0.73, 1.21)	0.0718	1.09	(0.66, 1.25)	0.2143
3	1.11	(0.83, 1.24)	0.9106	1.13	(1.05, 1.17)	0.0421
≥ 4	1.36	(1.17, 1.59)	< 0.0001	1.16	(1.06, 1.41)	0.0224
CCI (ref = 0)						
CCI ≥ 1	1.67	(1.46, 1.92)	< 0.0001	1.47	(1.25, 1.72)	< 0.0001
Coexisting comorbidities						
Hypertension	1.17	(1.04, 1.31)	0.0071	1.16	(1.01, 1.33)	0.0326
Hyperlipidemia	0.85	(0.77, 0.94)	0.0020	1.02	(0.9, 1.16)	0.7651
Coronary artery disease	0.95	(0.86, 1.05)	0.3560	1.06	(0.75, 1.08)	0.0700
Stroke	1.32	(1.18, 1.48)	< 0.0001	1.12	(0.99, 1.26)	0.0844
Depression	1.34	(1.09, 1.66)	0.0064	1.27	(1.02, 1.59)	0.0338
Anxiety	1.08	(0.94, 1.25)	0.2791	1.09	(0.93, 1.27)	0.2859
Heart failure	1.20	(1.08, 1.33)	0.0008	1.02	(0.9, 1.16)	0.7230
Peripheral vascular disease	1.05	(0.90, 1.23)	0.5326	1.04	(0.99, 1.09)	0.0930
Chronic obstructive pulmonary disease	1.22	(1.09, 1.36)	0.0005	1.01	(0.9, 1.14)	0.8373
Atrial fibrillation	1.04	(0.89, 1.22)	0.6322	0.91	(0.77, 1.08)	0.2862
Traumatic head injury	1.04	(0.84, 1.3)	0.7062	0.93	(0.75, 1.16)	0.5449
Hearing loss	1.32	(1.04, 1.69)	0.0250	1.15	(0.9, 1.48)	0.2704
Sleep apnea	0.83	(0.46, 1.49)	0.5249	0.92	(0.51, 1.67)	0.7851
Liver cirrhosis	1.07	(0.95, 1.19)	0.2608	1.06	(0.95, 1.19)	0.2966

Table 4 (continued)

	Crude OR (95% CI)		*P* value	Adjusted OR* (95% CI)		*P* value
Systemic lupus erythematosus	1.18	(0.86, 1.62)	0.2930	1.04	(0.76, 1.44)	0.8054
Antidiabetic medications						
Insulin	1.50	(1.10–2.00)	0.0100	1.45	(1.08–1.94)	0.0120
Sulfonylurea	1.20	(0.90–1.60)	0.1500	1.18	(0.88–1.55)	0.1600
SGLT2i	0.90	(0.60–1.30)	0.5000	0.88	(0.59–1.28)	0.4800
AGI	1.00	(0.70–1.50)	0.9500	0.98	(0.68–1.44)	0.9600
TZD	0.80	(0.50–1.20)	0.2500	0.78	(0.48–1.16)	0.2600
DPP4i	1.10	(0.80–1.50)	0.4000	1.07	(0.76–1.43)	0.4100
Others	1.30	(0.80–2.00)	0.2000	1.25	(0.75–1.95)	0.2100
Medication use						
Statin use	0.81	(0.73, 0.9)	< 0.0001	0.75	(0.56, 0.86)	0.0009

*Adjustment of age, sex, income levels, urbanization, ASA physical status, anesthesia duration hours, combination therapies in antidiabetic medications, antidiabetic medications, aDCSI Score, CCI scores, coexisting comorbidities, and medications use

cardiovascular surgeries such as CABG and valve replacement. This focus enhances the study's clinical significance, as T2DM patients are particularly prone to cardiovascular events and POD. Our PSM methodology not only ensured balance between cases and controls for known confounders but also evaluated the influence of metformin dosage on outcomes [41–43]. This approach provides evidence that metformin use is associated with significant reductions in POD following cardiovascular surgery in T2DM patients, including dose-dependent effects. Our study thus offers valuable insights into the potential protective role of metformin against POD in a high-risk population.

One plausible mechanism is metformin's glycemic control, as hyperglycemia has been implicated as a POD risk factor [44, 45]. Furthermore, metformin's anti-inflammatory action [46], particularly its modulation of pro-inflammatory cytokines such as IL-6 and TNF-α via the NF-kB pathway, could be relevant [47, 48]. Metformin, known for mitigating diabetes-associated dementia [22], might influence POD through its effects on p-Tau, Aβ plaque loading, and neuronal protection, as observed in diabetic mice [49]. This aligns with our findings, suggesting reduced POD risk with metformin use in T2DM patients. Metformin's ability to cross the blood–brain barrier rapidly positions it as a neuroprotective agent against diseases such as stroke and cognitive impairment [50–52]. Despite newer glucose-lowering agents, metformin remains a viable option due to its safety, affordability, and long-term use experience [53–55]. In addition, emerging research attributes metformin with properties beneficial to aging, such as enhancing insulin sensitivity, antioxidative effects, and vascular health improvement [56–58]. Given these multifaceted benefits, metformin's role in elderly DM patients' management, particularly for POD prevention, merits reevaluation. Our study underscores metformin's independent protective effect against POD, beyond its glucose-lowering capabilities, and suggests its potential as a therapeutic agent for various neurological conditions associated with aging.

Our research reveals that metformin independently acts as a safeguard against POD in patients with T2DM undergoing major cardiovascular surgery. In addition, our study has identified several new risk factors associated with POD in this patient group, as detailed in Table 4. These include age above 70 years, higher aDCSI and CCI scores, anesthesia lasting over 4 h, and the presence of depression. Interestingly, factors such as higher income levels, urban residency, and statin use emerged as protective clinical factors against POD. While some of these risk factors align with findings from previous research [59–61], the associations with higher aDCSI, extended anesthesia duration, higher income levels, urban residency, and statin use present novel insights that warrant further investigation. Our research reveals that the severity of T2DM (aDCSI) and extended anesthesia duration are independent risk factors for POD in patients with T2DM undergoing major cardiovascular surgery. In addition, the use of statins, higher income levels, and urban residency are associated with a decreased risk of developing POD in this patient group. These new discoveries are pivotal for future research and could significantly enhance our understanding of POD in T2DM patients. Implementing prevention strategies that focus on metformin use and these newly identified clinical factors could be key in reducing the incidence of delirium following cardiovascular surgery in T2DM patients. Given the widespread prevalence of T2DM and POD, assessing the cost-effectiveness and feasibility of employing metformin as a preventive measure on a larger scale is crucial. Such research endeavors hold the promise of profoundly impacting clinical practice and public health, potentially leading to more effective management of POD in T2DM patients undergoing cardiovascular procedures.

Our study, while contributing valuable insights into the association between metformin use and reduced POD risk in patients with T2DM undergoing cardiovascular surgery, does face several limitations. Primarily, our participant pool was exclusively Asian, which necessitates caution when extending these findings to non-Asian populations. In addition, the NHIRD lacks data on certain variables that could influence POD development, such as dietary habits, family medical history, educational background, and specific laboratory parameters. Another potential source of bias is the presence of undiagnosed preoperative cognitive impairment, even though our study methodology involved the exclusion of patients with known cognitive impairment prior to cardiac surgery. Despite these constraints, our large-scale study paves the way for future investigations by highlighting a probable link between metformin use and decreased POD risk in T2DM patients post-cardiovascular surgery. To further this field of research, future studies should focus on prospective clinical trials. These trials are crucial for establishing causality and exploring the underlying mechanisms of metformin's neuroprotective effects. A deeper understanding of these mechanisms could reveal novel targets for the prevention of POD, significantly contributing to the care and management of patients undergoing cardiovascular surgery.

Conclusion

Our study concludes that metformin use significantly reduces the risk of POD in patients with T2DM undergoing cardiovascular surgery. This protective effect appears dose-dependent, and metformin emerges as a key modifiable factor in preventing POD in this population.

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Availability of data and material The datasets supporting the study conclusions are included within this manuscript and its additional files.

Declarations

Conflict of interest The authors have no potential conflicts of interest to declare. The datasets supporting the study conclusions are included within the manuscript.

Ethical approval and consent The study protocols were reviewed and approved by the Institutional Review Board of Tzu-Chi Medical Foundation (IRB109-015-B).

Consent for publication Not applicable.

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