Kajitani N, Yamanashi T, Yoshioka D, et al. Association of Metformin Use on Postoperative Delirium Risk in Patients with Type 2 Diabetes: A Retrospective Cohort Study. *Delirium*. Published online January 2, 2026. doi:10.56392/001c.151691

Articles

Association of Metformin Use on Postoperative Delirium Risk in Patients with Type 2 Diabetes: A Retrospective Cohort Study

Naofumi Kajitani[1], Takehiko Yamanashi[1], Daisuke Yoshioka[1], Koji Komatsu[1], Hironori Furuse[1], Shiori Ikuta[1], Hideaki Matsuoka[1], Tsuyoshi Nishiguchi[1], Chika Ushida[1], Moyu Nakamoto[1], Kozo Miyatani[1], Yasuaki Kubouchi[1], Yoshinori Kitagawa[1], Tsuyoshi Okura[1], Hisashi Noma[2], Gen Shinozaki[3], Masaaki Iwata[1]

[1] Tottori University, [2] The Institute of Statistical Mathematics, [3] Stanford University

https://doi.org/10.56392/001c.151691

Delirium

Aim

Metformin has been reported to improve age-related diseases, including dementia. Prior studies have suggested that metformin use is associated with a decreased risk of delirium. This study aimed to analyze the medical records of surgical patients with comorbid type 2 diabetes to evaluate the relationship between metformin and both postoperative delirium.

Method

A retrospective cohort study of patients diagnosed with type 2 diabetes who underwent surgery for malignancy in the Departments of Gastrointestinal Surgery and Thoracic Surgery was conducted. A total of 1,159 patients were analyzed to examine metformin use and the incidence of delirium.

Results

Among the 1,159 patients, 1,026 were classified as the non-metformin-treated diabetes group and 133 as the metformin-treated diabetes group. The incidence of delirium was 17.0% in the non-metformin-treated group and 15.0% in the metformin-treated group. Metformin use was not associated with a reduced risk of delirium after adjustment for confounding factors (Relative risk: 0.94, 95% confidence interval [CI], 0.60~1.45, p = 0.766). The propensity score weighting analyses showed no significant association between metformin use and the incidence of postoperative delirium (Relative risk: 1.51, 95% CI, 0.62~3.69, p = 0.370).

Conclusion

In this study, metformin use was not significantly associated with postoperative delirium.

INTRODUCTION

Postoperative delirium (POD) is a major complication among surgical patients and can significantly affect prognosis.[1] Delirium is an acute disturbance of consciousness characterized by cognitive impairment, lack of attention, and confusion.[2,3] It is not merely a transient symptom; rather it has been closely associated with poor prognosis, including prolonged hospitalization, admission to a facility after discharge, and increased mortality.[3-5] Delirium also has a serious impact on patient's quality of life (QOL) and contributes to greater medical costs and resource utilization.[6-8] Risk factors for delirium include predisposing factors such as advanced age and pre-existing dementia, as well as precipitating factors such as systemic inflammatory events (e.g., infection or surgery) and the use of certain medications. In particular, POD is a major clinical concern because its incidence and severity tend to increase following surgery.[3,4,9,10] Despite ongoing research, the etiology of delirium remains poorly understood, and effective prevention and treatment strategies have yet to be established. Therefore, the prevention and management of delirium remain critical clinical challenges.

Antidiabetic medications have been investigated for their potential effects on aging and dementia risk.[11] In recent years, the possibility that GLP-1 receptor agonists may reduce the risk of dementia has attracted increasing attention.[11,12] At the same time, metformin, classical first-line treatment for type 2 diabetes, has also been examined for its potential to mitigate dementia risk and age-related changes.[13] Although a recent systematic review has reported that the evidence regarding the potential dementia-preventive effects of metformin remains controversial,[11] a study using nonhuman primates have shown that metformin administration can attenuate age-related changes.[14] In addition, previous studies have reported that metformin may also exert anti-inflammatory, antioxidant, and neuroprotective effects.[14-19] These findings suggest that metformin may play an important role not only in glycemic control but also in neuroprotection and long-term prognostic improvement. Collectively, this evidence raises the possibility that metformin could help prevent delirium and improve postoperative outcomes.

Although our previous study has indicated a potential link between metformin use and reduced risk of delirium or mortality,[20] the evidence remains limited by inconsistent definitions of metformin use and incomplete data on concurrent antidiabetic therapies. To address these limitations, we conducted a detailed analysis of the medical records of surgical patients with type 2 diabetes to evaluate the relationship between metformin and the occurrence of POD.

METHODS

STUDY DESIGN

This was a single-center, retrospective, observational study. Data were obtained from electronic medical records. The study was conducted in accordance with ethical guidelines for medical research involving human subjects and approved by the Faculty of Medicine, Tottori University Ethical Review Committee (approval number: 23A101). The opt-out process was conducted by posting a notice on the hospital website and bulletin board in accordance with the Tottori University Ethical Review Committee guidelines.

PARTICIPANTS

This study included patients who underwent surgery for malignant tumors at Tottori University Hospital between January 1, 2012, and December 31, 2022, in the Departments of Gastrointestinal Surgery and Thoracic Surgery. Eligible participants were aged 65 years or older and diagnosed with type 2 diabetes at the time of surgery. Patients with type 2 diabetes managed by lifestyle modification only were included if a diagnosis of type 2 diabetes was recorded by the attending physician.

For patients who underwent multiple surgeries, only data from the final surgery were included. Patients were excluded if they met any of the following criteria: refusal to provide medical records; a diagnosis of schizophrenia, mood disorder, or epilepsy at the time of surgery; or undergoing minor surgery associated with a very low risk of delirium. Patients with schizophrenia, mood disorders, or epilepsy were excluded because postoperative mental status changes could not be reliably distinguished from symptoms of the underlying psychiatric condition based solely on medical record review. Minor surgery was defined as procedures involving minimal tissue disruption, including excision of subcutaneous soft tissue tumors confined to the superficial layers and procedures such as inguinal hernia repair or biopsy that do not require extensive organ incision. This criterion was intended to create a more homogeneous study population by limiting the analysis to patients who underwent surgeries with a certain level of invasiveness.

PARTICIPANT CHARACTERISTICS

Demographic characteristics, Body Mass Index (BMI), blood test results, medical department, surgical method, blood loss, anesthesia time, and surgery time were extracted from medical records. Blood test results closest to the date of surgery were used for analysis. The Charlson Comorbidity Index (CCI) score was calculated based on preoperative assessments of comorbidities.[21]

Information regarding antidiabetic medication use at the time of surgical consultation was collected. Patients taking metformin at the time were classified as metformin users. In accordance with the package insert and the recommendations of the Japan Association for Diabetes Education and Care, all patients taking metformin had their antidiabetic regimen modified prior to surgery, and metformin was discontinued several days prior to the procedure. Information on medications other than antidiabetic agents was obtained from prescription records on the day before surgery.

ASSESSMENT FOR DELIRIUM

Delirium was assessed using medical records from postoperative days 1 to 5. POD was considered present when medical records documented changes in level of consciousness, memory impairment, disturbances in attention or orientation, hallucinations, delusions, or affective alterations—symptoms consistent with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for delirium. Each case was independently reviewed by two evaluators, at least one of whom was a psychiatrist specializing in delirium treatment. In cases of disagreement, a third psychiatrist reviewed the case and made a final determination. The assessors reviewed only postoperative medical records and did not have access to any information regarding metformin use. However, because clinical notes may occasionally reference medication changes, complete blinding could not be ensured. Patients who were assessed as having delirium at least once between postoperative days 1 and 5 were classified into the delirium group, whereas those who were never assessed as having delirium during this period were classified into the non-delirium group.

STATISTICAL ANALYSIS

All statistical analyses were performed using R version 4.4.3 (R Foundation for Statistical Computing, Vienna, Austria), and EZR version 1.68.[22] Fisher's exact test was used to compare the incidence of delirium between the metformin-treated and non-metformin-treated groups. To further examine the association between metformin use and delirium, a modified Poisson regression analysis[23] was performed, adjusting for the following covariates: age, sex, BMI, presence or absence of dementia, renal disease, and CCI score (excluding dementia and renal disease), HbA1c level, surgical method, amount of blood loss, duration of anesthesia, and the use of metformin, insulin, other antidiabetic agents, sleep medications, and antipsychotics. The amount of blood loss and duration of anesthesia were logtransformed before inclusion in the analysis. Missing data were treated using multiple imputation by chained equations[24] with 200 imputations. Missing data were present only for HbA1c. HbA1c was treated as a continuous variable, and missing values were imputed using predictive mean matching. The imputation model included the corresponding outcome and all covariates used in the multivariable analyses. As a sensitivity analysis, we also conducted propensity score weighting analyses. All p-values were two-sided, and statistical significance was set at 0.05.

RESULTS

DEMOGRAPHICS

A total of 1,159 patients were included in the analysis. There were no participants who refused data usage. The mean age was 74.9 years (standard deviation [SD]: 6.19), and 71.3% were male (Table 1). Among the 1,159 patients, 133 had a history of metformin use. The non-metformin-treated group was older than the metformin-treated group (mean age [SD]: 75.1 [6.24] vs. metformin treated group 73.3 [5.56] years, t-test, $p = 0.001$) and had a significant lower BMI (mean [SD]:22.6 [3.59] vs. 23.6 [3.37] years, t-test, $p = 0.003$). In preoperative blood test results, HbA1c levels were lower in the non-metformin-treated group compared with the metformin-treated group (mean age [SD]: non-metformin-treated group 6.63 [0.99] vs. metformin treated group 7.04 [0.95], t-test $p < 0.001$) (Table 1). Additional information regarding dementia, renal disease, CCI (excluding dementia and renal disease), blood tests, surgical method, amount of blood loss, anesthesia time, medication use, and POD is presented in Table 1.

INCIDENCE OF POSTOPERATIVE DELIRIUM AND HISTORY OF METFORMIN USE

The incidence of delirium was 15.0% in the metformin-treated group and 17.0% in the non-metformin group; however, the difference was not statistically significant ($p = 0.624$, Fisher's exact test) (Table 1). Modified Poisson regression analysis indicated that a history of metformin use did not be significantly associated with the risk of POD (Relative risk: 0.94, 95% confidence interval [CI]: 0.60~1.45, $p = 0.766$) (Table 2). Even in the propensity score weighting analyses, no significant association was observed between metformin use and the incidence of POD (Relative risk: 1.51, 95% CI: 0.62~3.69, $p = 0.370$) (Table 3).

DISCUSSION

In this study, we analyzed the medical records of patients who underwent tumor-related surgery in the Departments of Gastroenterological Surgery and Thoracic Surgery to evaluate the association of metformin use with POD. However, the findings did not provide evidence that metformin use was associated with the risk of POD.

Increasing evidence suggests that metformin may help prevent delirium. Our prior study indicated that a history of oral metformin use was associated with a reduced risk of delirium upon hospital admission.[20] Similarly, another study reported that metformin use reduced risk of delirium in elderly patients with type 2 diabetes, with greater protective effects observed at higher doses.[25] A cohort study using the TriNetX network found that metformin use was associated with a reduced risk of both delirium and mortality when compared with dipeptidyl peptidase-4 inhibitors.[26] Additionally, cumulative metformin administration has been shown to decrease the risk of POD in patients with type 2 diabetes following cardiovascular surgery, demonstrating a dose-dependent protective effect.[27] Continuous metformin use also appeared to slightly reduce the incidence of POD after non-cardiac surgery, although the difference was not statistically significant, and it was associated with reduced major complications, particularly renal impairment and early discharge.[28]

Contrary to prior reports suggesting a protective effect, our findings did not confirm that metformin use reduces the risk of POD. These findings should be interpreted with caution, considering the observational study design and specific characteristics of the study population, including racial and ethnic composition and BMI. Several prior studies that found a delirium-preventive effect of metformin included a high proportion of obese participants.[20,26,28] A secondary analysis of one study reported that the delirium risk–reducing effect of metformin was observed only in obese patients.[29] Given that most participants in this study's cohort were of normal weight, this difference in BMI distribution may have attenuated the potential benefit of metformin and could partly account for the discrepancy with prior studies that included a higher proportion of obese participants. This difference in baseline BMI distribution could partly explain the discrepancy between our findings and those of prior studies. Additionally, these prior reports were conducted in non-Asian populations.[20,26,28] Therefore, metformin may be less effective in Asian populations than in Caucasian individuals. Unlike Taiwanese cohorts, which determined a correlation between a history of metformin use and reductions in delirium risk, these studies did not provide information on BMI or obesity status[26, 28]; additionally, differences in cohort characteristics may account for the discrepancy in the findings. Moreover, because the data were drawn from routine clinical practice over the past 10 years, temporal (period) effects may have influenced the outcomes. These include improvements in surgical techniques, refinement of anesthetic management, enhanced perioperative care protocols, and advances in adjuvant therapies. Future studies should therefore incorporate detailed information on cancer characteristics and treatment advances.

This study has several limitations. First, as an observational study, it cannot establish causality. Second, although we adjusted for potential confounding factors, it was difficult to completely eliminate the influence of factors such as patients' underlying diseases, concomitant medications, hospitalization environment, and treatment environment. However, residual confounding may persist despite adjustment. Third, the lack of sufficient data on the cumulative

Table 1. Patient demographics

Classification	All subjects	Metformin −	Metformin +		
N	1159	1026	133	P-value	Statistical test
Male (n) [%]	826 [71.3]	731 [71.2]	95 [71.4]	>0.99	
Mean Age (years old) [SD]	74.9 [6.2]	75.1 [6.2]	73.3 [5.6]	0.001	t = 3.29
Mean BMI (kg/m^2) [SD]	22.7 [3.6]	22.6 [3.6]	23.6 [3.4]	0.003	t = -2.98
Dementia (n) [%]	24 [2.1]	23 [2.2]	1 [0.8]	0.51	
Renal disease (n) [%]	22 [1.9]	22 [2.1]	0 [0]	0.16	
Mean CCI excluding Dementia, Renal disease [SD]	3.7 [0.9]	3.7 [0.9]	3.6 [0.8]	0.56	t = 0.59
Mean ASA-PS [SD]	2.39 [0.53]	2.39 [0.53]	2.38 [0.52]	0.86	t = 0.18
Mean HbA1c (%) [SD]	6.68 [1.00]	6.63 [0.99]	7.04 [0.95]	<0.001	t = -4.44
Mean Total bilirubin (mg/dL) [SD]	0.66 [0.36]	0.67 [0.36]	0.64 [0.32]	0.38	t = 0.88
Mean Albumin (g/dL) [SD]	3.73 [0.63]	3.71 [0.64]	3.88 [0.55]	0.003	t = -2.95
Mean AST (U/L) [SD]	43.4 [135.5]	41.5 [124.0]	58.3 [203.5]	0.18	t = -1.34
Mean ALT (U/L) [SD]	37.1 [104.7]	36.1 [102.5]	45.3 [120.3]	0.34	t = -0.96
Mean γ-GTP (U/L) [SD]	49.4 [75.0]	49.3 [72.9]	49.5 [90.1]	0.98	t = -0.02
Mean Sodium (mmol/L) [SD]	140.3 [3.0]	140.3 [3.0]	140.0 [2.9]	0.35	t = 0.94
Mean Potassium (mmol/L) [SD]	4.27 [0.44]	4.26 [0.44]	4.31 [0.44]	0.21	t = -1.27
Mean Chloride (mmol/L) [SD]	104.8 [3.4]	104.8 [3.4]	104.3 [2.9]	0.09	t = 1.67
Mean Urea nitrogen (mg/dL) [SD]	17.6 [7.4]	17.7 [7.6]	16.7 [5.7]	0.16	t = 1.40
Mean Creatinine (mg/dL) [SD]	0.94 [0.77]	0.95 [0.81]	0.84 [0.27]	0.13	t = 1.50
Mean CRP (mg/dL) [SD]	0.76 [2.31]	0.79 [2.40]	0.55 [1.43]	0.26	t = 1.13
Mean White blood cell (10^3/μL) [SD]	7.20 [3.44]	7.14 [3.40]	7.63 [3.67]	0.12	t = -1.55
Mean Hemoglobin (g/dL) [SD]	11.9 [1.92]	11.9 [1.92]	12.2 [1.97]	0.06	t = -1.86
Gastrointestinal surgery (n) [%]	815 [70.3]	717 [69.9]	98 [73.7]	0.42	
Thoracic surgery (n) [%]	344 [29.7]	309 [30.1]	35 [26.3]	0.42	
Surgery in multiple medical departments (n) [%]	84 [7.3]	81 [7.9]	3 [2.3]	0.01	
Surgery in a single department (n) [%]	1075 [92.8]	945 [92.1]	130 [97.7]	0.01	
Surgical method					
Open abdominal (n) [%]	386 [33.3]	337 [32.8]	49 [36.8]	0.38	
Open thoracic (n) [%]	61 [5.3]	54 [5.3]	7 [5.3]	1	
Laparoscopic (n) [%]	359 [31.0]	317 [30.9]	42 [31.6]	0.92	
Thoracoscopic (n) [%]	245 [21.1]	230 [22.4]	15 [11.3]	0.002	
Robotic (n) [%]	108 [9.3]	88 [8.6]	20 [15.0]	0.03	
Mean Anesthesia duration (min) [SD]	379.2 [252.2]	377.6 [259.9]	391.6 [182.5]	0.55	t = -0.60
Mean Amount of blood loss (mL) [SD]	222.6 [476.6]	215.2 [468.6]	280.0 [533.0]	0.14	t = -1.47
Insulin (n) [%]	101 [8.7]	86 [8.4]	15 [11.3]	0.26	
Biguanide excluding metformin (n) [%]	0 [0]	0 [0]	0 [0]	NA	
DPP-4 inhibitor (n) [%]	412 [35.5]	315 [30.7]	97 [72.9]	<0.001	
GIP/GLP-1 receptor agonist (n) [%]	0 [0]	0 [0]	0 [0]	NA	
GLP-1 receptor agonist (n) [%]	11 [0.9]	5 [0.5]	6 [4.5]	0.001	
SGLT2 inhibitor (n) [%]	45 [3.9]	26 [2.5]	19 [14.3]	<0.001	
α-glucosidase inhibitor (n) [%]	106 [9.1]	95 [9.3]	11 [8.3]	0.87	

Glimin (n) [%]	0 [0]	0 [0]	0 [0]	NA	
Sulfonylurea (n) [%]	171 [14.8]	112 [10.9]	59 [44.4]	<0.001	
Thiazolidinedine (n) [%]	100 [8.6]	63 [6.1]	37 [27.8]	<0.001	
Benzodiazepine receptor agonist (n) [%]	203 [17.5]	181 [17.6]	22 [16.5]	0.81	
Melatonin receptor agonist (n) [%]	19 [1.6]	19 [1.9]	0 [0]	0.15	
Orexin receptor antagonist (n) [%]	26 [2.2]	22 [2.1]	4 [3.0]	0.53	
Antipsychotics (n) [%]	11 [0.9]	11 [1.1]	0 [0]	0.63	
Antidepressant (n) [%]	28 [2.4]	25 [2.4]	3 [2.3]	1	
Antihistamine (n) [%]	83 [7.2]	75 [7.3]	8 [6.0]	0.72	
Anticholinergic (n) [%]	1 [0.1]	1 [0.1]	0 [0]	1	
Mean ICU stay (days) [SD]	3.0 [11.8]	3.0 [12.3]	2.9 [5.7]	0.96	t = 0.05
Delirium (n) [%]	194 [16.7]	174 [17.0]	20 [15.0]	0.62	

Abbreviation: DM, type 2 diabetes mellitus; Met, Metformin; SD, Standard deviation; BMI, Body mass index; CCI, Charlson comorbidity index; ICU, Intensive Care Unit.

Table 2. Result of the modified Poisson regression

	RR	95%CI			P-value
Age	1.07	1.05	-	1.10	<0.001
Male	1.34	0.98	-	1.82	0.063
BMI	1.00	0.96	-	1.04	0.957
Dementia	2.60	1.57	-	4.30	<0.001
Renal disease	1.41	0.55	-	3.60	0.471
CCI excluding Dementia, Renal disease	1.18	1.05	-	1.34	0.007
HbA1c	1.01	0.88	-	1.16	0.923
Surgical method					
Open abdominal	Ref	Ref	-	Ref	-
Open thoracic	0.78	0.42	-	1.45	0.431
Laparoscopic	0.80	0.55	-	1.15	0.232
Thoracoscopic	0.86	0.53	-	1.40	0.547
Robotic	0.51	0.25	-	1.03	0.059
Anesthesia duration	3.65	1.84	-	7.23	<0.001
Amount of blood loss	1.24	0.96	-	1.61	0.103
Metformin	0.94	0.60	-	1.45	0.766
Insulin	1.34	0.83	-	2.14	0.227
Other antidiabetic agents	1.24	0.93	-	1.65	0.142
Benzodiazepine receptor agonist	1.35	1.00	-	1.82	0.047
Melatonin receptor agonist	1.17	0.50	-	2.75	0.710
Orexin receptor antagonist	2.51	1.51	-	4.19	<0.001
Antipsychotics	1.85	1.05	-	3.26	0.035

Amount of blood loss and anesthesia duration were adjusted by log transformation. Of the 1,159 subjects, 80 lacked HbA1c data, and the missing data were imputed using multiple imputation by chained equations.
Abbreviation: BMI, Body Mass Index; CCI, Charlson Comorbidity Index

Table 3. Results of Propensity Score Weighting

Model	RR	95%CI			P-value
Propensity Score Weighting	1.51	0.62	-	3.69	0.370

Propensity Score Weighting was performed using stabilized inverse probability weights derived from the propensity score model. The propensity score model included demographic, clinical, diabetes-related, and perioperative variables. Covariate balance after weighting was assessed using standardized mean differences.(N=1159).

and daily doses of metformin is another limitation. This is because neither the dose nor the duration of metformin use was uniformly recorded in the medical charts. Prior studies have suggested that the effects of metformin are more pronounced at higher cumulative doses,[25,27] and collecting more detailed dosage information may enable a more accurate evaluation of the relationship between metformin and relevant outcomes. Fourth, delirium was diagnosed retrospectively, meaning that detection may have been influenced by a specific delirium phenotype. In particular, hypoactive delirium is less likely to be documented in medical records, and therefore may have been under-detected, resulting in a potential increase in false negatives. This could have potentially influenced the main findings on the risk of delirium. Fifth, the relatively small sample size and single-center nature of this study further limit the generalizability of our findings. Sixth, we excluded patients who underwent minimally invasive procedures to ensure a more homogeneous study population. However, this exclusion limits the generalizability of our findings, as the results may not be applicable to patients undergoing less invasive surgeries. Finally, while focusing on Japanese patients is a strength because it minimizes the confounding effects of racial differences such as genetic background, dietary habits, and healthcare access, it also limits the generalizability of this study's findings to populations in other countries or those with different ethnic compositions. Further studies are required to consider the cultural background, healthcare systems, diet, genetic factors, as well as other factors that may influence the risk of delirium and the efficacy of metformin.

In conclusion, metformin use was not significantly associated with POD in this study.

FUNDING / SUPPORT

The Mitsubishi Foundation

SPONSOR'S ROLE

None

CONFLICT OF INTEREST

Gen Shinozaki is co-founder of Predelix Medical LLC and has pending patents as follows: "Non-invasive device for predicting and screening delirium," PCT application no. PCT/US2016/064937 and US provisional patent no. 62/263,325; "Prediction of patient outcomes with a novel electroencephalography device," US provisional patent no. 62/829,411; "Epigenetic Biomarker of Delirium Risk" in the PCT Application No. PCT/US19/51276 and U.S. Provisional Patent No. 62/731,599. Masaaki Iwata has received research funding from OSAKA GAS CO.,LTD. and Daikin Industries, Ltd. for projects unrelated to the present work. The other authors declare no conflicts of interest.

ACKNOWLEDGEMENT

The authors express their gratitude to Ms. Iguchi for her assistance with data extraction, and to Dr. Sunada for contributing to the design of the research plan.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this manuscript, the authors used ChatGPT (GPT-5, OpenAI, San Francisco, CA, USA) to improve content readability and correct grammatical errors. After using this tool, the authors carefully reviewed and revised the content as required and take full responsibility for the final version of the manuscript.

AUTHOR CONTRIBUTIONS

N. Kajitani collected and organized the clinical data, wrote the initial draft, and edited the final version of the manuscript. T. Yamanashi provided research ideas, collected clinical data, organized data, wrote the initial draft, and edited the final form of the manuscript. T. Nishiguchi, C. Ushida, and M. Nakamoto edited the initial drafts of the manuscript. D. Yoshioka, K. Komatsu, H. Furuse, S. Ikuta, H. Matsuoka, K. Miyatani, Y. Kubouchi, Y. Kitagawa, and T. Okura collected clinical data. H. Noma analyzed data. G. Shinozaki and M. Iwata reviewed the manuscript critically.

ACCESS TO DATA AND DATA ANALYSIS

T. Yamanashi. had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DATA AVAILABILITY

The Data supporting the findings of this study are available from the corresponding author, T. Yamanashi, upon reasonable request.

Accepted: November 22, 2025 CET. Published: January 02, 2026 CET.

REFERENCES

1. Aldecoa C et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. *Eur J Anaesthesiol*. 2017;34(4):192-214. doi:10.1097/EJA.0000000000000594

2. Girard TD et al. Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study. *Lancet Respir Med*. 2018;6(3):213-222. doi:10.1016/S2213-2600(18)30062-6. PMID:29508705

3. Inouye SK. Delirium in older persons. *N Engl J Med*. 2006;354(11):1157-1165. doi:10.1056/NEJMra052321

4. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383(9920):911-922. doi:10.1016/S0140-6736(13)60688-1. PMID:23992774

5. Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. *Nat Rev Neurol*. 2009;5(4):210-220. doi:10.1038/nrneurol.2009.24. PMID:19347026

6. Caplan GA et al. The financial and social costs of delirium. *Eur Geriatr Med*. 2020;11(1):105-112. doi:10.1007/s41999-019-00257-2

7. Kinchin I et al. Cost-effectiveness of clinical interventions for delirium: A systematic literature review of economic evaluations. *Acta Psychiatr Scand*. 2023;147(5):430-459. doi:10.1111/acps.13457

8. Igarashi M et al. Incremental medical cost of delirium in elderly patients with cognitive impairment: analysis of a nationwide administrative database in Japan. *BMJ Open*. 2022;12(12):e062141. doi:10.1136/bmjopen-2022-062141. PMID:36521906

9. Kurisu K et al. Association between polypharmacy and the persistence of delirium: a retrospective cohort study. *Biopsychosoc Med*. 2020;14:25.

10. Ormseth CH et al. Predisposing and Precipitating Factors Associated With Delirium: A Systematic Review. *JAMA Netw Open*. 2023;6(1):e2249950. doi:10.1001/jamanetworkopen.2022.49950. PMID:36607634

11. Hui EK et al. Effect of diabetes medications on the risk of developing dementia, mild cognitive impairment, or cognitive decline: A systematic review and meta-analysis. *J Alzheimers Dis*. 2025;104(3):627-648. doi:10.1177/13872877251319054. PMID:40017057

12. Cheng HW et al. Impact of Glucagon-Like Peptide-1 Receptor Agonists on the Dementia Incidence in Patients With Type 2 Diabetes Mellitus: A Population-Based Longitudinal Cohort Study. *Diabetes Metab Res Rev*. 2025;41(5):e70058. doi:10.1002/dmrr.70058. PMID:40481813

13. Chen S et al. Metformin in aging and aging-related diseases: clinical applications and relevant mechanisms. *Theranostics*. 2022;12(6):2722-2740. doi:10.7150/thno.71360. PMID:35401820

14. Yang Y et al. Metformin decelerates aging clock in male monkeys. *Cell*. 2024;187(22):6358-6378.e29. doi:10.1016/j.cell.2024.08.021

15. Petrasca A et al. Metformin has anti-inflammatory effects and induces immunometabolic reprogramming via multiple mechanisms in hidradenitis suppurativa. *Br J Dermatol*. 2023;189(6):730-740. doi:10.1093/bjd/ljad305

16. Kristófi R, Eriksson JW. Metformin as an anti-inflammatory agent: a short review. *J Endocrinol*. 2021;251(2):R11-r22. doi:10.1530/JOE-21-0194

17. Buczyńska A et al. Examining the clinical relevance of metformin as an antioxidant intervention. *Front Pharmacol*. 2024;15:1330797.

18. Kruczkowska W et al. Overview of Metformin and Neurodegeneration: A Comprehensive Review. *Pharmaceuticals (Basel)*. 2025;18(4). doi:10.3390/ph18040486. PMID:40283923

19. Sabzali M et al. Anti-inflammatory, Antioxidant, and Antiapoptotic Action of Metformin Attenuates Ethanol Neurotoxicity in the Animal Model of Fetal Alcohol Spectrum Disorders. *Neurotox Res*. 2022;40(2):605-613. doi:10.1007/s12640-022-00499-2

20. Yamanashi T et al. The potential benefit of metformin to reduce delirium risk and mortality: a retrospective cohort study. *Aging (Albany NY)*. 2022;14(22):8927-8943. doi:10.18632/aging.204393. PMID:36399107

21. Charlson M et al. Validation of a combined comorbidity index. *J Clin Epidemiol*. 1994;47(11):1245-1251. doi:10.1016/0895-4356(94)90129-5

22. Kanda Y. Investigation of the freely available easy-to-use software "EZR" for medical statistics. *Bone Marrow Transplant*. 2013;48(3):452-458. doi:10.1038/bmt.2012.244. PMID:23208313

23. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol*. 2004;159(7):702-706. doi:10.1093/aje/kwh090

24. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2011;30(4):377-399. doi:10.1002/sim.4067

25. Sun M et al. Metformin Use and Risk of Delirium in Older Adults With Type 2 Diabetes. *Diabetes Care*. Published online 2024. doi:10.2337/figshare.26978161.v1

26. Sun M et al. Metformin vs. second-line therapy for delirium prevention in type 2 diabetes: A multinational study. *Diabetes Res Clin Pract*. 2025;225:112270.

27. Lu Z et al. Metformin's impact on delirium in diabetic cardio surgery patients. *J Anesth*. Published online 2025. doi:10.1007/s00540-025-03504-y

28. Paredes S et al. Metformin Use in Type 2 Diabetics and Delirium After Noncardiac Surgery: A Retrospective Cohort Analysis. *Anesth Analg*. 2024;138(6):1304-1312. doi:10.1213/ANE.0000000000006863

29. Seki T et al. Associations of Metformin Use History With Delirium and Mortality in Patients With Type 2 Diabetes Mellitus: A Retrospective Cohort Study. *J Acad Consult Liaison Psychiatry*. Published online 2025. doi:10.1016/j.jaclp.2025.07.003