ปัจจัยเสี่ยงของภาวะเลือดเป็นกรดจากกรดแลคติกในเลือดสูงเนื่องจากยาเม็ทฟอร์มิน ในคนไข้เบาหวานชนิดที่ 2 ที่ใช้ยาเม็ทฟอร์มิน
Risk Factors of Metformin-associated Lactic Acidosis in Type 2 Diabetic Patients Using Metformin

นิพนธ์ต้นฉบับ **Original Article**

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บทคัดย่อ

วัตถุประสงค์: เพื่อทดสอบปัจจัยเสี่ยงของภาวะเลือดเป็นกรดจากกรดแลคติกในเลือดสูงเนื่องจากยาเม็ทฟอร์มิน (MALA) ในคนไข้เบาหวานชนิดที่ 2 ที่ใช้ยาเม็ทฟอร์มิน **วิธีการศึกษา:** การศึกษาแบบเคส-คอนโทรลมีตัวอย่างเป็นคนไข้เบาหวานชนิดที่ 2 ที่กินยาเม็ทฟอร์มินที่มีข้อมูลการรักษาในเวชระเบียนของโรงพยาบาลมหาสารคามในช่วง 1 มกราคม 2561 ถึง 31 ธันวาคม 2563 เคสคือคนไข้ที่เกิด MALA ส่วนคอนโทรลคือคนไข้ที่ไม่เกิด MALA ทดสอบปัจจัยเสี่ยง 38 ปัจจัยที่อาจสัมพันธ์กับ MAL โดยการวิเคราะห์ univariate จากนั้นทดสอบปัจจัยที่สัมพันธ์อย่างมีนัยสำคัญโดย multiple logisic regression analysis แสดงความเสี่ยงด้วยค่า adjusted odds ratio (adj. OR) พร้อมค่า 95% confidence interval (CI) **ผลการศึกษา:** มีเคส 37 ราย และคอนโทรล 74 ราย พบว่ามี 3ปัจจัยที่สัมพันธ์กับ MALA ได้แก่ เพศชาย (adj. OR = 6.319, 95% CI = 2.166 - 18.433, *P*-value = 0.001) ยาเม็ทฟอร์มินขนาดสูง ≥ 2,000 มก.ต่อวัน (adj. OR = 12.153, 95% CI = 4.076 - 36.238, *P*-value < 0.001) และภาวะไตเสื่อมเรื้อรังระยะ 2 และ 3 (adj. OR = 7.709, 95% CI = 1.511 - 39.339, *P*-value = 0.014) **สรุป:** เพศชาย ยาเม็ทฟอร์มินขนาดสูง และโรคไตเรื้อรังระยะ 2 และ 3 มีความเสี่ยงในการเกิด MALA มากกว่าเพศหญิง ยาเม็ทฟอร์มินขนาดต่ำ และโรคไตเรื้อรังระยะ 1 หรือไม่มีโรคไตเรื้อรัง

คำสำคัญ: ภาวะเลือดเป็นกรดจากกรดแลคติกในเลือดสูงเนื่องจากยาเม็ทฟอร์มิน, คนไข้เบาหวานชนิดที่ 2, ปัจจัยเสี่ยง, การรักษา, ผลลัพธ์ทางคลินิก

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Abstract

Objective: To investigate risk factors, treatment modalities, and clinical outcomes of metformin-associated lactic acidosis (MALA). **Method:** In this case-control study, type 2 diabetic patients taking metofrmin in the medical records of Mahasarakham Hospital between 1 January 2018 to 31 December 2020 were reviewed. Patients who developed lactic acidosis were cases; while those who did not were controls. A total of 38 risk factors were tested were tested for associations with MALA using univariate analysis. Significant factors were further tested in multiple logistic regression analysis. Adjusted odds ratio (adj. OR) with 95% confidence interval (CI) were presented. **Results:** A total of 37 and 74 cases and cxontrols were included, respectively. Three risk factors were significantly associated with MALA: men (adj. OR = 6.319, 95% CI = 2.166 - 18.433, *P*-value = 0.001), metformin dose of ≥ 2,000 mg/day (adj. OR = 12.153, 95% CI = 4.076 - 36.238, *P*-value < 0.001), and chronic kidney disease (CKD) stage 2 or 3 (adj. OR = 7.709, 95% CI = 1.511 - 39.339, *P*-value = 0.014). **Conclusion:** Men, high dose metformin and CKD stage 2 or 3 were significantly more likely to experience MALA than women, metformin lower dose, and CKD stage 1 or no CKD.

Keywords: metformin-associated lactic acidosis, type 2 diabetic patients, risk factors, treatment, clinical outcomes

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Introduction

Metformin is an effective antidiabetic drug for controlling blood glucose levels. The American Diabetes Association (ADA) guidelines recommend metformin as the first drug for patients with diabetes type 2.[1] Metformin reduces diabetes-related complications and mortality.[2] Metformin inhibits gluconeogenesis in the liver, stimulates glycolysis, and transports glucose to hepatocytes. It also suppresses the expression of genes involved in gluconeogenesis and lipogenesis. Metformin can help prevent both macrovascular (e.g., atherosclerosis: myocardial infarction, and stroke) and microvascular problems (e.g., diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy). It can, however, have major side effects, such as metformin-associated lactic acidosis (MALA). Studies have reported that the incidence of MALA ranges from 2.3 to 138 cases per 100,000 person-year.[3-9]

Based on previous research and literature, MALA risk factors studied were age, gender, metformin dose, Charlson comorbidity score, diabetes duration, alcoholism, tissue hypoxia or poor tissue perfusion (e.g., severe dehydration, severe diarrhea, hemorrhage, and shock), heart failure, liver illness, renal disease, sepsis, and a variety of medicines were also investigated as risk factors.[10-12]

Lactic acidosis can be caused by various medications through a variety of mechanisms. Some medicines including clozapine, diltiazem, nifedipine and procainamide can cause hypoperfusion, hypoxia, and anaerobic glycolysis by lowering cardiac output. Although some medications such as simvastatin, telbivudine, and nucleoside reverse transcriptase inhibitors block the formation and function of mitochondrial proteins, metabolic acidosis can be exacerbated by any medicines that affect the renin angiotensin aldosterone system or produce hyperkalemia (e.g., cyclogenase inhibitors, β-adrenergic blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, direct renin inhibitors, ketoconazole, spironolactone, amiloride and triamterene). As a result, these medications can enhance MALA.[13]

The reported mortality rate for MALA is 50%.[14] Recently, a systematic review and meta-analysis of cases and studies reported overall mortality with MALA to be 36.2% (95% CI: 29.6 – 43.94).[15] Based on renal function, the recommended maximum dose of metformin is 3,000, 2,000, 1,000, and 500 mg per day for creatine clearance (CrCl) of 120, 60, 30, and 15 mL/min, respectively. MALA patients should cease taking metformin and receive supportive therapy such as hydration and electrolyte correction, decrease metformin doses, and receive IV sodium bicarbonate and hemodialysis. Prompt diagnosis and treatment can help patients survive. Patients with severe MALA may need hemodialysis and incur high costs for treatment.[16,17] In Thailand, among diabetic patients with estimated glomerular filtration rate (eGFR) of > 30 mL/min/1.73 m^2 using metformin as monotherapy or in combination with other antidiabetic drugs, more than 80% of hospitalized patients taking metformin for diabetes had at least one indicator of irrational drug use.[18]

Therefore, many diabetic patients are at risk for MALA. The goals of this study were to investigate risk factors of MALA in patients who taking metformin. Specifically, the factor of metformin high exposure was defined as those of the upper limits of the recommended dose (≥ 2,000 mg/day) versus those less than 2,000 mg/day.[19]

Methods

Study design

This was a case-control study of diabetic patients with MALA. The study protocol and ethics were approved by the Institutional Review Boards of Mahasarakham University (235/2563) and Mahasarakham Hospital (COA NO. 63/040 and MSKH_REC 63-02-048).

Study population and sample

Data of patients from the medical records of Mahasarakham Hospital receiving care between January 2018 and December 2020, were retrospectively extracted and evaluated. A total of 9,201 diabetic type II patients using metformin were screened for eligibility. Cases were patients who had MALA and controls were those who did not. Thirty-seven patients with MALA were included in the study. With a ratio of cases to controls of 1:2, 74 controls were recruited using simple random sampling. A total of 111 patients with type 2 diabetes taking metformin were included in this study.

To be eligible, both cases and controls had to be patients with type 2 diabetes who used metformin and were admitted to the hospital between January 1, 2018, and December 31, 2020. For **Cases**, they had to satisfy either 1) the MALA diagnostic criteria (i.e., arterial pH of < 7.35 and plasma lactate of > 5.0 mmol/L), 2) be diagnosed with lactic acidosis by a physician based on the International Classification of Diseases and Related Health Problem 10th Revision (ICD-10) code of E87.2 with the code of E11.9 for diabetes mellitus type 2, or 3) be reported on MALA with a pharmacist's note. For **Controls**, they were not identified with MALA by the MALA diagnostic criteria (i.e., arterial pH of < 7.35 and plasma lactate of > 5.0 mmol/L), diagnosis with lactic acidosis by a physician based on the ICD-10 codes, or report of MALA by the pharmacist. Each control admitted to the hospital between January 2018 and December 2020 was selected regardless of the MALA diagnosis date of the cases.

Potential cases and controls were excluded if any of these criteria were met: diabetic ketoacidosis (DKA) (i.e., blood sugar > 250 mg/dL, ketone body > 3 mmol/L, pH < 7.3 and $HCO3^-$ < 18), cancer patients, tuberculosis patients, and patients infected with the Human Immunodeficiency Virus

(HIV), incomplete data to define MALA, death before MALA diagnosis, patients with multiple disorders where it was not possible to distinguish between MALA and other diagnoses, or patients admitted to the hospital for more than 7 days with no MALA. All clinical characteristics were from the singular episode of care.

Procedures

From the medical records, information of 38 risk factors both demographic and clinical characteristics were extracted. These included gender, age, smoking, HbA1c, Charlson comorbidity index, alcoholism or alcohol dependence, metformin dose, shock, severe dehydration, severe diarrhea, tissue hypoxia, hypertension, dyslipidemia, chronic kidney disease (CKD) stage, infectious diseases, benign prostatic hyperplasia, anemia, acute stroke, old CVA, pneumonia, pulmonary tuberculosis, cardiovascular disease, acute renal failure or acute kidney injury, sepsis, ACEIs, ARBs, CCBs, thiazide diuretics, beta blockers, statins, fibrates, sulfonylureas, thiazolidinediones, insulin, aspirin, NSAIDs, herbs and eGFR.

Statistical analysis

Descriptive statistics including mean ± standard deviation or median (interquartile range) as appropriate, and frequency with percentage were used to summary all variables. In univariate analysis, differences of all variables between cases and controls were performed using Student's t-tests or Mann-Whitney U test as appropriate for continuous variables and chi-square test or Fisher's exact test as appropriate for categorical variables. Variables found significant from univariate analysis were further tested for the association with MALA in multiple logistic regression analysis adjusted for each other. Adjusted odds ratio (adj. OR) was presented with 95% confidence interval (95% CI). Risk prediction equation was generated. Predicted risk of MALA based on each combination of the significant factors was estimated and receiver operating characteristic curve showing sensitivity and specificity was generated. Statistical significance was set a type I error of 5%. All statistical analyses were performed using STATA 16.0 software.

Results

With a total of 111 type 2 diabetic who were using metformin included, 37 patients with MALA were cases and 74 patients with no MALA were controls. Age, Body mass index (BMI), hospital stay, HbA1C, Charlson comorbidity index were not different between cases and controls. Gender, alcohol consumption, smoking, metformin dose, eGFR baseline, arterial pH, serum lactate and eGFR on admission were significantly different between cases and controls (*P*-value < 0.05) (Table 1). The study group had an average hospital stay of 4 days with a range of 1 - 14 days.

Table 1 Baseline characteristics of cases and controls (N = 111).

Variables		Total (%) (N = 111)	Cases (n = 37)	Controls (n = 74)	*P*-value
Gender	Male	46 (41.4)	23 (62.2)	23 (31.1)	0.002*
	Female	65 (58.6)	14 (37.8)	51 (68.9)	
Age (years), mean ± S.D.		62.05 ± 10.97	61.62 ± 11.05	62.27 ± 10.99	0.692**
BMI (kg/m^2), mean ± S.D.		22.68 ± 6.96	20.59 ± 9.73	23.73 ± 4.79	0.319**
Alcohol consumption	Yes	11 (9.9)	5 (13.5)	6 (8.1)	< 0.001*
	No	75 (67.6)	11 (29.7)	64 (86.5)	
	No data	25 (22.5)	21 (56.8)	4 (5.4)	
Smoking	Yes	9 (8.1)	5 (13.5)	4 (5.4)	< 0.001*
	No	77 (69.4)	11 (29.7)	66 (89.2)	
	No data	25 (22.5)	21 (56.8)	4 (5.4)	
Hospital stays (days), mean ± S.D.		4.56 ± 4.25	4.31 ± 4.31	5.62 ± 4.94	0.160**
HbA1c (%)	< 7	17 (15.3)	9 (24.3)	8 (10.8)	0.051*
	≥ 7	49 (44.1)	11 (29.7)	38 (51.4)	
	No data	45 (40.5)	17 (45.9)	28 (37.8)	
Metformin dose (mg/d), mean ± S.D.		1418.47 ± 655.78	1891.89 ± 578.97	1181.76 ± 558.84	< 0.001**
≥ 2,000		69 (62.2)	12 (10.8)	57 (51.4)	
< 2,000		42 (37.8)	25 (22.5)	17 (15.3)	
Alcoholism or alcohol dependence	Yes	0 (0)	0 (0)	0 (0)	N/A
	No	111 (100)	37 (100)	74 (100)	
Shock	Yes	16 (14.4)	16 (14.4)	0 (0)	< 0.001*
	No	95 (85.6)	21 (18.9)	74 (66.7)	
Severe diarrhea	Yes	4 (3.6)	4 (3.6)	0 (0)	0.004*
	No	107 (96.4)	33 (29.7)	74 (66.7)	
Tissue hypoxia	Yes	4 (3.6)	4 (3.6)	0 (0)	0.004*
	No	107 (96.4)	33 (29.7)	74 (66.7)	
Hypertension	Yes	78 (70.3)	31 (27.9)	47 (42.3)	0.028*
	No	33 (29.7)	6 (5.4)	27 (24.3)	
CKD (stage 2 or 3)	Yes	11 (9.9)	7 (6.3)	4 (3.6)	0.025*
	No	100 (90.1)	30 (27)	70 (63.1)	
Acute stroke	Yes	14 (12.6)	1 (0.9)	13 (11.7)	0.026*
	No	97 (87.4)	36 (32.4)	61 (55)	
Acute renal failure	Yes	31 (27.9)	31 (27.9)	0 (0)	< 0.001*
	No	80 (72.1)	7 (5.7)	74 (66.7)	
Sepsis	Yes	3 (2.7)	3 (2.7)	0 (0)	0.013*
	No	108 (97.3)	34 (30.6)	74 (66.7)	
Charlson comorbidity index score (points)	< 2	13 (11.7)	4 (10.8)	9 (12.2)	0.835*
	≥ 2	98 (88.3)	33 (89.2)	65 (87.8)	
eGFR before admission (mL/min/1.73 m²), mean ± S.D.		37.29 ± 41.87	23.39 ± 36.81	44.23 ± 42.74	< 0.001**
Laboratory test at first day admission					
Arterial pH	< 7.35	28 (25.2)	28 (75.7)	0 (0)	< 0.001*
	≥ 7.35	7 (6.3)	6 (16.2)	1 (1.4)	
	No data	76 (68.5)	3 (8.1)	73 (98.6)	
Serum lactate (mmol/L)	≤ 5	9 (8.1)	7 (18.9)	2 (2.7)	< 0.001*
	> 5	29 (26.1)	29 (78.4)	0 (0)	
	No data	73 (65.8)	1 (2.7)	72 (97.3)	
eGFR on admission (mL/min/1.73 m²)	< 15	31 (27.9)	31 (83.8)	0 (0)	< 0.001*
	≥ 15	80 (72.1)	6 (16.2)	74 (100)	
HbA1c (%)	< 7	17 (15.3)	9 (24.3)	8 (10.8)	0.051*
	≥ 7	49 (44.1)	11 (29.7)	38 (51.4)	
	No data	45 (40.5)	17 (45.9)	28 (37.8)	
Drug used with metformin					
Sulfonylureas	Yes	67 (60.4)	28 (25.2)	39 (35.1)	0.020*
	No	44 (39.6)	9 (8.1)	35 (31.5)	
NSAIDs	Yes	5 (4.5)	5 (4.5)	0 (0)	0.001*
	No	106 (95.5)	32 (28.8)	74 (66.7)	

* Chi-square test.
** Independent t-test.

Univariate tests revealed that among the 38 factors tested, 13 were significantly associated with MALA. These included gender (*P*-value = 0.002), BMI (*P*-value = 0.026), high metformin dose (*P*-value < 0.001), shock (*P*-value < 0.001), severe diarrhea (*P*-value = 0.004), tissue hypoxia (*P*-value = 0.004), hypertension (*P*-value = 0.028), CKD (stage 2 or 3) (*P*-value = 0.025), acute stroke (*P*-value = 0.026), acute renal failure (*P*-value < 0.001,), sepsis (*P*-value = 0.013), sulfonylureas (*P*-value = 0.020), and NSAIDs (*P*-value = 0.001) (Table 1).

In the multiple logistic regression, there were seven of the 13 factors that had zero counts in either cases or controls (i.e., BMI, shock, severe diarrhea, tissue hypoxia, acute renal failure, sepsis, and NSAIDs). In this zero-count situation, calculation of odds ratio was not allowed. Therefore, only 6 factors (i.e., gender, high metformin dose, hypertension, CKD (stage 2 and 3), acute stroke and sulfonylureas) were further tested in multiple logistic regression. It was found that, of the six factors tested, only gender, metformin high dose and CKD (stage 2 or 3) were significantly associated with MALA (Table 2).

Table 2 Associations between MALA and its risk factors based on multiple logistic regression (N = 111).

Risk factors	adj. OR	95% CI for adj. OR		*P*-value
		lower	upper	
Gender (male)	7.250	2.367	22.209	0.001
Metformin high dose	8.214	2.537	26.591	< 0.001
Hypertension	1.140	0.328	3.962	0.837
CKD (stage 2 or 3)	8.255	1.454	46.854	0.017
Acute stroke	0.423	0.045	9.989	0.452
Sulfonylureas	2.962	0.896	9.784	0.075

The multiple logistic regression with three predictors on MALA indicated that men, metformin dose of ≥ 2,000 mg/day, and CKD stage 2 or 3 were 6.319, 12.153, and 7.709 times significantly more likely to have MALA, respectively, when compared with women, metformin dose of < 2,000 mg/day, and CKD stage 1 or no CKD, respectively (*P*-value = 0.001, < 0.001, and = 0.014, respectively) (Table 3).

Table 3 Associations between MALA and its risk factors based on multiple logistic regression (N = 111).

Risk factors	B	adj. OR	95% CI for adj. OR		*P*-value
			lower	upper	
Constant	-2.895				
Gender (male)	1.844	6.319	2.166	18.433	0.001
Metformin high dose	2.498	12.153	4.076	36.238	< 0.001
CKD (stage 2 or 3)	2.042	7.709	1.511	39.339	0.014

Hosmer and Lemeshow test of goodness-of-fit *P*-value = 0.758.

Based on these three significant predictive factors, the model for risk prediction was as follows:

Probabilities for MALA = ln(odds) = -2.895 + (1.844x(gender) + 2.498x(metformin high dose) + 2.042x(CKD),

where probability of MALA of men compared with women, metformin dose of ≥ 2,000 mg/day compared with < 2,000 mg/day, and CKD stage 2 or 3 compared with stage 1 or no CKD.

Based on the model, the combination of risk factors with the highest risk of MALA was men-metformin dose of ≥ 2,000 mg/day-CKD stage 2 or 3 (predicted risk = 97.00%), followed by female-metformin dose of ≥ 2,000 mg/day-CKD stage 2 or 3 (predicted risk = 83.80 %) and male-metformin dose of ≥ 2,000 mg/day-CKD stage 1 or no CKD (predicted risk = 80.96%). The combination with the least risk was male-metformin dose of < 2,000 mg/day-CKD stage 1 or no CKD (predicted risk = 25.90%) (Table 4).

Table 4 Predicted risks of MALA of risk factor combinations (N = 111).

Risk factor combinations	Risk score	Predicted risk (%)
Male, metformin dose < 2,000 mg/d, CKD stage 1 or no CKD	-1.051	25.90
Female, metformin dose ≥ 2,000 mg/d, CKD stage 1 or no CKD	-0.397	40.20
Female, metformin dose < 2,000 mg/d, CKD stage 2 or 3	-0.853	29.90
Male, metformin dose ≥ 2,000 mg/d, CKD stage 1 or no CKD	1.447	80.96
Male, metformin dose < 2,000 mg/d, CKD stage 2 or 3	0.991	72.90
Female, metformin dose ≥ 2,000 mg/d, CKD stage 2 or 3	1.645	83.80
Male, metformin dose ≥ 2,000 mg/d, CKD stage 2 or 3	3.489	97.0x

The combination of gender, dose of metformin and CKD was a good predictor of MALA based on the ROC curve with the area under the curve of 0.794 (*P*-value < 0.001) (Figure 1).

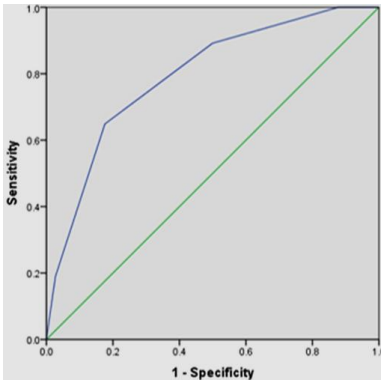

Figure 1 Receiver operating characteristic curve of the risk factor combination gender, dose of metformin, and CKD.

Note: Area under the curve = 0.794, 95% confidence interval 0.707 – 0.881, *P*-value < 0.001.

Discussions and Conclusion

In this case-control study in Thai type 2 diabetic patients using metformin, gender, metformin dose, and chronic kidney disease (stage 2 or 3) were significant risk factors for MALA. Male patients had a higher risk of MALA (adj. OR = 6.319, 95% CI = 2.166 - 18.433, *P*-value = 0.001). This could be in part because male patients (18.52%) were alcohol drinkers, while female patients were not (data not shown). No previous study has shown gender as a risk factor for MALA. More studies are needed on the association of gender and MALA.

Metformin dosage of more than 2,000 mg/d was a significant risk factor (adj. OR = 12.153, 95% CI = 4.076 - 36.238, *P*-value < 0.001). Kuan et al (2019) conducted a systematic review of 559 metformin-associated lactic acidosis cases and reported that 60% of cases in patients with impaired kidney function were using a metformin dose that exceeded published guidelines.[20] Chronic kidney disease stage 2 or 3 was also a significant risk factor for MALA (adj. OR = 7.709, 95% CI = 1.511 - 39.339, *P*-value = 0.014). Richy and colleagues reported that the incidence of MALA tended to increase across normal, mild, moderate, and severe renal disease groups with 7.6, 4.6, 17.0, and 39 cases per 100,000 patient-years, respectively.[4] Similar results were also reported in patients with renal impairment in retrospective nested case-control study and systematic reviews.[21,22] Sambol and co-workers showed that clearance of metformin decreased 74 - 78% and 23- 33% in moderate-to-severe and mild chronic renal impairment, respectively.[23] It was recommended that the metformin dose for patients with chronic kidney disease stage 3a (i.e., eGFR 45 - 59 mL/min/1.73 m^2) to be not more than 1,500 mg/d.[24] In this study, 4 of 5 patients (80%) who had chronic kidney disease stage 3 were taking metformin 2,000 - 3,000 mg/day and had MALA (data not shown). Diabetic patients taking metformin should have the dose adjusted according to their renal function.

By univariate analysis, we found other significant risk factors such as sepsis, severe diarrhea , tissue hypoxia and shock which was consistent with a previous study of DeFronzo et al. [25] However, since no presence of each of these factors in controls, these factors were not included in the multiple logistic regression for calculating odds ratio. It must be noted that lactic acidosis can also be caused by other drugs with different mechanisms, such as ACEIs, ARBs, beta blockers, aspirin and NSAIDs, and isoniazid.[26]

There are several limitations in this study. A retrospective study is unable to provide complete data, especially some data such as laboratory tests of renal or liver function tests that were not available in controls. We used the measures of laboratory tests before admission with MALA, but not tests that were completed more than one-year prior to admission. No data on eGFR, arterial pH and serum lactate were available in the control group, so we were not able to calculate OR for these factors. Most of patients who had MALA were referred from other hospitals, and so some data were missing. Since we did not have serum metformin levels, we could not make comparisons between those with MALA and controls.

In conclusion, male gender, metformin dosage of more than 2,000 mg/day, and chronic renal failure stage 2 or 3 were risk factors for MALA. We should therefore screen for these factors to prevent MALA. We developed a model for predicting the risk of MALA and calibrated it by using Hosmer and Lemeshow's goodness of fit test (*P*-value = 0.758). Three risk factors could predict 97% of the risk score. However, this study did not perform a discrimination test for patients at low and high risk of MALA. To study these further, we will need a new cohort of patients for external validation of both the calibration and discrimination tests. In addition, further studies may derive a clinical prediction score for MALA and evaluate the sensitivity and specificity of the score for confirmation in clinical practice.

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