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Research Article

Risk factors associated with metformin associated lactic acidosis (MALA) in type 2 diabetic patients receiving metformin

Pemmarin Potisarach[1], Juntip Kanjanasilp[2], Nayrata Pinnetdharn[3], Sansanee Wangvoralak[3], Siraprapa Sonsri[4], Thitima Srimarueang[4], Krongkan Sawamichai[5], Phongsathorn Tanawsri[5], Sirawan Tonja[5], Natedow Khamsita[5], Pattarin Kittiboonyakun[2]*

[1] International Primary Care Practice Research Unit (iPCPRU), Faculty of Pharmacy, Mahasarakham University, Kham-Riang Subdistrict, Kantharawichai District, Maha Sarakham Province, Thailand
[2] Health Services and Pharmacy Practice Research and Innovation (HSPRI), Faculty of Pharmacy, Mahasarakham University, Kham-Riang Subdistrict, Kantharawichai District, Maha Sarakham Province, Thailand
[3] Department of Fishery Management, Faculty of Fisheries, Kasetsart University Bangkok, Thailand
[4] Clinical Pharmacy Service Division, Surin Hospital, Muang District, Surin Province, Thailand
[5] Faculty of Pharmacy, Mahasarakham University, Kham-Riang Subdistrict, Kantharawichai District, Maha Sarakham Province, Thailand

ABSTRACT

Metformin-associated lactic acidosis (MALA) is a rare but potentially fatal condition characterized by bloodstream lactic acid levels exceeding 5.0 mmol/L, leading to acidemia (blood pH less than 7.35), with mortality rates reaching up to 50% if not promptly and appropriately managed. However, there is limited evidence regarding the risk factors associated with the occurrence of MALA in diabetic patients receiving metformin within the Thai context. The aim of research was to investigate factors associated with MALA in type 2 diabetic patients taking metformin. A retrospective matched case-control study was conducted in a total of 272 type 2 diabetic patients. Data were collected from Surin Hospital's electronic medical records from 2017 to 2021. Descriptive statistics and Chi-square tests were used. Binary logistic regression analysis with Backward Likelihood ratio (LR) selection method was used to determine the optimal final model of the predictor of MALA occurrence, at significance level of 0.01. During the 5-year period, 58,206 patients received treatment with metformin and only 136 cases were diagnosed with MALA. The majority of participants were female (56.6%) and had an average age of 60 years. It was shown that history of using combined pain relief medications had a 38.29-fold higher likelihood of developing MALA compared to those who did not use this medication (OR = 38.29, 99% CI 5.96-245.87). This study highlighted the importance of implementing comprehensive monitoring system for diabetic patients, with consideration of identified risk factors. Such an approach can help reduce the risk of MALA and enhance patient safety and outcomes.

Keywords:
Metformin associated lactic acidosis; MALA; Risk factors; Metformin

1. INTRODUCTION

Diabetes mellitus (DM) is a chronic non-communicable disease that significantly impacts on the burden of the health care system in Thailand, with the number of patients increasing every year. The prevalence of diabetes among individuals aged 15 years and above has been reported to be 9.5% in 2020, which has increased 21% from 2009 [1]. In 2024, the reported prevalence of DM in adults was 10.2%. This increase has a direct impact on the cost of providing care to patients with DM. The management of DM includes life-style modifications and

***Corresponding author:**
* Pattarin Kittiboonyakun Email: pattarin.k@msu.ac.th

pharmacotherapy management [1]. Despite the availability of newer groups of medications, such as Sodium-glucose Cotransporter-2 (SGLT-2) inhibitors and Glucagon-like peptide-1 (GLP-1) receptor agonists, metformin continues to be widely used in clinical practice and is the first line drug recommended in Thailand [1]. Metformin's side effects are usually well-tolerated, with mainly gastrointestinal (GI) side effects [2,3]. However, Metformin Associated Lactic Acidosis (MALA) has been reported as a serious but rare side effect of metformin (<1%), which could potentially lead to life-threatening situations and has a mortality rate up to 30%-50% [2,3]. Based on systematic reviews including retrospective studies, clinical trials and large case series, it was found that the overall incidence of lactic acidosis in metformin users varies across studies from approximately 3 to 10 per 100,000 person-years and was generally indistinguishable from the background rate in the overall population with diabetes[4]. Research conducted by JH et al[5] has documented a significant annual increase in metformin-associated lactic acidosis (MALA) cases globally, with instances rising from 521 cases in 2015 to 1,939 cases in 2018 across countries including the United Kingdom, France, Germany, and Italy, and from 111 cases to 243 cases within the United States during the same period. The rise in MALA cases was also accompanied by an increase in acute kidney injury, following the approval by the US Food and Drug Administration (FDA) for the use of metformin in diabetic patients with mild to moderate chronic kidney disease, as determined by estimated glomerular filtration rate[5]. a nested case-control study conducted by Alvarez CA et al[6], involving 320,882 patients reported that MALA occurred in 2,665 individuals, resulting in an overall incidence rate of 2.00 (95% CI 1.93-2.08) per 1,000 person-years. This study additionally employed a propensity score-matched cohort design, identifying a significant correlation between advanced stages of chronic kidney disease (CKD) and heightened risks of MALA, with the highest risk occurring in patients classified as stage 4 or 5 CKD, thus reinforcing the contraindication for metformin in this patient group. Besides renal function, previous studies[7-9] have identified additional significant risk factors associated with the occurrence of MALA, including peripheral artery disease, cancer, heart failure, liver failure, respiratory failure, and sepsis. Interestingly, investigations by Kim et al[8] and DeFronzo et al[9] have revealed that diabetic patients with a history of alcohol use showed an increased likelihood of developing MALA.

While most existing research on MALA has been conducted in ASEAN and Western countries. Only a few studies were undertaken in Thailand. A study by Russameethum W and Rungprai D[10], which analyzed spontaneous reports of adverse drug reactions from 2005 to 2017, provided by the Health Product Vigilance Center in Thailand's FDA, identified 169 patients with MALA. The calculated incidence rate from 2016 to 2017 was 4.6 cases per 100,000 patient-years, with the majority of patients being women and averaging over 60 years of age, 10.1% of whom experienced acute kidney injury. Commonly prescribed concurrent medications included sulfonylureas, angiotensin-converting enzyme inhibitors, and diuretics, with MALA leading to hospitalizations in 87.30% of cases and a cure rate of 49.10%. Additionally, a report from the Thai FDA[11] compiled data on MALA cases from January 1, 1998, to October 31, 2021, revealing a total of 812 cases, predominantly reported from the southern regions of Northeastern Thailand, particularly Surin, Burirum, Chaiyaphum, and Nakhon Ratchasima Province, which accounted for the highest proportion (24.63%) of cases within the most recent decade. It is essential to note that the incidence of MALA might be underreported due to the voluntary nature of adverse event reporting and the complexities associated with diagnosis of MALA in the past. Consistent findings with the Thai FDA report were observed in a study by Siangtrong W et al[12], which employed an analytical cross-sectional design at Buriram Hospital from 2012 to 2017, reporting a total of 108 MALA patients with an overall mortality rate of 33.33%. Significant predictors of mortality included elevated lactate levels, a blood pH of less than 7, and the time elapsed from admission to the initiation of renal replacement therapy. A case-control study by Kanjanasilp J et al[13] conducted between January 2018 and December 2020 at Mahasarakham Hospital, a provincial hospital located in the central of northeastern Thailand demonstrated that male gender, high-dose metformin use, and CKD stages 2 or 3 were significant predictors of MALA occurrence, concerning with a limited sample size of 111 participants, which included 37 MALA cases and 74 controls.

Despite the significant number of reported cases in this region, the previous study used descriptive research methodology, not an analytical approach. In addition, there has been limited research addressing risk factors associated with MALA in diabetic populations, particularly, those including history of alcohol consumption, history of using herbal medicines, history of non-steroidal anti-inflammatory drugs (NSAIDs) use and history of taking combined pain relief medications, are needed to be further explored in the southern areas of the northeastern Thailand.

Therefore, this study aimed to investigate the risk factors associated with the occurrence of MALA among patients with type 2 diabetes taking metformin at Surin Hospital by using a retrospective matched case-control method. Identifying these factors is essential for establishing an effective MALA surveillance system, ultimately contributing to improve patient safety and clinical management for diabetic patients receiving metformin.

2. MATERIALS AND METHODS

A retrospective matched case-control study was conducted in patients with type 2 DM treated with metformin from 2017 to 2021 at Surin Hospital, Surin Province, Thailand.

2.1. Population, cases, and controls

This study involved with type 2 diabetes who were managed with metformin and had received treatment at Surin Hospital, Surin Province, Thailand. The cases included in this study were selected based on the diagnosis of MALA, which was identified using the International Classification of Diseases (ICD-10) codes, E87.2 for lactic acidosis and E11.9 for type 2 DM. Based on the hospital's protocol, MALA was diagnosed when these criteria presented: history of using metformin, pH < 7.35, serum lactate level > 5 mmol/L, and HCO_3 < 10 mmol/L. We excluded patients who did not have type 2 DM, those whose final diagnosis changed, as well as those who experienced type A lactic acidosis or diabetic ketoacidosis (DKA) from our study. We deliberately selected control groups from patients with type 2 DM who were receiving metformin during the same period as the cases. A 1:1 matching of cases and controls was performed in this study based on gender and age.

2.2. Risk factors and exposure to metformin

In this study, we defined the risk of exposure to metformin as either having metformin at any time before the study or with the three months preceding it. Chronic medical conditions and concomitant use of medications such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and NSAIDs etc. were collected retrospectively from patients' medical records and electronic health database. Risk factors such as history of alcohol consumption, herbal supplement use, or other medication use were collected retrospectively from patients' medical records. To ensure the accuracy of this information, researchers (KS, PT, ST, NK) contacted all reachable patients in the case group by telephone to obtain exposure history.

2.3. Statistical analysis

The data was analyzed using Statistical Package for the Social Sciences (SPSS) Version 29.0 for Windows. Descriptive statistics was used to describe the characteristics of the patients, which were presented as frequency (as a percentage) and means with standard deviation (SD). Chi-square test was used to test a preliminary association between categorical risk factors and metformin exposure. Only factors identified as significantly associated with MALA were selected as independent variables for further causal analysis. The causal relationship between these factors and MALA occurrence was analyzed using a binary logistic regression model. Initially, a binary logistic regression model with a single regressor was performed for each independent variable. The significance of each factor was tested using the Wald test at a significance level of 0.01 ($\alpha = 0.01$). All variables found to be significant factors were used to construct a binary logistic regression model with multiple regressors to determine the optimal final model. The Backward Likelihood Ratio (LR) selection method was used to identify the optimal final model at a significance level of 0.01 in this study. The results of the binary logistic regression analysis were presented as odds ratios with their corresponding 99% confidence interval. The model's performance was described based on the percent of prediction, NagelKerke R^2 and the Akaike Information Criteria (AIC) value.

3. RESULTS

Participants' characteristics showed that the majority was females (56.6%) and the average age was 60.2 years for both case and controls. The most commonly prescribed dosage of metformin was 2,000 mg/day (52.9%). The average laboratory values of the study participants were as follows: HbA1C was 8.15%, body temperature was 36.6 ˚C, systolic blood pressure was 123.2 mmHg, diastolic blood pressure was 68.13 mmHg, heart rate was 90.94 beats per minute, respiratory rate was 23.65 breaths per minute, blood glucose level was 184.61 mg%, eGFR was 47.42 mL/min/1.73 m^2, serum creatinine level was 4.76 mg/dL, AST level was 191.49 U/L, and ALT level was 92.90 U/L. The majority of participants did not consume alcohol (74.1%), as shown in Table 1.

Chi-square test revealed significant associations between the occurrence of MALA and some factors, including healthcare insurance status, daily metformin dosage, and kidney function. Additionally, MALA occurrence was significantly related to chief complaints including nausea/vomiting ($p < 0.001$), diarrhea ($p < 0.001$), and oliguria ($p < 0.001$). Furthermore, significant associations were identified between MALA occurrence and a history of alcohol consumption ($p = 0.007$), herbal medicine use ($p < 0.001$), NSAIDs use ($p < 0.001$), and the use of combined pain relief medications ($p < 0.001$). Moreover, the occurrence of MALA was significantly linked to medication use for chronic diseases ($p = 0.003$), chronic kidney disease ($p = 0.003$), and dyslipidemia ($p < 0.001$).

Table 1. Characteristics of participants.

		Total (n=272) (%)	Case (n=136) (%)	Control (n=136) (%)
Gender	Male	118 (43.40)	59 (43.38)	59 (43.38)
	Female	154 (56.60)	77 (56.60)	77 (56.60)
Age	Year	60.19 ± 10.01	60.19 ± 10.03	60.19 ± 10.03
Health care insurance coverage	Universal Health Care	202 (74.30)	120 (86.30)	82 (60.30)
	Social Security	18 (6.60)	3 (2.20)	15 (11.03)
	Civil Servants	40 (14.70)	9 (6.50)	31 (22.79)
	Others (self-pay, disability)	11 (4.00)	4 (2.90)	7 (5.10)
History of alcohol consumptions	Yes	64 (25.90)	38 (34.20)	26 (19.10)
	No	183 (74.10)	73 (65.80)	110 (80.90)
Daily dose of metformin (mg/day)	1,000 mg/day	61 (22.40)	23 (16.50)	38 (27.90)
	1,500 mg/day	21 (7.70)	9 (6.50)	12 (8.80)
	2,000 mg/day	144 (52.90)	81 (58.30)	63 (46.30)
	2,500 mg/day	3 (1.10)	2 (1.40)	1 (0.70)
	Other dosage	43 (15.90)	21 (17.30)	22 (16.30)
HbA1C (%)		8.15 ± 2.54	8.34 ± 2.98	8.10 ± 2.45
BT (C)		36.61 ± 0.55	36.50 ± 0.66	36.72 ± 0.39
SBP (mmHg)		123.17 ± 24.85	114.80 ± 29.97	131.42 ± 14.41
DBP (mmHg)		68.13 ± 17.27	60.20 ± 19.37	75.94 ± 10.03
HR (beat/min)		90.94 ± 17.15	97.47 ± 18.80	84.46 ± 12.36
RR (breath/min)		23.65 ± 7.80	27.39 ± 9.94	20.15 ± 0.70
DTX (mg%)		184.61 ± 157.43	224.13 ± 233.35	158 ± 62.67
eGFR (mL/min/1.73 m^2)		47.42 ± 41.61	10.12 ± 14.07	84..99 ± 21.36
Scr (mg/dL)		4.76 ± 5.34	8.28 ± 3.93	1.21 ± 4.08
AST (U/L)		191.49 ± 735.75	250.70 ± 856.32	33.98 ± 21.92
ALT (U/L)		92.90 ± 360.49	118.07 ± 420.36	25.94 ± 19.28

BT = body temperature, SBP = systolic blood pressure, DBP = diastolic blood pressure, HR = heart rate, RR = respiratory rate, DTX = blood glucose level monitoring during admission, eGFR = estimated glomerular filtration rate, Scr = serum creatinine, AST = aspartate aminotransferase, ALT = alanine transaminase.

The finding from the binary logistic regression analysis with a single independent variable that the occurrence of MALA was significantly associated with risk factors including a history of alcohol consumption (Wald = 7.12, p = 8.00×10^{-3}), a history of herbal medicine use (Wald = 10.73, p = 1.00×10^{-3}), and a history of using combined pain relief medications (Wald = 11.48, p = 1.00×10^{-3}). Additionally, the use of medication for chronic kidney diseases and for dyslipidemia was also significantly associated with MALA occurrence (Wald = 7.80, p = 5.00×10^{-3}; Wald = 27.23, p = 1.81×10^{-7}) (Table 2).

When these significant variables were included in the binary logistic regression model with multiple independent variables, the result in Model 4 showed that only a history of alcohol consumption and a history of using combined pain relief medications remained significantly associated with MALA occurrence at significant level 0.01 (Wald = 5.19, p = 0.02 and Wald = 15.41, p = 2.87×10^{-7}, respectively) (Table 3). However, the optimal regression equation derived using the Backward LR selection method identified the history of using combined pain relief medications as the strongest predictor of MALA occurrence (Model 5) (Table 3). This model exhibited the lowest Akaike Information Criterion (AIC = 10.47), a high overall correct classification rate (overall percent of prediction = 93.9%), and a Nagelkerke R^2 of 0.23. The findings further indicated that participants with a history of using combined pain relief medications had a 38.29-fold higher likelihood of developing MALA compared to those who did not use this medication (OR = 38.29), corresponding to a 99% confidence interval of 5.96-245.87 (Table 3).

4. DISCUSSION

The study demonstrated that a history of taking combined pain relief medications was the most significant predictor of MALA among diabetic patients receiving metformin. This is the first study reporting history of taking combined pain relief medications as a strong risk factor for the occurrence of MALA in diabetic patients residing in the southern areas of the Northeastern Thailand, highlighting the health-seeking behaviors of patients who need pain relief medications

Table 2. Results of binary logistic regression analysis for factors associated with the occurrence of MALA (Sigle independent variable).

Risk factors	coefficient	Wald test	p-value	OR	99%CI of OR
Model 1					
Constant	-1.06	39.43*	3.39×10^{-10}	0.34	-
Nausea/vomiting	23.63	8×10^{-6} ns	0.99	-	-
Likelihood ratio test = 5.40					AIC = 9.39
Model 2					
Constant	-0.71	22.49*	2.00×10^{-6}	0.49	-
Diarrhea	21.91	2.1×10^{-5} ns	0.99	3.27×10^{10}	-
Likelihood ratio test = 5.64					AIC = 9.645
Model 3					
Constant	-0.29	4.82*	2.982×10^{-12}	0.03	-
Oliguria	22.85	3×10^{-6} ns	0.11	2.15×10^{10}	-
Likelihood ratio test = 5.91					AIC = 9.91
Model 4					
Constant	-0.41	7.38*	7.00×10^{-3}	0.66	-
History of alcohol uses	0.79	7.12*	8.00×10^{-3}	2.20	-
Likelihood ratio test=10.21					AIC = 14.20
Model 5					
Constant	-2.41	64.12*	1.168×10^{-15}	0.09	-
History of taking combined pain relief medications	3.11	11.48*	1.00×10^{-3}	22.33	(2.10, 236.99)
Likelihood ratio test=6.47					AIC = 10.47
Model 6					
Constant	-2.83	53.07*	3.22×10^{-13}	0.06	-
History of using herbal medicines	1.95	10.73*	1.00×10^{-3}	7.000	(1.51, 32.34)
Likelihood ratio test=7.22					AIC = 11.21
Model 7					
Constant	-2.30	57.84*	2.84×10^{-14}	0.10	-
History of NSAIDs uses	0.92	2.08 ns	0.15	2.50	(0.48, 12.86)
Likelihood ratio test=7.29					AIC = 11.29
Model 8					
Constant	0.04	0.02 ns	0.89	-	-
Medication use for chronic diseases	-0.05	0.03 ns	0.88	0.95	(0.42, 2.15)
Likelihood ratio test=10.21					AIC = 14.26
Model 9					
Constant	-0.11	0.79 ns	0.37	-	-
Medication use for chronic kidney diseases	1.45	7.80*	5.00×10^{-3}	4.26	(1.11, 16.18)
Likelihood ratio test=9.21					AIC = 13.21
Model 10					
Constant	0.48	9.62*	2.00×10^{-3}	1.61	-
Medication use for dyslipidemia	-1.46	27.23*	1.81×10^{-7}	0.23	(0.13, 0.41)
Likelihood ratio test=10.34					AIC = 14.34

Note: * Reject the null hypothesis (H_0) when the Wald statistic test exceeds $\chi^2_{0.01,1} = 6.635$; ns indicates non-significance at $\alpha = 0.01$; OR refers to the odd ratio; 99%CI of OR refers to the 99% Confidence interval of the odd ratios.

from local drugstores or grocery stores within their communities. This result was different from previous studies[6,7,9,12-15] showing that stage of CKD and hepatocellular dysfunction, acute kidney injury are significant risk factors for the development of MALA.

The regimen of combined pain relief medications included NSAIDs, prednisolone, muscle relaxants, and tramadol in one package, which is generally accessible and cost-effective options based on most of the patients' perspective to provide effective pain relief. These medications are frequently used by individuals experiencing severe musculoskeletal pain such as construction workers and farmers. Despite having law and regulations in place to control the use of

Table 3. Optimal binary logistic regression model identified using the Backward Likelihood Ratio selection method.

Risk factors	Regression coefficient	Wald test	p-value	Odd ratio	99% CI for Odd ratio
Model 1					
Constant	-3.52	24.92*	5.97×10^{-7}	0.03	
History of alcohol uses	2.03	5.94*	1.50×10^{-2}	7.61	(1.48, 38.90)
History of taking combined pain relief medications	4.27	11.55*	1.00×10^{-3}	71.63	(6.09, 841.49)
History of using herbal medicines	1.40	2.61	0.11	4.06	(0.74, 22.23)
Medication use for chronic kidney diseases	-0.27	1.7×10^{-2}	0.89	0.76	(0.01, 48.59)
Medication use for dyslipidemia	-1.57	2.98	0.08	0.21	(0.03, 1.24)
Likelihood ratio test = 18.25	Overall % of prediction = 93.9		Nagelkerke r^2 =0.40		AIC = 30.25
Model 2					
Constant	-3.52	25.01*	5.70×10^{-7}	0.03	
History of alcohol uses	2.03	5.95*	1.50×10^{-2}	7.61	(1.49, 38.84)
History of taking combined pain relief medications	4.25	11.64*	1.00×10^{-3}	69.82	(6.08, 800.74)
History of using herbal medicines	1.39	2.58	0.11	4.02	(0.73, 21.90)
Medication use for dyslipidemia	-1.57	3.00	0.08	0.21	(0.03, 1.23)
Likelihood ratio test = 17.82	Overall % of prediction = 93.9		Nagelkerke r^2 =0.40		AIC = 27.82
Model 3					
Constant	-3.12	26.34*	2.87×10^{-7}	0.04	
History of alcohol uses	1.84	5.29*	0.02	6.29	(1.32, 30.14)
History of taking combined pain relief medications	4.27	13.81*	2.02×10^{-4}	71.43	(7.52, 678.47)
Medication use for dyslipidemia	-1.62	3.20	0.07	0.20	(0.03, 1.17)
Likelihood ratio test = 12.79	Overall % of prediction = 93.9		Nagelkerke r^2 =0.37		AIC = 20.79
Model 4					
Constant	-3.12	38.03*	8.60×10^{-5}	0.03	
History of alcohol uses	1.77	5.19*	0.02	5.88	(1.28, 27.03)
History of taking combined pain relief medications	4.10	15.41*	2.87×10^{-7}	60.44	(7.79, 468.43)
Likelihood ratio test = 8.99	Overall % of prediction = 93.9		Nagelkerke r^2 =0.31		AIC = 14.99
Model 5**					
Constant	-2.95	57.97*	2.66×10^{-14}	0.05	
History of taking combined pain relief medications	3.65	14.76*	1.22×10^{-4}	38.29	(5.96, 245.87)
Likelihood ratio test = 6.47	Overall % of prediction = 93.9		Nagelkerke r^2 =0.23		AIC = 10.47

Note: * Reject the null hypothesis (H_0) when the Wald statistic test exceeds $\chi^2_{0.01,1} = 6.635$; ns indicates non-significance at $\alpha = 0.01$

** Optimal binary logistic regression model derived using the Backward likelihood ratio selection (LR) method.

these illegally combined medicines in Thailand both in a drug store and a grocery store, the use of it has still existed in the community. Beyond their limited regulations, these combined pain relief medications are associated with adverse effects, including gastrointestinal issues, edema, and worsening cardiovascular and renal functions, which may elevate the risk of MALA in diabetic patients.

A history of alcohol consumption was identified as another significant risk factor for the occurrence of MALA. Remarkably, the correlation observed between alcohol use and elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in both MALA cases and the control group suggests considerable liver dysfunction, which may lead to chronic hepatotoxic effects. Consequently, such effects could enhance vulnerability to the development of MALA due to metabolic disturbances associated with metformin in the liver. These findings were consistent with prior research indicating that liver disease and alcohol abuse are substantial risk factors for the onset of MALA [7-8, 15], emphasizing the importance of thorough assessment of history of alcohol use and liver function tests in diabetic patients.

This study's primary strength lied in its methodological approach, combining a matched case-control design and using binary logistic regression analysis with Backward Likelihood ratio (LR) selection method to determine the optimal final model

of the predictor of MALA occurrence. In addition, we adopted a uniformly stringent significance threshold of 0.01 to control of the probability of Type I error across all stages of the binary logistic regression analysis, including both a single independent variable and multiple independent variables in model. The result of strong risk factors could then facilitate the clinical-decision making to the establishment of MALA surveillance system. Secondly, it represented the first study in Thailand to demonstrate that inappropriate combination of pain medications is the strongest predictor of MALA development among diabetic patients. These results propose valuable clinical insights, highlighting the necessity for vigilant monitoring of patients with these risk factors during metformin therapy. Regular surveillance is crucial for patient safety, enabling timely medication adjustments to mitigate potential complications. Furthermore, patient education regarding MALA symptoms, including abdominal pain, nausea, vomiting, and muscle weakness is strongly recommended. Thirdly, it also emphasizes the necessity of screening patients for these risk factors before initiating metformin therapy. This proactive approach can help identify individuals at higher risk and allow for better management strategies.

This study had several limitations. Firstly, the sample size was suboptimal for a matched case-control study, potentially limiting statistical power. Secondly, the participants' characteristics were specific to the research settings in the southern region of the Northeastern Thailand, an area with a higher prevalence of MALA cases compared to other parts of the northeast. This geographical specificity may impact the broader applicability of the findings. However, focusing on this high-burden area also offers important advantages: it enables the identification of region-specific risk factors, such as the potential combined use of pain relief medications, and provides crucial evidence to inform an active surveillance system tailored to local needs. Thirdly, the study was susceptible to recall bias, as data on inappropriately combined pain relief medications and herbal medicine use were collected retrospectively via telephone interviews. This method of data collection could have led to either underestimation or overestimation of actual usage patterns. Fourthly, the diagnosis of MALA cases in this study was based on clinical assessment according to hospital protocol and current clinical practice guidelines. Confirmation of the diagnosis by measuring serum metformin levels was not performed due to the unavailability of metformin concentration testing. Collectively, these factors may constrain the generalizability of the research outcomes.

Future studies should address these limitations by employing larger sample sizes, expanding geographical coverage, and utilizing more robust data collection methods to enhance the validity and generalizability of findings in this critical area of research.

5. CONCLUSIONS

This study demonstrated critical risk factors associated with the development of MALA in diabetic patients, which was the use of inappropriately combined pain relief medications and history of alcohol consumption. These findings highlight the imperative for implementing comprehensive pre-screening protocols for diabetic patients initiating metformin therapy. Furthermore, they highlight the necessity of establishing rigorous monitoring systems and enhancing patient education, particularly for individuals exhibiting multiple risk factors for MALA. Such risk factors encompass not only those identified in this study but also previously established contributors, including impaired renal function, heart failure, hepatic disorders, alcohol dependence, and sepsis.

The results of this investigation have significant implications for clinical practice and patient management. They suggest a paradigm shift towards a more personalized approach in metformin therapy, emphasizing the need for tailored risk assessment and monitoring strategies. Implementation of these findings could potentially mitigate the incidence of MALA, a severe complication with high morbidity and mortality rates.

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Author contribution

Pemmarin Potisarach: Conceptualization, Methodology, Investigation, Project administrator, Supervision, Validation, Visualization, Roles/Writing – original draft, Writing – reviewing and editing

Juntip Kanjanasilp: Conceptualization, Methodology, Supervision, Writing – reviewing and editing

Nayrata Pinnetdharn: Conceptualization, Methodology, Data Management and Statistical Analysis, Writing – reviewing and editing

Sansanee Wangvoralak: Conceptualization, Methodology, Data Management and Statistical Analysis, Writing – reviewing and editing

Thitima Punruang: Conceptualization, Investigation, Administration of Data Collection, Writing – reviewing and editing

Siraprapa Sonsri: Conceptualization, Investigation, Data Collection, Writing – reviewing and editing

Krongkan Sawamichai: Methodology, Investigation, Data Collection, Writing – reviewing and editing
Phongsathorn Tanawsri: Methodology, Investigation, Data Collection, Writing – reviewing and editing
Sirawan Tonja: Methodology, Investigation, Data Collection, Writing – reviewing and editing
Natedow Khamsita: Methodology, Investigation, Data Collection, Writing – reviewing and editing
Pattarin Kittiboonyakun: Initiation, Conceptualization, Methodology, Investigation, Formal analysis, Project administrator, Supervision, Validation, Visualization, Roles/Writing – original draft, Writing – reviewing and editing

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Conflict of interest
None to declare.

Ethics approval
This project was approved and reviewed by the Ethics Committee for Research Involving Human Subjects, Surin Hospital (approval number: 11/2022) and Mahasarakham University Ethics Committee For Research Involving Human Subjects ” (approval number: 089-074/2023).

Declaration of generative AI and AI-assisted technologies in the writing process
During the preparation of the revision of this work, the authors only used ChatGPT to help improving and refining the language and readability of the manuscript. The author reviewed and edited the output as necessary and accepted full responsibility for the content of the final manuscript.

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REFERENCES

1. Diabetes Association of Thailand Under the Patronage of Her Royal Highness Princess Maha Chakri Sirindhorn. Clinical practice guideline for diabetes 2023. 2nd ed. Bangkok: Srimuang printing; 2024.
2. Jakmatakul R. Review article: Metformin-associated lactic acidosis. JPMAT. 2018;8(1):147-51.
3. Onngam S. Prescribing pattern of metformin in type 2 diabetic patients with various estimated glomerular filtration rates (eGFR). Thai J Pharm Prac. 2021;13(1):1-14.
4. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: a systematic review. JAMA. 2014 Dec;312(24):2668-75.
5. Flory JH, Hennessy S, Bailey CJ, Inzucchi SE. Reports of lactic acidosis attributed to metformin, 2015–2018. Diabetes Care. 2020;43(1):244-6.
6. Alvarez CA, Halm EA, Pugh MJ, McGuire DK, Hennessy S, Miller RT, et al. Lactic acidosis incidence with metformin in patients with type 2 diabetes and chronic kidney disease: A retrospective nested case-control study. Endocrinol Diab Metab. 2021;4:e00170. doi:10.1002/edm2.170.
7. Lepelley M, Giai J. Yahiaoui N, Chanoine S, Villier C. Lactic acidosis in diabetic population: Is metformin implicated? Results of a matched case-control study performed on the type 2 diabetes population of Grenoble Hospital University. J Diabetes Res. 2016;8.
8. Kim MJ, Han JY, Shin JY, Kim SI, Lee JM, Hong S, et al. Metformin-associated lactic acidosis: predisposing factors and outcome. Endocrinol Metab (Seoul). 2015;30(1):78–83. doi:10.3803/EnM.2015.30.1.78.
9. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risk. Metab Clin Exp. 2016;65:20-9.
10. Russameethum W. The study of metformin-associated lactic acidosis using the data from spontaneous reports of adverse drug reactions from the health product vigilance center, food and drug administration, Ministry of Public Health, Thailand. 2019.
11. Siangtrong W, Iamrerksiri B, Yimrattanabowon P, Chindavech N, Prajonsan J, Kumpila U. Risk factors related to mortality of metformin associated lactic acidosis in patients with type 2 diabetes mellitus of Buriram Hospital, Thailand. J Health Sci. 2019;28(5):1067-76.
12. Kanjanasilp J, Kuncharoenrut N, Seehawong A, Jittayanan B. Risk factors of metformin-associated lactic acidosis in type 2 diabetic patients using metformin. Thai Pharm Health Sci J. 2023;18(1):84-9.
13. Kobpungton P, Chueamuangphan N. Associated factors of metformin associated lactic acidosis in diabetic patients at Chiangrai Prachanukroh Hospital. Chiangrai Med J. 2020;12(1):44-51.
14. Aharaz A, Pottegård A, Henriksen DP, Hallas J, Beck-Nielsen H, Lassen AT. Risk of lactic acidosis in type 2 diabetes patients using metformin: A case control study. PLoS One. 2018 May 8;13(5):e0196122. doi: 10.1371/journal.pone.0196122. PMID: 29738540; PMCID: PMC5940216.
15. Tajdini P, Foroutan M. Renal manifestations of metformin-associated lactic acidosis; new findings. J Renal Inj Prev. 2024; 13(4): e32258. doi: 10.34172/jrip.2024.32258.