Observational Study

Medicine

OPEN

Clinical presentations and prognosis of metformin-associated lactic acidosis patients in the intensive care unit

A 20-year survey

Chun-Chieh Yang, MD[a], Shih-Feng Weng, PhD[b], Kuei-Ling Tseng, MS[c], and Chung-Han Ho, PhD[d,e,*]

Abstract

Metformin-associated lactic acidosis (MALA) is a rare but serious adverse event. It is associated with a high mortality rate and is diagnosed by the peak lactate level (PLL). This study examines the relationship between the clinical presentations and PLL in patients under metformin therapy admitted to the intensive care unit (ICU) to better diagnose MALA and prevent a worsening prognosis. The mortality distribution of clinical characteristics among patients with MALA was also examined.

Methods: We retrospectively analyzed 82 adult patients with MALA admitted to the ICU over 20 years. The association between the clinical parameters and mortality post-MALA was estimated using logistic regression analysis.

Results: Patients with MALA admitted to the ICU presented with clinical symptoms mainly associated with the head (40.24%), chest (41.46%), and abdomen (35.37%). Additionally, the PLL distribution significantly varied with age, APACHE II = Acute Physiology and Chronic Health Evaluation II (APACHE II) score, various laboratory parameters like nadir arterial bicarbonate level, multiple treatment modalities such as renal replacement therapy, and mortality. The overall mortality rate was 17.07%. After adjustment of age and gender, the significant predictors of mortality were APACHE II score, PLL, vasoactive support, ventilator support, and cardiopulmonary resuscitation.

Conclusions: Despite MALA being a rare event, it is necessary to evaluate its clinical characteristics, especially the associated PLL and mortality. In the current study, higher levels of APACHE II score and PLL show a greater likelihood of mortality in MALA patients.

Abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II, BUN = blood urea nitrogen, 95% CI = 95% confidence interval, CPR = cardiopulmonary resuscitation, Cr = serum creatinine, ICU = intensive care unit, MALA = Metformin-associated lactic acidosis, OR = odds ratio, PLL = peak lactate level, PT = prothrombin time, PT-INR = prothrombin time-international normalized ratio.

Keywords: intensive care unit, metformin-associated lactic acidosis, mortality, peak lactate level

1. Introduction

Metformin is a widely used oral antihyperglycemic agent and is the recommended drug of choice for patients diagnosed with type 2 diabetes mellitus without contraindications.[1] It acts as an insulin sensitizer that improves glycemic control, suppresses hepatic glucose production, and increases peripheral tissue insulin sensitivity.[2]

One of the fatal complications associated with metformin usage is metformin-associated lactic acidosis (MALA). The antihyperglycemic effect of metformin may be the potential cause of MALA.[3] Although metformin could damage the lactate clearance, lactic acidosis is from the lack of lactate clearance than increased production.[4] MALA is a rare but serious adverse event in a susceptible patient with a high mortality rate.[5–9] A systematic review study indicated the overall mortality rate of MALA was about 36.2%.[10] Lactate levels are frequently used in critical care medicine to determine the severity of an illness,[11,12] while a previous study reported that it is an effective indicator in monitoring the treatment status of MALA.[13]

Lactic acidosis is also a clinically similar condition commonly seen in patients admitted to the intensive care unit (ICU) with a complaint of hemodynamic instability. In contrast, MALA is not

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Intensive Care Medicine, Chi Mei Medical Center, Tainan, Taiwan, [b] Department of Healthcare Administration and Medical Informatics, Kaohsiung Medical University, Kaohsiung, Taiwan, [c] Department of Respiratory Therapy, Chi Mei Medical Center, Tainan, Taiwan, [d] Department of Medical Research, Chi Mei Medical Center, Tainan, Taiwan, [e] Department of Information Management, Southern Taiwan University of Science and Technology, Tainan, Taiwan.

**Correspondence: Chung-Han Ho, Department of Medical Research, Chi Mei Medical Center, Tainan, Taiwan. (e-mail: ho.c.hank@gmail.com).*

How to cite this article: Yang C-C, Weng S-F, Tseng K-L, Ho C-H. Clinical presentations and prognosis of metformin-associated lactic acidosis patients in the intensive care unit: A 20-year survey. Medicine 2022;101:27(e29918).

Received: 23 March 2022 / Received in final form: 1 June 2022 / Accepted: 14 June 2022

http://dx.doi.org/10.1097/MD.0000000000029918

a common occurrence in the ICU, and the incidence of MALA in ICU was about 0.6% to 1%.[9,14] However, compared to lactic acidosis, the potential complications arising from MALA are a bigger challenge for ICU physicians. Currently, MALA is mainly managed based on supportive treatments because no specific treatment exists.[9] Successful supportive treatments, including of vasoactive support, ventilator support, renal replacement therapy, and cardiopulmonary cerebral resuscitation, can prevent organ failure in patients with MALA.[15]

For a rare disease like MALA, it is necessary to assimilate prior data to alert the patients under metformin therapy and consequently the physicians in charge of these patients to prevent worse outcomes. Therefore, this study examines the relationship between the clinical presentations and the peak lactate level (PLL) in patients with MALA admitted to the ICU. Furthermore, we will assess the mortality distribution of clinical characteristics for patients with MALA.

2. Materials and Methods

2.1. Subjects and study design

This study was designed as a retrospective observational study in the ICUs (96 beds) in the Chi Mei Hospital, a tertiary care hospital in Taiwan. All adult patients admitted to the ICU with MALA from January 2000 to December 2019 were evaluated as potential subjects based on the reports in the Chi Mei Medical Center database. Patient enrollment was based on the following inclusion criteria: blood PLL of >5 mmol/L, currently prescribed metformin for regulating diabetic sugar levels, and severity of lactic acidosis could not be fully explained by the clinical presentation of MALA. According to the criteria, 107 ICU patients with MALA were selected for this study. However, after excluding the patients with data missing in either of the inclusion criteria, 82 study subjects were finally enrolled in our study. Furthermore, the patients were segregated based on the PLL and then categorized by mortality for further analysis. The selection criteria for the enrolled patients are as shown in the flowchart (Fig. 1). In cases where the patient has multiple ICU admissions, only the first episode of MALA was considered for statistical analysis.

2.2. Ethical considerations

The Institutional Review Board of Chi Mei Medical Center (IRB-10912-011) approved this study and waived the need for informed consent due to the de-identified dataset. The methods were conducted following the approved guidelines on STROBE.

2.3. Measurements

Clinical and laboratory records during the ICU stay were compiled and examined. The medical records included the following information: age, gender, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, treatment modalities (vasoactive support, ventilator support, renal replacement therapy, and cardiopulmonary resuscitation [CPR]), and the mortality status at ICU discharge. Renal replacement therapy included hemodialysis or continuous venovenous hemofiltration.

In addition to the above criteria, the initial clinical presentations for major symptoms were categorized as specified below:

- Head: disturbed consciousness, dizziness, syncope, and blurred verbal expression.
- Chest: shortness of breath, chest pain, and chest tightness.
- Abdomen: vomiting, diarrhea, abdominal pain, and nausea.
- Others: generalized weakness.

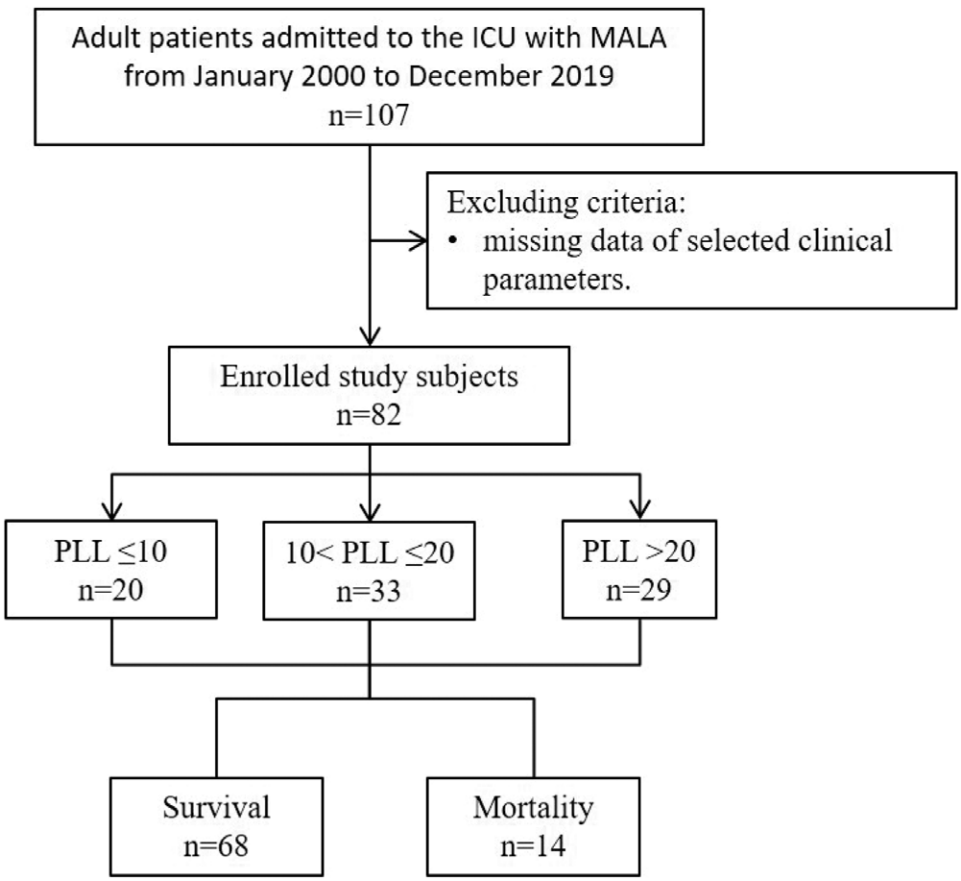

Figure 1. The flowchart of patient selection. ICU = intensive care unit, MALA = metformin-associated lactic acidosis, PLL = peak lactate level.

Table 1

Clinical and laboratory characteristics.

Characteristics	All MALA patients (N = 82)
Age (yr), mean ± SD	67.63 ± 12.29
Males, n (%)	46 (56.10)
APACHE II score, mean ± SD	25.22 ± 9.09
Peak lactate level (mmol/L), mean ± SD	17.39 ± 8.38
Nadir arterial pH, mean ± SD	7.10 ± 0.23
Nadir arterial bicarbonate level (mmol/L), mean ± SD	8.51 ± 5.64
Blood urea nitrogen (mg/dL), mean ± SD	61.47 ± 31.88
Blood creatinine (mg/dL), mean ± SD	4.91 ± 3.70
Prothrombin time-INR, mean ± SD	1.36 ± 0.42
Hypoglycemic event, n (%)	8 (9.76)
Vasoactive support, n (%)	48 (58.54)
Ventilator support, n (%)	51 (62.20)
Renal replacement therapy, n (%)	45 (54.88)
Cardiopulmonary resuscitation, n (%)	11 (13.41)
Head	33 (40.24)
Chest	34 (41.46)
Abdomen	29 (35.37)
Weakness	9 (10.98)

Data are expressed as mean ± SD (extreme values).

APACHE II = Acute Physiology and Chronic Health Evaluation II, INR = international normalized ratio, MALA = metformin-associated lactic acidosis, SD = standard deviation.

In all cases, laboratory parameters such as PLL, nadir arterial pH, nadir arterial bicarbonate level, blood urea nitrogen, serum creatinine, and prothrombin time (PT) were also factored in the examination. The PT is presented hereafter as PT-international normalized ratio (PT-INR).

2.4. Statistical analysis

Descriptive statistical analysis was used in this study. All variables are represented as the mean ± standard deviation or number with a percentage. The difference in categorical variables between groups was compared using Fisher exact test. The groups were analyzed as continuous variables. Comparison between the 3 groups of PLL distribution was performed using analysis of variance. Student *t* test was used for the comparison of the survival and mortality groups. The odds ratio (OR) and 95% confidence interval (95% CI) were estimated using logistic regression analysis, with Firth penalized likelihood approach for finding the association between the variables and mortality. Firth approach was used to estimate the bias of rare outcome parameters.[16,17] The age- and sex-adjusted OR with 95% CI of each parameter was represented as a Forest plot after considering age and gender effects. All statistical analyses were performed using IBM SPSS for Windows, version 26.0 (IBM Corp., Armonk, NY), except for logistic regression with Firth approach, which was estimated using SAS Version 9.4 for Windows software (SAS Institute, Cary, NC). All reported *P* values were 2-tailed, and the statistical significance was set at *P* value of <.05.

3. Results

During the 20 years of this retrospective study, 82 patients with MALA were admitted to the ICU. The average age of these patients was 67.63 ± 12.29 years, of which 46 (56.10%) patients were males and had an average APACHE II score of 25.22 ± 9.09. The baseline clinical and laboratory characteristics, including PLL (17.39 ± 8.38 mmol/L), nadir arterial pH (7.10 ± 0.23), nadir arterial bicarbonate level (8.51 ± 5.64 mmol/L), blood urea nitrogen (61.47 ± 31.88 mg/dL), serum creatinine (4.91 ± 3.70 mg/dL), PT-INR (1.36 ± 0.42), hypoglycemic event (n = 8; 9.76%), vasoactive support (n = 48; 58.54%), ventilator support (n = 51; 62.20%), renal replacement therapy (n = 45; 54.88%), and CPR (n = 11; 13.41%), are shown in Table 1. Additionally, symptoms of the head (40.24%), chest (41.46%), and abdomen (35.37%) were the most frequent clinical presentations of patients with MALA admitted to the ICU.

When segregated by PLL, the various groups were defined as PLLs <10 mmol/L in 24.39% of patients, PLLs between 10 and 20 mmol/L in 40.24% of patients, and PLLs >20 mmol/L in 35.37% of patients (Table 2). Patients with PLL >20 mmol/L were significantly younger (*P* = .0186) and had a higher APACHE II score (*P* = .0116), lower nadir arterial pH (*P* < .001), lower nadir arterial bicarbonate level (*P* < .001), and higher PT-INR (*P* = .0150). Additionally, this patient group had a significantly higher percentage of those undergoing treatment by renal replacement therapy (n = 22; 75.86%; *P* = .0145), vasoactive support (n = 26; 89.66%; *P* < .001), ventilator support (n = 22; 75.86%; *P* = .0145), and CPR (n = 8; 27.59%; *P* = .0133). Examination of the mortality distribution showed a significant difference (*P* = .0221) among the 3 groups. Patients with MALA with PLLs of >20 mmol/L had the highest mortality rate (n = 8; 27.59%) of the 3 groups. However, there was no significant difference in the clinical presentations of the various symptoms between the different PLL groups (Fig. 2).

With the mortality of 14 ICU patients, the mortality rate observed was 17.07%, and the characteristics for patients with MALA between survival and mortality are illustrated in Table 3. The patients with mortality had significantly higher APACHE II scores than survivors (32.86 ± 11.59 vs 23.65 ± 7.69, *P* = .0120). The PLLs of patients with mortality (22.07 ± 7.55 mmol/L) were also significantly higher than those of the survivors (16.42 ± 8.26 mmol/L, (*P* = .0206). Additionally, patients with

Table 2

Clinical and laboratory characteristics in MALA patients with different PLL.

Peak lactate level (mmol/L)	PLL≦10 (N = 20)	10< PLL≦20 (N = 33)	PLL >20 (N = 29)	*P* value
Age, mean ± SD	71.35 ± 10.51	69.82 ± 13.18	62.59 ± 11.02	.0186*
Male, n (%)	10 (50.00)	18 (54.55)	18 (62.07)	.6893
APACHE II score, mean ± SD	20.80 ± 6.61	24.97 ± 8.84	28.55 ± 9.73	.0116*
Nadir arterial pH, mean ± SD	7.26 ± 0.20	7.16 ± 0.18	6.93 ± 0.18	<.001*
Nadir arterial bicarbonate level (mmol/L), mean ± SD	15.63 ± 4.89	7.82 ± 3.74	4.40 ± 2.38	<.001*
Blood urea nitrogen (mg/dL), mean ± SD	56.45 ± 25.64	65.96 ± 34.42	59.82 ± 33.09	.5471
Blood creatinine (mg/dL), mean ± SD	3.71 ± 2.54	5.02 ± 3.75	5.61 ± 4.21	.2069
Prothrombin time-INR, mean ± SD	1.20 ± 0.33	1.30 ± 0.39	1.53 ± 0.46	.0150*
Renal replacement therapy, n (%)	3 (15.00)	20 (60.61)	22 (75.86)	<.001*
Hypoglycemic event, n (%)	1 (5.00)	1 (3.03)	6 (20.69)	.0718
Vasoactive support, n (%)	2 (10.00)	20 (60.61)	26 (89.66)	<.001*
Ventilator support, n (%)	7 (35.00)	22 (66.67)	22 (75.86)	.0145*
Cardiopulmonary resuscitation, n (%)	0 (0.0)	3 (9.09)	8 (27.59)	.0133*
Mortality, n (%)	0 (0.0)	6 (18.18)	8 (27.59)	.0221*

APACHE II = Acute Physiology and Chronic Health Evaluation II, INR = international normalized ratio, MALA = metformin-associated lactic acidosis, PLL = peak lactate level, SD = standard deviation.

**P* value <.05.

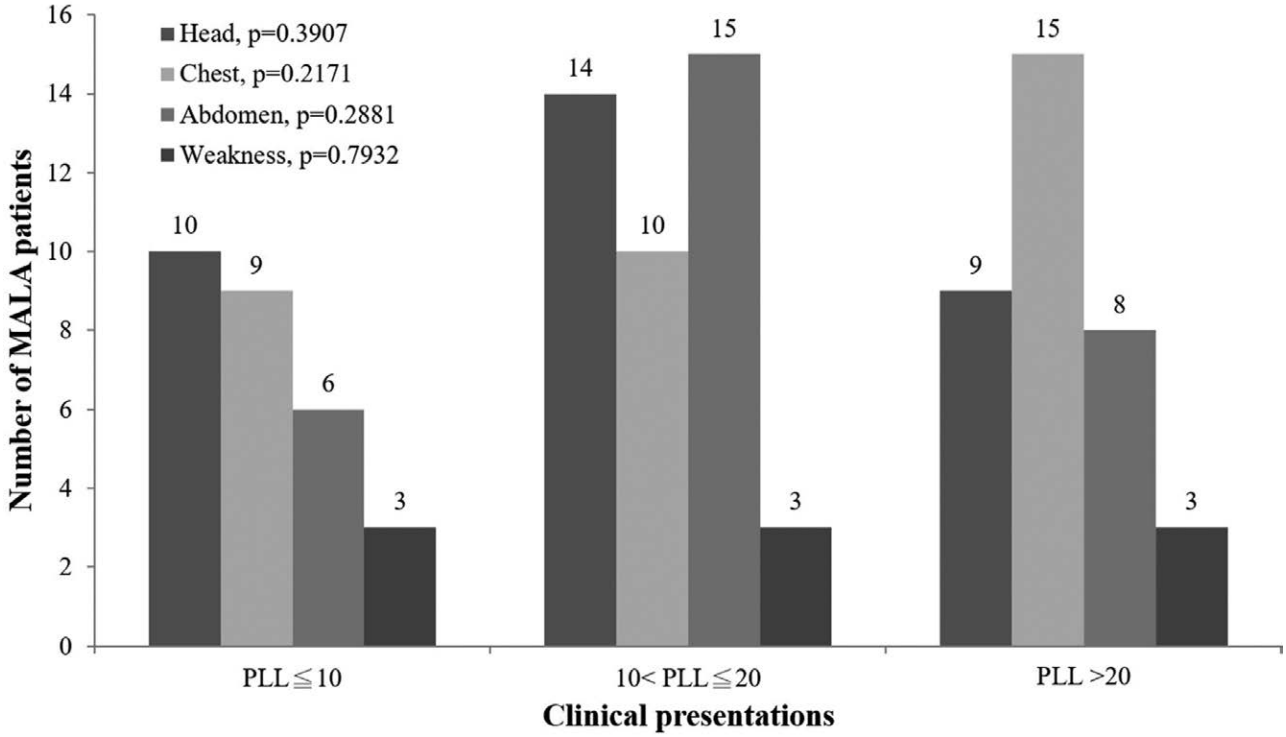

Figure 2. The frequency of the clinical presentations for major symptoms among different PLL groups. MALA = metformin-associated lactic acidosis, PLL = peak lactate level.

Table 3

Compare clinical and laboratory characteristics for MALA patients between survival and mortality.

	Survival (N = 68)	Mortality (N = 14)	*P* value
Age, mean ± SD	67.54 ± 12.95	68.07 ± 8.69	.8848
Males, n (%)	39 (57.35)	7 (50.00)	.7688
APACHE II score, mean ± SD	23.65 ± 7.69	32.86 ± 11.59	.0120*
Peak lactate level (mmol/L), mean ± SD	16.42 ± 8.26	22.07 ± 7.55	.0206*
Nadir arterial pH, mean ± SD	7.12 ± 0.23	7.03 ± 0.25	.1769
Nadir arterial bicarbonate level (mmol/L), mean ± SD	8.77 ± 5.95	7.29 ± 3.73	.3742
Blood urea nitrogen (mg/dL), mean ± SD	59.86 ± 32.00	69.29 ± 31.20	.3167
Blood creatinine (mg/dL), mean ± SD	5.03 ± 3.83	4.32 ± 3.10	.5143
Prothrombin time-INR, mean ± SD	1.32 ± 0.38	1.54 ± 0.57	.1890
Hypoglycemic event, n (%)	5 (7.35)	3 (21.43)	.1323
Vasoactive support, n (%)	34 (50.00)	14 (100)	.0002*
Ventilator support, n (%)	37 (54.41)	14 (100)	.0007*
Renal replacement therapy, n (%)	34 (50.00)	11 (78.57)	.0759
Cardiopulmonary resuscitation, n (%)	5 (7.35)	6 (42.86)	.0024*

APACHE II = Acute Physiology and Chronic Health Evaluation II, INR = international normalized ratio, MALA = metformin-associated lactic acidosis, SD = standard deviation.
*P value <.05.

mortality presented with significantly higher requirements for vasoactive support (P = .0002), ventilator support (P = .0007), and CPR (P = .0024) than survivors. The percentage of patients with mortality (78.70%) who received renal replacement therapy was borderline significant compared to that of the survivors (50.00%; P = .0759).

A Forest plot was used to illustrate the association between each variable and mortality (Fig. 3). After adjustment of age and sex, vasoactive support (odds ratio [OR]: 29.90; 95% confidence interval [CI]: 1.85–482.23; P = .0166), ventilator support (OR: 25.20; 95% CI: 1.56–407.75; P = .0231), and CPR (OR: 8.17; 95% CI: 2.05–32.54; P = .0029) showed a significant association with the mortality status of patients with MALA. Additionally, the likelihood of mortality increased 1.11-fold per unit of APACHE II scores (95% CI: 1.04–1.19; P = .0034) and 1.09-fold per unit of PLL (95% CI: 1.01–1.18; P = .0223) among patients with MALA. Patients with renal replacement therapy presented with a borderline significant association of mortality compared with patients without renal replacement therapy (OR: 3.40; 95% CI: 0.93–12.37; P = .0639).

4. Discussion

Symptoms of the head (40.24%), chest (41.46%), and abdomen (35.37%) were major clinical presentations in the 82 patients with MALA admitted to the ICU over the course of 20 years. The PLL distribution showed significant differences with age, APACHE II score, mortality, various laboratory measurements, and treatment modalities, but without the association of any specific symptoms. In addition, 17.07% of patients with MALA died in the ICU. The significant predictors of mortality risk were APACHE II score, PLL, vasoactive support, ventilator support,

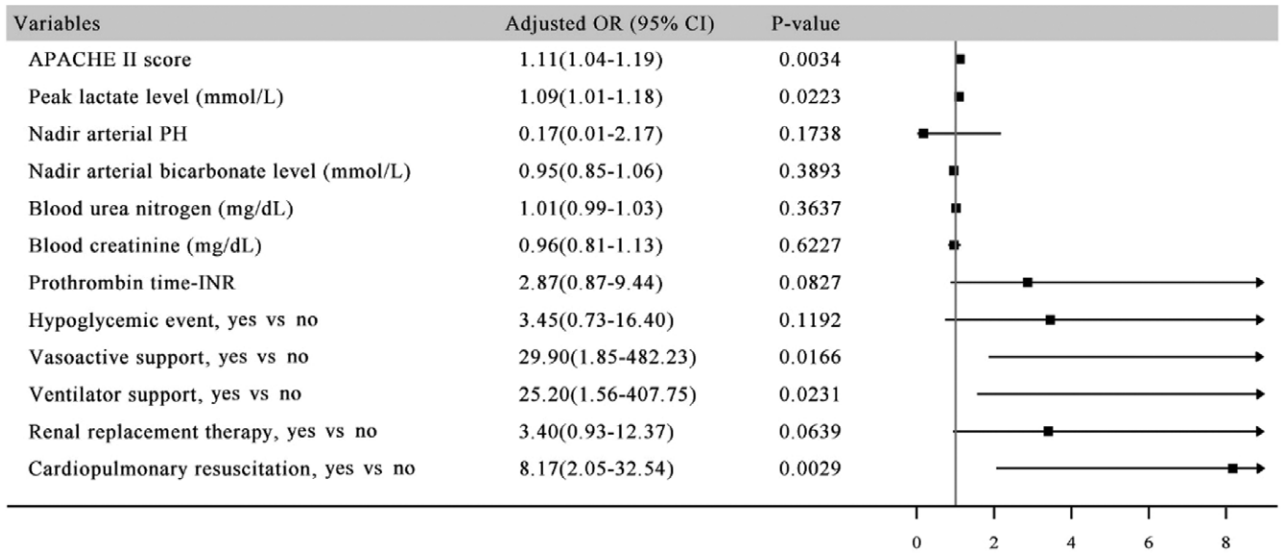

Figure 3. The association between each of the selected variables and mortality. APACHE II = Acute Physiology and Chronic Health Evaluation II, CI = confidence interval, INR = international normalized ratio, OR = odds ratio.

and CPR. Patients with MALA and renal replacement therapy indicated higher mortality with borderline statistical significance. Compared with prior studies,[18–21] similar outcomes were noted for the clinical parameters, with a slight difference in the frequency of occurrence.

The clinical presentations of patients with MALA are complex, especially for those in the ICU. Gastrointestinal disorders and neurologic dysfunction are major clinical presentations among patients with MALA.[5] Many studies have indicated that the most common symptoms are those associated with the abdomen, including vomiting, diarrhea, abdominal pain, and nausea.[22–25] However, some patients also presented with disturbed consciousness,[26] syncope, and breathing problems.[27] In accordance with the symptoms generally associated in patients with MALA, most clinical presentations observed during this study were classified as the head (40.24%), chest (41.46%), and abdomen (35.37%). The PLL presented significant distribution difference with age, APACHE II score, and mortality. The different PLL groups also showed significant differences in association with laboratory parameters such as nadir arterial pH, nadir arterial bicarbonate level, and PT-INR; and treatment modalities including vasoactive support, ventilator support, CPR, and renal replacement therapy. However, the clinical presentations of major symptoms among the different PLL groups did not show any statistical significance. Overall, the symptoms of our study subjects were similar to those seen in previous studies. Although our results indicate no association between major clinical presentations and PLL, physicians still need to consider the presentation of these symptoms in patients with MALA.

In the current study, the mortality rate was approximately 17%, which is lower compared to that reported in previous studies.[6,9,14,15,28] One possible reason is that the ICU clinicians were well aware of the potential side effects associated with MALA and took care to avoid the potential risks. However, some studies have also reported a similar mortality rate.[29,30] Yeh et al[30] reported that high lactate levels, especially those >20 mmol/L, are a significant risk factor for MALA-related mortality. Similarly, we observed that patients with PLL of >20 mmol/L had the highest mortality rate of 27.59% among all 3 PLL groups. When the Forest plot was used to express the association between each clinical parameter and mortality, APACHE II score and PLL were significant predictors of mortality in patients with MALA. An Australian study had previously indicated that the severity of illness score and arterial pH on admission were good predictors of mortality for patients with MALA in ICU.[14] Another study also reported the direct association between lactate concentration and mortality.[31] In the current study, the parameters of vasoactive support, ventilator support, and CPR presented the large variations in the upper limit of the 95% CI. These parameters also were significantly associated with mortality in ICU. Successful supportive treatments can prevent organ failure in patients with MALA.[14]

Lactic acidosis is a common occurrence in the ICU, and the intensity of lactic acidosis is strongly associated with increased mortality.[32–37] Traditionally, lactic acidosis was defined as lactate concentration being >5 mmol/L at a pH <7.35[38]; however, mixed acid–base disturbances are relatively common, and the final arterial blood pH depends on whether acidosis or alkalosis is predominant. In our study, we identified PLL of >5 mmol/L and simultaneous arterial blood pH of >7.35 in 15 patients (18.29%) due to mixed acid–base disorders. Complex acid–base disorders are not rare in the ICU; therefore, the traditional definition of lactic acidosis is only appropriate if there is no evidence of mixed acid–base disorders. Theoretically, lactic acidosis can be classified into 2 subtypes based on the association with the balance of oxygen delivery and consumption. Type A is associated with hypoperfusion or tissue hypoxia, related to the imbalance of oxygen delivery and consumption. Contrarily, type B lactic acidosis includes conditions affecting the production and elimination of lactate, unrelated to the oxygen debt.[39,40] MALA is considered as a type B lactic acidosis. Vasoactive support was used in 2 of 20 patients (10.00%) with PLLs of <10 mmol/L; 20 of 33 patients (60.61%) with PLLs between 10 and 20 mmol/L; and 26 of 29 patients (89.66%) with PLLs of >20 mmol/L. This implied that severe type B lactic acidosis may also bring about hemodynamic instability like type A lactic acidosis or the coexistence of type A and B lactic acidosis. However, the overall clinical outcome was better than expected in such conditions. Mortality was observed in 0 of 20 patients (0.00%) with PLLs of <10 mmol/L; 6 of 33 patients (18.18%) with PLLs between 10 and 20 mmol/L; and 8 of 29 patients (27.59%) with PLLs of >20 mmol/L. If we restrict the subject inclusion according to the traditional definition of lactic acidosis, the mortality rate was 17.81% in 67 patients with pH of <7.35 and lactate concentration of >5 mmol/L.

This study has several limitations. First, this was restricted to a single center, and the retrospective observational study may not have enough statistical power to represent all characteristics of MALA. However, considering that MALA is a rare event, we were able to collect this information due to the long duration of

the study (>20 years). Second, one of the diagnostic criteria for MALA was prior knowledge that the patient was undergoing metformin treatment for diabetes. As the metformin concentration in the patient before admittance could not be measured effectively in the hospital, this could have resulted in a selection bias. Finally, considering the probability of coexistent type A and type B lactic acidosis, we could not determine the extent of lactic acidosis contributed by MALA. Therefore, in different clinical situations, such as the coexistence of sepsis or liver or renal dysfunction, type B lactic acidosis may be caused by more than just MALA.

5. Conclusions

In conclusion, despite MALA being a rare event, it is necessary to understand the clinical characteristics of MALA, especially the PLL and mortality. Understanding these clinical characteristics could help identify patients with high mortality risk in the ICU. In the current study, higher APACHE II scores and PLLs were significant predictors of mortality in patients with MALA.

Author contributions

Conceptualization, Chun-Chieh Yang and Kuei-Ling Tseng; methodology, Shih-Feng Weng and Chung-Han Ho; validation, Chun-Chieh Yang, Kuei-Ling Tseng, and Chung-Han Ho; formal analysis, Kuei-Ling Tseng, Shih-Feng Weng, and Chung-Han Ho; data curation, Kuei-Ling Tseng; writing—original draft preparation, Chun-Chieh Yang, Kuei-Ling Tseng, Shih-Feng Weng, and Chung-Han Ho; writing—review and editing, Chun-Chieh Yang and Chung-Han Ho; All authors have read and agreed to the published version of the manuscript.

References

[1] Foretz M, Guigas B, Bertrand L, et al. Metformin: from mechanisms of action to therapies. Cell Metab. 2014;20:953–66.
[2] Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Ann Intern Med. 2002;137:25–33.
[3] Cusi K, Consoli A, Defronzo RA. Metabolic effects of metformin on glucose and lactate metabolism in noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab. 1996;81:4059–67.
[4] Owen MR, Doran E, Halestrap AP. Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. Biochem J. 2000;348:607–14.
[5] Seidowsky A, Nseir S, Houdret N, et al. Metformin-associated lactic acidosis: a prognostic and therapeutic study. Crit Care Med. 2009;37:2191–6.
[6] Misbin RI, Green L, Stadel BV, et al. Lactic acidosis in patients with diabetes treated with metformin. N Engl J Med. 1998;338:265–6.
[7] Lalau JD, Race JM. Lactic acidosis in metformin-treated patients. Prognostic value of arterial lactate levels and plasma metformin concentrations. Drug Saf. 1999;20:377–84.
[8] Gan SC, Barr J, Arieff AI, et al. Biguanide-associated lactic acidosis. Case report and review of the literature. Arch Intern Med. 1992;152:2333–6.
[9] Peters N, Jay N, Barraud D, et al. Metformin-associated lactic acidosis in an intensive care unit. Crit Care. 2008;12:R1491–5.
[10] Blumenberg A, Benabbas R, Sinert R, et al. Do patients die with or from metformin-associated lactic acidosis (MALA)? Systematic review and meta-analysis of pH and lactate as predictors of mortality in MALA. J Med Toxicol. 2020;16:222–9.
[11] Hernandez G, Bellomo R, Bakker J. The ten pitfalls of lactate clearance in sepsis. Intensive Care Med. 2019;45:82–5.
[12] Bruno RR, Wernly B, Binneboessel S, et al. Failure of lactate clearance predicts the outcome of critically ill septic patients. Diagnostics. 2020;10:1105.
[13] Bakker J, Nijsten MW, Jansen TC. Clinical use of lactate monitoring in critically ill patients. Ann Intensive Care. 2013;3:121–8.
[14] Biradar V, Moran JL, Peake SL, et al. Metformin-associated lactic acidosis (MALA): clinical profile and outcomes in patients admitted to the intensive care unit. Crit Care Resusc. 2010;12:191–95.
[15] Moioli A, Maresca B, Manzione A, et al. Metformin associated lactic acidosis (MALA): clinical profiling and management. J Nephrol. 2016;29:783–9.
[16] Firth D. Bias reduction of maximum likelihood estimates. Biometrika. 1993;80:27–38.
[17] Heinze G, Puhr R. Bias-reduced and separation-proof conditional logistic regression with small or sparse data sets. Stat Med. 2010;29:770–7.
[18] Heaney D, Majid A, Junor B. Bicarbonate haemodialysis as a treatment of metformin overdose. Nephrol Dial Transplant. 1997;12:1046–7.
[19] Broder G, Weil MH. Excess lactate: an index of reversibility of shock in human patients. Science. 1964;143:1457–9.
[20] Teale KF, Devine A, Stewart H, et al. The management of metformin overdose. Anaesthesia. 1998;53:698–701.
[21] Vecchio S, Giampreti A, Petrolini VM, et al. Metformin accumulation: lactic acidosis and high plasmatic metformin levels in a retrospective case series of 66 patients on chronic therapy. Clin Toxicol (Phila). 2014;52:129–35.
[22] Fadden EJ, Longley C, Mahambrey T. Metformin-associated lactic acidosis. BMJ Case Rep. 2021;14:e239154.
[23] Ali S, Labuschagne H, Azarov N, et al. Metformin-associated lactic acidosis mimicking ischaemic bowel. BMJ Case Rep. 2018;2018:bcr2017221686.
[24] Umeda T, Minami T, Bartolomei K, et al. Metformin-associated lactic acidosis: a case report. Drug Saf Case Rep. 2018;5:8.
[25] Deepak V, Neel S, Lohana AC, et al. Metformin-associated lactic acidosis successfully treated with continuous renal replacement therapy. Cureus. 2019;11:e5330.
[26] Vural HZ, Koseoglu OF, Soylu S, et al. Metformin-associated lactic acidosis developed as a result of a suicidal attempt. Med Bul Sisli Etfal Hosp. 2020;54:252.
[27] Mammadova N, Soukup J, Shkodivskyi P, et al. A patient with severe metformin-associated lactic acidosis complicated by acute coronary syndrome: a case report. BMC Nephrol. 2022;23:174.
[28] Dell'Aglio DM, Perino LJ, Kazzi Z, et al. Acute metformin overdose: examining serum pH, lactate level, and metformin concentrations in survivors versus nonsurvivors: a systematic review of the literature. Ann Emerg Med. 2009;54:818–23.
[29] Mariano F, Pozzato M, Inguaggiato P, et al. Metformin-associated lactic acidosis undergoing renal replacement therapy in intensive care units: a five-million population-based study in the North-West of Italy. Blood Purif. 2017;44:198–205.
[30] Yeh H-C, Ting I-W, Tsai C-W, et al. Serum lactate level and mortality in metformin-associated lactic acidosis requiring renal replacement therapy: a systematic review of case reports and case series. BMC Nephrol. 2017;18:1–11.
[31] Boucaud-Maitre D, Ropers J, Porokhov B, et al. Lactic acidosis: relationship between metformin levels, lactate concentration and mortality. Diabet Med. 2016;33:1536–43.
[32] Kruse J. Blood lactate and oxygen transport. Intensive Care World. 1987;4:121–25.
[33] Kruse J, Mehta K, Carlson R. Definition of clinically significant lactic acidosis. Chest. 1987;92:100S.
[34] Weil MH, Afifi AA. Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). Circulation. 1970;41:989–1001.
[35] Adrogué HJ, Madias NE. Management of life-threatening acid-base disorders. First of two parts. N Engl J Med. 1998;338:26–34.
[36] Cady LD Jr., Weil MH, Afifi AA, et al. Quantitation of severity of critical illness with special reference to blood lactate. Crit Care Med. 1973;1:75–80.
[37] Kruse JA, Zaidi SA, Carlson RW. Significance of blood lactate levels in critically ill patients with liver disease. Am J Med. 1987;83:77–82.
[38] Mizock BA. Controversies in lactic acidosis: implications in critically III patients. JAMA. 1987;258:497–501.
[39] Stacpoole PW. Lactic acidosis. Endocrinol Metab Clin North Am. 1993;22:221–45.
[40] Kajbaf F, Lalau JD. The prognostic value of blood pH and lactate and metformin concentrations in severe metformin-associated lactic acidosis. BMC Pharmacol Toxicol. 2013;14:22.