Clinical presentations and prognosis of metformin-associated lactic acidosis patients in the intensive care unit
A 20-year survey

Chun-Chieh Yang, MD,¹ Shih-Feng Weng, PhD,² Kuei-Ling Tseng, MS,³ and Chung-Han Ho, PhD,¹,⁴,§

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, vasopnoetic 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. It acts as an insulin sensitizer that improves glycemic control, suppresses hepatic glucose production, and increases peripheral tissue insulin sensitivity.

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. Although metformin could damage the lactate clearance, lactic acidosis is from the lack of lactate clearance than increased production. MALA is a rare but serious adverse event in a susceptible patient with a high mortality rate. A systematic review study indicated the overall mortality rate of MALA was about 36.2%. Lactate levels are frequently used in critical care medicine to determine the severity of an illness, while a previous study reported that it is an effective indicator in monitoring the treatment status of MALA.

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
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 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.

![Flowchart of patient selection](image)

Figure 1. The flowchart of patient selection. ICU = intensive care unit, MALA = metformin-associated lactic acidosis, PLL = peak lactate level.
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, with Firth penalized likelihood approach for binary logistic regression. Firth regression analysis was used for modeling the association between the variables and mortality. Firth penalized likelihood approach for binary logistic regression was used for examining the association between the variables and mortality. Firth penalized likelihood approach for binary logistic regression was used for examining the association between the variables and mortality. Firth penalized likelihood approach for binary logistic regression was used for examining the association between the variables and mortality. Firth penalized likelihood approach for binary logistic regression was used for examining the association between the variables and mortality. Firth penalized likelihood approach for binary logistic regression was used for examining the association between the variables and mortality. Firth penalized likelihood approach for binary logistic regression was used for examining the association between the variables and mortality.
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).

### Table 3

|                | 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 | 1.94 ± 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 (54.11) | 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.

### 4. Discussion

Symptoms of the head (40.24%), chest (41.46%), and abdomen (33.37%) 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,
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.[22–23] However, some patients also presented with disturbed consciousness.[26] 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.[6,8,14,15,26] 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.

### Variables

| Variables                        | Adjusted OR (95% CI) | P-value |
|---------------------------------|----------------------|---------|
| APACHE II score                 | 1.11(1.04-1.19)      | 0.0034  |
| Peak lactate level (mmol/L)     | 1.09(1.01-1.18)      | 0.0223  |
| Nadir arterial PH               | 0.17(0.01-2.17)      | 0.1738  |
| Nadir arterial bicarbonate level (mmol/L) | 0.95(0.85-1.06) | 0.3893  |
| Blood urea nitrogen (mg/dL)     | 1.01(0.99-1.03)      | 0.3637  |
| Blood creatinine (mg/dL)        | 0.96(0.81-1.13)      | 0.6227  |
| Prothrombin time-INR            | 2.87(0.87-9.44)      | 0.0827  |
| Hypoglycemic event, yes vs no   | 3.45(0.73-16.40)     | 0.1192  |
| Vasoactive support, yes vs no   | 29.90(1.85-482.23)   | 0.0166  |
| Ventilator support, yes vs no   | 25.20(1.56-407.75)   | 0.0231  |
| Renal replacement therapy, yes vs no | 3.40(0.93-12.37) | 0.0639  |
| Cardiopulmonary resuscitation, yes vs no | 8.17(2.05-32.54) | 0.0009  |

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.
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 and Chung-Han Ho; All authors have read and agreed to the published version of the manuscript.

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