



Mortality and renal prognosis in isolated metformin-associated lactic acidosis treated with continuous renal replacement therapy and citrate-calcium-anticoagulation

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Introduction: Use of metformin increases plasma lactate concentration and may lead to metformin-associated lactic acidosis (MALA). Previous studies have suggested severe MALA to have a mortality of 17%-21%, but have included patients with other coincident conditions such as sepsis. The treatment of choice is continuous renal replacement therapy (CRRT), which has been performed using heparin analogues or no anticoagulation in former studies.

Materials and Methods: Patients admitted to the Intensive Care Unit of Turku University Hospital Finland with lactic acidosis without any other recognizable etiology than concomitant metformin treatment who required CRRT between years 2010 and 2019 were included. CRRT was performed using regional citrate-calcium-anticoagulation. Data extracted included patient demographics, comorbidities, and clinical parameters at 6-hour intervals about 72 hours from admission. Creatinine and estimated glomerular filtration rate (eGFR) were measured at 1 year after MALA. **Results:** A total of 23 patients with isolated MALA were included in the study. Median (IQR) pH was 6.88 (6.81-7.07) and lactate 16.1 (11.9-23.0) mmol/L on admission. Median (IQR) duration of CRRT was 62 (41-70) hours. Seven patients (30%) required mechanical ventilation with a mean duration of 6.0 ± 3.0 days. 90-day mortality was 4.3% and 1-year mortality 13.0%. Creatinine ($P = .02$) and eGFR ($P = .03$) remained significantly altered at 1 year of follow-up compared to baseline.

Conclusions: MALA can be treated effectively and safely with CRRT and citrate-calcium-anticoagulation, usually required for 2-3 days. Mortality of patients with MALA treated with CRRT is low when other conditions inducing lactic acidosis are excluded. MALA episode may be associated with long-lasting kidney injury.

1 | INTRODUCTION

Metformin is a biguanide class antihyperglycemic agent and considered a first-line medication for type 2 diabetes mellitus (T2D),

which has been estimated to involve 392 million people globally.^{1,2} Adverse effects associated with metformin are mostly gastrointestinal (eg, diarrhea and abdominal pain) and are usually mild.³

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Metformin has been shown to decrease mitochondrial respiration⁴ and serum bicarbonate and to increase serum lactate *in vivo*.⁵ The mechanism of the metformin-induced lactatemia has been suggested to be related to the anti-hyperglycemic effect of metformin⁶ and decreased lactic clearance in the liver.⁷ However, exact mechanisms remain, at least partly, controversial. Current guidelines recommend against metformin use in males with serum creatinine $\geq 132 \mu\text{mol/L}$ and females $\geq 123 \mu\text{mol/L}$.⁸

Lactic acidosis (LA) is a life-threatening condition which has been shown to have a mortality rate of ~25%.⁹ LA is traditionally divided into type A caused by tissue hypoxia and type B in which hypoxia is absent, resulting from renal or hepatic failure, diabetes, or adverse effects of drugs or toxins.¹⁰ Metformin-associated lactic acidosis (MALA) is defined as lactatemia exceeding 5 mmol/L and pH < 7.35 in a clinical scenario that metformin usage is considered causative of LA.¹¹ In the onset of severe gastroenteritis, subsequent dehydration, or renal failure, metformin may exacerbate lactic acidosis.¹² Some reports have associated excessive alcohol use to markedly increased risk of MALA in patients on metformin therapy.¹³

MALA may be treated efficiently with renal replacement therapy (RRT), which potently removes metformin and lactate and corrects acid base imbalance and other metabolic consequences of acute kidney injury.¹⁴ However, reported mortality in RRT-treated MALA has been as high as 17%–21% as previous studies have included patients with other acute comorbidities such as sepsis, hepatic cirrhosis, and cardiac failure.^{15,16}

RRT may be performed either by means of intermittent hemodialysis or continuous renal replacement therapy (CRRT), the latter being the preferred modality in hemodynamically compromised patients. In previous studies using CRRT to treat MALA, the anticoagulation for CRRT has been carried out with heparin or heparin analogs. Therefore, we aimed to evaluate the outcome and kidney function in the short- and long term (90 and 365 days) in critically ill MALA patients without other acute comorbidities admitted to the intensive care unit requiring CRRT. Furthermore, we assessed the safety of regional citrate-calcium-anticoagulation for CRRT in MALA.

2 | METHODS

Patients with B-type lactic acidosis and concomitant metformin use who were admitted to the ICU of Turku University Hospital, Finland and requiring CRRT between January 1, 2010, and September 31, 2019 were included in this retrospective single-center study. MALA cases were identified as per documentation in the medical record and from the laboratory results. The inclusion criteria were pH < 7.2 and blood lactate of $>5 \text{ mmol/L}$ on admission. Patients with earlier history of chronic kidney disease (CKD) (KDIGO Stage 3b, eGFR < $45 \text{ mL/min/1.73 m}^2$), chronic severe liver disease, and patients under 18 years of age were excluded from the study. Patients with B-type lactic acidosis likely due to isolated MALA were screened by carefully excluding other potential causes of lactic

Editorial Comment

The authors report from a single center how 23 patients with isolated metformin-associated lactic acidosis were successfully treated with continuous veno-venous hemodialysis using regional citrate-calcium-anticoagulation. In 1-year follow-up, survival was good, but approximately a third developed chronic kidney disease.

acidosis. Therefore, patients with septic or cardiogenic shock, arterial thrombosis leading to end-tissue hypoxemia, significant rhabdomyolysis, other medications, or substances such as acetaminophen, ethylene glycol, or methanol potentially responsible for lactic acidosis and patients with hypermetabolic lactic acidosis due to hematological malignancies were excluded from the main analysis. None of the patients considered to have isolated MALA had been diagnosed with or suspected to have sepsis and none had positive blood cultures. A total of 45 patients with metformin and type B lactic acidosis during the study period were screened for inclusion and 23 patients were considered to have isolated MALA.

For the purpose of this study, blood pH, bicarbonate, lactate, electrolytes, glucose and blood pressure, vasoactive medication and diuresis, were recorded at 6-h intervals from the ICU admission to 72 hours following admission in the isolated MALA group. Other data extracted from patients' medical records included reason for ICU admission, demographics, medical conditions (both chronic and acute), medications, and other relevant laboratory results. Creatinine and eGFR were assessed at baseline (within 1 year prior to ICU admission), on admission and at hospital discharge and at 1 year of follow-up in survivors (available follow-up creatinine closest to one year, but at least 6 months following MALA).

2.1 | CRRT modality

CVVHD for all patients was performed according to a standard protocol employed in our centre using Fresenius Multifiltrate CRRT monitors and 1.80 m² polysulfone hemofilter Ultraflux EMiC2 HCO membranes with CiCa dialysate to achieve regional citrate anticoagulation (Fresenius Medical Care, Bad Hamburg, Germany). Post-filter-ionized calcium levels were used for anticoagulation monitoring. The starting citrate dose used was 4 mmol per liter of treated blood—a standard dose recommended for CiCa-CVVHD by the manufacturer. The citrate dose was then titrated during the treatment to achieve a target Ca⁺⁺ level and thereby sufficient regional anticoagulation without systemic effects. Blood and dialysate flow rates were prescribed according to the weight of the patient and by the caring ICU physician to target a dialysis dose of 30 mL/kg/h.

2.2 | Statistical methods

Results are expressed as mean \pm standard deviation (SD) for normally distributed variables and median [interquartile range (IQR)] for skewed continuous variables, unless stated otherwise. Univariate associations between the study variables were analyzed by calculating the Pearson's correlation coefficients. Comparisons between creatinine and eGFR, respectively, at baseline and 1 year following discharge were done using Wilcoxon signed-rank tests. The between group comparisons concerning ICU, 90-day, and 1-year mortality were performed using Fisher's exact test. All statistical analyses were performed using statistical analysis system, SAS version 9.3 (SAS Institute Inc, Cary NC).

2.3 | Compliance with ethical standards

The study was approved by the Hospital District of Southwest Finland (Reference number: T143/2016). This was a retrospective register-based study of patients from an anonymized dataset that only involved recording data from medical records. According to Finnish law and Ethics committee of South-West Finland Hospital District this study did not require consent from patients to participate.

2.4 | Data availability

Data that support the findings of this study are available from the datasets of the Department of Anesthesiology and Intensive Care and the Informatics Department of Turku University Hospital upon reasonable request and after permission of the Ethics Committee from Southwest Finland Hospital District.

3 | RESULTS

Forty-five patients of the patients treated with CRRT in our unit between years 2010 and 2019 met the definition of B-type lactic acidosis, and were on metformin medication. After a careful screening process, 23 of the 45 patients met the definition of isolated MALA, had no other potential causes of lactic acidosis than metformin use (apart from chronic excessive alcohol use), and were included in the study (4.7% of all CRRT-patients during the time period).

In the remaining 22 patients, another acute comorbidity (apart from metformin-use) was considered as the primary etiology for lactic acidosis. Etiologies for lactic acidosis of the remaining patients included sepsis, cardiogenic shock, liver failure, brain stem infarction, and severe ethanol poisoning.

The baseline characteristics of the isolated MALA patients at ICU admission are shown in Table 1. Mean age was 67 ± 8 (range 56-83) years and 34.8% were female. Median pH was 6.88 (6.81-7.07), and blood lactate 16.1 (11.9-23.0) mmol/L on admission (Table 2).

TABLE 1 Patient characteristics

Age (y)	67 \pm 8
Sex (Male/Female)	15/8
Weight (kg)	93 \pm 25
BMI (kg/m ²)	31.7 \pm 8.3
Metformin dose (mg)	2000 (2000-3000)
Baseline plasma creatinine (μ mol/L)	81 \pm 23
Baseline eGFR (mL/min/1.73 m ²)	77 (53-98)
History of alcohol abuse (n/%)	14 (60.9%)
Comorbidities [n (%)]	
Hypertension	16 (69.6%)
Obesity (BMI > 30 kg/m ²)	13 (56.5%)
Coronary artery disease	6 (26.1%)
Hypercholesterolemia	6 (26.1%)
Atrial fibrillation	5 (21.7%)
Heart failure	4 (17.4%)
Medication [n (%)]	
ACE-/ATR2-inhibitor	16 (69.6%)
Hydrochlorothiazide	7 (30.4%)
Insulin	6 (26.1%)
NSAID	3 (13.0%)
Beta-blocker	8 (34.8%)
Lipid-lowering medication	9 (39.1%)
Second oral agent for T2D	6 (26.1%)

Note: Continuous variables are expressed as mean \pm SD or median with interquartile range

TABLE 2 Status on admission

Plasma creatinine (μ mol/L)	549 (180-908)
eGFR (mL/min/1.73 m ²)	6 (5-31)
pH (U)	6.88 (6.81-7.07)
Base Excess (mmol/L)	-27.5 (21.6-28.3)
Blood lactate (mmol/L)	16.1 (11.9-23.0)
Alanine Transaminase (IU/L)	34 (25-54)
International Normalized Ratio	1.2 \pm 0.2
Anion Gap (mEq/L)	33 \pm 8
Bicarbonate (mmol/L)	6.5 (5.1-9.0)
Blood glucose (mmol/L)	9.1 (5.4-13.6)
Mean arterial pressure (mmHg)	66.1 \pm 14.3
Hourly urine output (mL/h)	0 (0-5)
SAPS II	36 (29-54)
Apache II	19.8 \pm 7.2
Consciousness (Glasgow Coma Scale)	14 (13-15)

Note: Continuous variables are expressed as mean \pm SD or median with interquartile range.

Fourteen (60.9%) patients had a history of previous alcohol misuse. Baseline creatinine was 81 ± 23 μ mol/L and baseline eGFR 77 (53-98) mL/min/1.73 m².

The median time between ICU admission and start of CRRT was 2 (1.4-3.2) hours. At CRRT, initiation 20 patients had pH < 7.15, four patients had hyperkalemia (>6 mmol/L), and all but one patient had a urine output of less than 0.1 mL/kg/h. Median RRT duration was 62 (41-70) h (range 12.3-142.3 hours). None of the patients showed signs of citrate accumulation defined as plasma total calcium/ionized calcium -ratio >2.5 during CRRT. Seven patients (30%) required mechanical ventilation with a mean time of 6.0 ± 3.0 days, and 91% (21 patients) needed vasopressor therapy. Mean duration of ICU stay was 5.3 ± 3.3 (range 2-16) days. A 90-day mortality was 4.3% and 1-year mortality 13.0%. None of the of the isolated MALA patients died in the ICU. None of the survived patients required RRT after hospital discharge (Table 3).

The patients that were excluded from the analyses due to acute comorbidities had significantly higher ICU (31.8%, $P = .004$), 90-day (45.5%, $P = .002$), and 1-year-mortality (54.5%, $P = .005$) compared to the patients with isolated MALA. Median of highest norepinephrine dose was 0.175 (0.120-0.410) µg/kg/min for excluded patients and did not differ from the MALA group ($P = .65$).

Duration of vasoactive treatment was recorded for the first 72 hours (Figure 1). Five patients required norepinephrine for over 72 hours. The duration of norepinephrine therapy was associated with lactate ($r = 0.49$, $P = .02$) and pH ($r = -0.48$, $P = .02$) at 24 hours following ICU admission. Three patients required additional vasoactive treatment. One patient received vasopressin infusion within 6 hours, one patient received epinephrine infusion within 24 hours, and one patient received levosimendan infusion within 60 hours of ICU admission.

Blood lactate declined rapidly using continuous RRT with 68.2% of patients achieving normal lactate (<2.0 mmol/L) (Figure 2) and 64% normal pH (>7.35) within 24 hours of ICU admission (Figure 3). Lactate at 24 hours was significantly associated with total duration of RRT required ($r = 0.63$, $P = .002$) and pH at 24 hours was

associated with both RRT duration ($r = -0.57$, $P = .005$) and ICU stay ($r = -0.47$, $P = .03$). The first 24 hours median hourly urine output was 15 (9-58) mL/h [0.22 (0.09-0.70) mL/kg/h] (Figure 4). The determinants of first 24 hours mean hourly urine output, were SAPS-II ($r = -0.46$, $P = .04$), plasma creatinine ($r = -0.46$, $P = .04$), and eGFR ($r = 0.56$, $P = .01$) at ICU admission and highest recorded SOFA score ($r = -0.52$, $P = .02$). ICU stay was also associated with the highest recorded SOFA score ($r = 0.53$, $P = .001$). About 39% of the patients had plasma creatinine <100 µmol/L when discharged from the hospital. Median creatinine at discharge was 104 (82-139) µmol/L and mean eGFR was 57 ± 27 mL/min/1.73 m². Creatinine at discharge was not associated with baseline creatinine or creatinine or eGFR on ICU admission, but instead it was directly correlated with duration of ICU stay ($r = 0.55$, $P = .006$), ventilator treatment ($r = 0.50$, $P = .02$), and dialysis duration ($r = 0.60$, $P = .003$) and inversely with pH at 24 hours of admittance to the ICU ($r = -0.61$, $P = .002$).

Mean creatinine was 101 ± 33 µmol/L and eGFR 66 ± 25 mL/min/1.73 m² for 20 survived patients at 1 year after discharge. Median time to 1 year creatinine recording was 369 (301-487) days. Creatinine ($P = .02$) and eGFR ($P = .03$) stayed significantly higher at 1-year follow-up compared to baseline values (Figure 5). All patients had baseline eGFR > 45 mL/min/1.73 m², but at 1 year of follow-up, 30% of survivors had eGFR below 45 mL/min/1.73 m² corresponding to KDIGO stage 3b CKD. One-year eGFR or creatinine values were not associated with the duration of ICU stay, maximal SOFA score, diuresis in the beginning of treatment, creatinine, or eGFR at baseline or on admission.

4 | DISCUSSION

More than 250 000 Finnish patients with diabetes were prescribed metformin in 2018,¹⁷ corresponding to 4.5% of the whole population

Highest recorded SOFA	9.8 ± 2.9
Highest requirement of norepinephrine (µg/kg/min)	0.16 (0.13-0.27)
Duration of CRRT (h)	62 (41-70)
Mean hourly urine output during 0-24 h (mL/h)	15 (9-58)
Dose of dialysis 12 h after admission (mL/kg/h)	32.3 ± 6.8
Fluid balance 24 h after admission (mL)	3450 ± 2219
Mechanical ventilation (n/%)	7/30.4
Duration of mechanic ventilation (d)	6.0 ± 3.0
Duration of ICU stay (d)	4 (3-7)
Mortality 30 d (n/%)	1/4.3
Mortality 90 d (n/%)	1/4.3
Mortality 365 d (n/%)	3/13.0
Plasma creatinine at discharge (µmol/L)	104 (82-139)
eGFR at discharge (mL/min/1.73 m ²)	57 ± 27
Plasma creatinine 365 d (µmol/L)	101 ± 33
eGFR 365 d (mL/min/1.73 m ²)	66 ± 25

TABLE 3 Outcomes

Note: Continuous variables are expressed as mean ± SD or median with interquartile range.

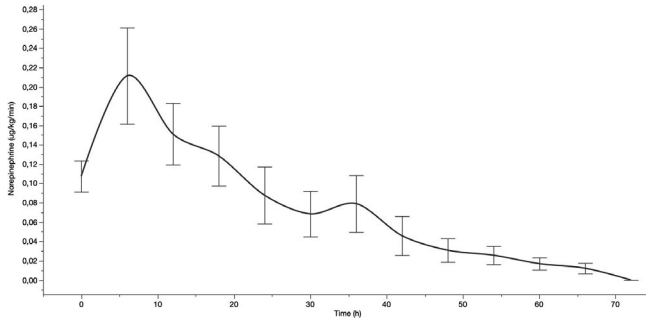


FIGURE 1 Mean (SE) requirement of norepinephrine infusion during first 72 hours of ICU admission

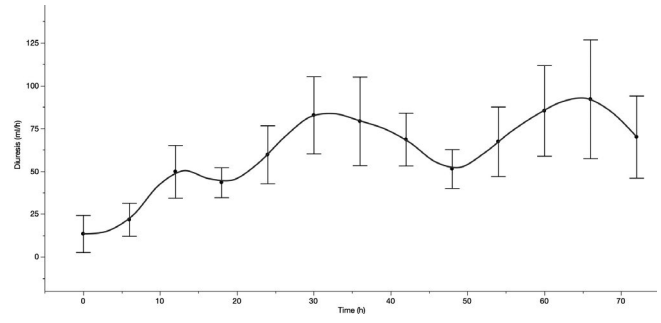


FIGURE 4 Mean (SE) urinary output during first 72 hours of ICU admission

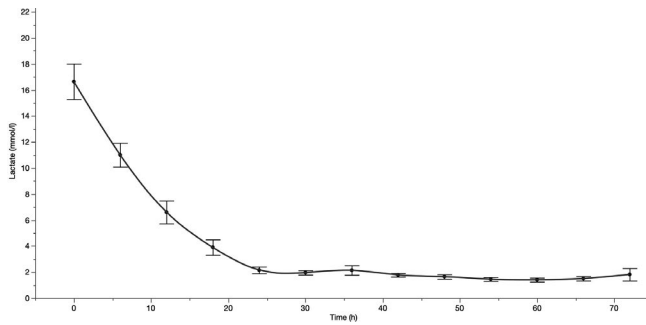


FIGURE 2 Mean (SE) serum lactate level during first 72 hours of ICU admission

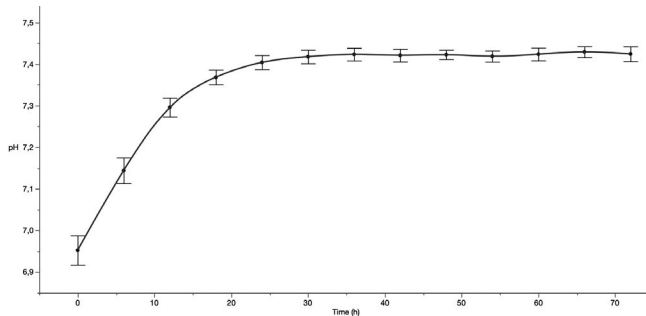


FIGURE 3 Mean (SE) pH level during first 72 hours of ICU admission

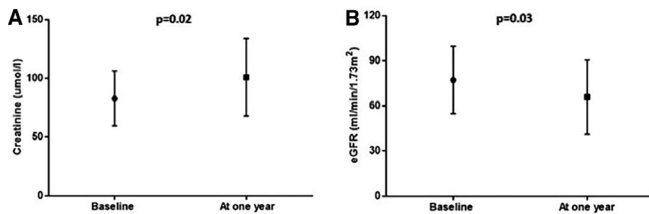


FIGURE 5 Mean (SD) creatinine (a) and eGFR (b) at baseline and 1 year after MALA

renal survival in isolated MALA requiring CRRT and intensive care treatment.

Our data show that the prognosis of MALA is favorable when disease states predisposing patients to A-type lactic acidosis have been carefully excluded. The in-hospital mortality was 4.3% and markedly lower compared to earlier reports. In previous studies the in-hospital mortality has been reported to be 17.2%-51.8%.^{15,16,18} In a recent, so far, the largest retrospective study with 117 patients diagnosed with MALA and treated with RRT, the ICU mortality was 21.4%.¹⁹ The low mortality observed in the current study is most likely explained by exclusion of patients with sepsis, septic shock, liver failure, cardiac failure, and marked chronic renal disease on contrary to previous studies. It is plausible that in a notable proportion of patients included in previous studies, metformin has been a bystander or only partly responsible for the lactic acidosis observed in the critically ill patients with other acute comorbidities. In line with this assumption, the patient group with other acute comorbidities (sepsis, cardiovascular, hepatic etc) had a markedly higher ICU, 90-day and 1-year mortality in the present study compared to patients with isolated MALA. In these comorbid patients mortality was similar to earlier reports^{15,16}

The safe use of metformin in patients with other chronic risk factors for developing lactic acidosis is still under debate. Available data suggest cautious use of metformin in patients with mild to moderate kidney disease,⁸ but also in patients with chronic alcohol misuse.²⁰ Only three (13%) of our patients with isolated MALA had mildly elevated plasma creatinine (115-126 µmol/L) before the admission, which suggests that use of metformin in our patients was justifiable based on plasma creatinine. However, 61% of our patients had history of alcohol abuse. Alcohol use and thiamine deficiency have been shown to inhibit the aerobic pathway of pyruvate and to inhibit lactate clearance in the liver, which both may predispose lactate accumulation.²¹ Furthermore, chronic alcohol abuse is often associated with poor nutrition and a risk of dehydration that may help induce acute kidney injury and MALA.

None of the isolated MALA patients required RRT for over 6 days. Blood lactate and pH at 24 hours after ICU admission were significant determinants of the length of CRRT-requirement and pH

in Finland. Severe MALA requiring intensive care and renal replacement therapy is a rare, but potentially lethal adverse effect of metformin therapy. Therefore, we aimed to study the patient and

was also associated with the duration of ICU stay. Blood lactate, however, declined rapidly using CRRT with regional citrate anticoagulation with two-thirds of patients achieving normal lactate and pH by 24 hours of ICU admission. Peak serum creatinine level has been earlier shown to be associated with mortality of MALA patients.¹⁵ The mortality in our study was so rare that its determinants could not be studied. Instead creatinine at discharge was directly correlated with duration of ICU stay, ventilator treatment, and duration RRT, and inversely with pH at 24 hours of admittance to the ICU. The novel finding of the current study was that eGFR and creatinine remained altered 1 year after MALA compared to their baseline values, suggesting that isolated MALA and concomitant acute kidney injury may lead to CKD. None of the survived patients required RRT after hospitalization.

Regional citrate-calcium-anticoagulation is widely used for CRRT and is superior to systemic anticoagulation (eg, low-molecular heparine) in terms of bleeding-risk and circuit and filter patency during treatment.¹⁹ Persistent lactic acidosis with negative lactate clearance has been suggested to be a relative contraindication for use of citrate-calcium-anticoagulation due to increased citrate accumulation risk.²⁰ Citrate and lactate metabolism are both attenuated in states of severe shock and liver failure. None of the patients in the present study, however, showed signs of citrate accumulation. In accordance with our findings, a recent retrospective study demonstrated that the risk of citrate accumulation is rather related to lactate kinetics than initially elevated lactate concentration.²⁰ Therefore, our current results show for the first time that regional citrate-calcium-anticoagulation for CRRT is a safe and effective means to treat MALA. Apart from sporadic case reports, previous studies have not utilized citrate-calcium-anticoagulation for CRRT in MALA.

Our study has limitations. We were not able to measure metformin concentrations, since these are not routinely measured in Finland. It could have been useful to study the association between metformin concentrations and the severity of MALA and to know whether toxic concentrations of metformin were present. However, previous studies have not associated metformin dose or plasma concentrations with prognosis of MALA.¹⁵ Furthermore, many of the previous studies have included several chronic and/or acute conditions potentially confounding the primary cause of lactic acidosis, a scenario that we aimed to carefully exclude. Therefore, we believe we were able to screen all isolated MALA patients without confounding conditions during a 10-year period treated with CRRT and citrate-calcium-anticoagulation in our hospital district involving 470 000 citizens.

Our current results clearly show that the prognosis of patients with isolated MALA is good although renal function may remain impaired from baseline levels after an episode of MALA.

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CONFLICT OF INTERESTS

P. Uusalo has received honoraria for speaking at symposia organized by Orion Pharma. M. Järvisalo declares no conflicts of interest.

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