Metformin-associated Lactic Acidosis Requiring Intensive Care in a Regional Hospital in Hong Kong and Predictive Factors for Mortality

Metformin-associated lactic acidosis (MALA) has estimated the incidence of 3–9/100,000 patient-years[1] and mortality rate ranging from 9.1% to 61% with inconsistent prognostic factors[1-3] [Table 1].

Patients admitted to Intensive Care Unit (ICU) of Queen Elizabeth Hospital in Hong Kong between January 2011 and December 2015 were included in the retrospective study if they met the following criteria: (1) metformin as usual treatment or overdose; (2) peak lactate >5 mmol/L; (3) pH <7.35 and bicarbonate <22 mmol/L. Patients were excluded if they were admitted for (1) postcardiac arrest or (2) postoperative care or (3) conditions other than MALA in which investigators identify as the main cause of lactic acidosis. This study was performed in compliance with ethical standard of the Helsinki declaration and approved by the research ethics committee.

Eighty-four patients with elevated lactate level had taken metformin as usual medication or overdose. Twenty-five patients were excluded due to postcardiac arrest ($n = 4$), postoperative care ($n = 15$), extracorporeal membrane oxygenation therapy ($n = 4$), nonacidemia ($n = 1$), and massive ST-elevation myocardial infarction ($n = 1$).

The baseline characteristics of the eligible patients were summarized in Table 2.

Compared with the 54 survivors, the 5 nonsurvivors had higher Acute Physiology and Chronic Health Evaluation IV (APACHE IV) scores ($P = 0.005$), APACHE IV predicted

Table 1: Summary of major cohorts in metformin-associated lactic acidosis

First author	Country	Period	Mortality (%)	Precipitating factors (%)	Number of patients	Metformin level	Factors for mortality identified
Spiller	US	1996-2000	13	N/A	68	N/A	N/A
Renda	Italy	2001-2011	25	89	59	N/A	Low pH and absence of ARF
Lalau	France	NA	45	100	49	Any level	Low metformin level
Li Cavoli	Italy	2008-2009	10	100	47	N/A	N/A
Misbin	US	1995-1996	42	91	47	N/A	N/A
Seidowsky	France	1998-2007	33	69	42	>2 mg/L	LODS age, arterial pH, arterial lactate level, PT activity, mechanical ventilation and need for vasoactive support. Also intentional overdose good prognosis
Peters	France	2002-2007	30	100	30	N/A	Reason for admission and initial PT
Vishwanath Biradar	Australia		30%	65	17	N/A	APACHE III score, arterial pH on admission and male sex
Farshad Kajbaf	France	1995-2010	47	95	58	Any level	Sepsis, multidrug overdoses and the presence of at least two triggering factors for lactic acidosis
Vecchio S	Italy	2007-2011	26	100	66	>4 mg	Just exclude lactate and metformin level as factors for mortality
Yeung CW	HK	2006-2010	30	96	23	Any level	Shock and high plasma lactate levels
Duong JK	Australia	2008-2011	20	93	15	N/A	N/A
Our study	HK	2011-2015	8.5	93.2	59	N/A	APACHE IV score, APACHE IV predicted mortality risk, temperature, heart rate and $PaCO_2$, lower first 24 h urine volume and serum albumin; mechanical ventilation, sepsis, higher median maximum dosage of noradrenaline infusion, longer median time from hospital admission to RRT

N/A: Not available; APACHE: Acute Physiology and Chronic Health Evaluation; RRT: Renal replacement therapy; LODS: Logistic organ dysfunction system; ARF: Acute renal failure; PT: Prothrombin time

mortality risk ($P = 0.003$), temperature ($P = 0.032$), heart rate ($P = 0.035$), and PaCO$_2$ ($P = 0.002$); and lower first 24-h urine volume ($P = 0.013$) and serum albumin ($P = 0.012$). They were more likely to be on mechanical ventilation ($P = 0.014$) and suffer from sepsis ($P = 0.001$). They had higher maximum dosages of noradrenaline infusion ($P = 0.009$) and longer

Table 2: Patient baseline characteristics, precipitating factors, and outcome

Characteristics	MALA patients ($n=59$)
Age	68.4 (11.7)
BMI (kg/m^2)	20.8 (2.9)
Baseline creatinine (μmol/L)	103.1 (31.1)/1.16 (0.35)
eGFR (ml/min/1.73 m^2)	65.5 (28.8)
Metformin dosage¥	2000 mg (1000-2125)
Heart rate	94.9 (28)
Respiratory rate	22.2 (5.3)
Mean arterial blood pressure (mmHg)	65.3 (16.1)
Maximum noradrenaline (mcg/kg/min)¥	0.61 (0.11-1.73)
Noradrenaline and adrenaline	12 (20.3)
First 24 h urine in ICU (ml)¥	479 (89-1398)
Blood tests upon admission	
Potassium (mmol/L)	6.1 (1.24)
Urea (mmol/L)	25.3 (8.9)
Creatinine (μmol/L)	546.8 (294)
pH	6.98 (0.23)
Bicarbonate (mmol/L)	6.5 (4.9)
Peak lactate (mmol/L)	14.5 (6.2)
Mechanical ventilation/RRT	
Mechanical ventilation* (%)	28 (47.5)
PF ratio¥	359 (208-489)
Initial RRT* (%)	
CVVH	44 (74.6)
CVVHDF	11 (18.6)
No	4 (6.8)
Time from admission to RRT (min)¥	409 (160-860)
Time from RRT to free from RRT (days)¥	1.83 (0.82-3.47)
Composite severity score	
APACHE IV score	112.0 (28.1)
APACHE IV risk	0.46 (0.27)
SOFA score¥	9 (7-11)
Outcome	
ICU mortality* (%)	5 (8.4)
30 days mortality* (%)	7 (11.9)
1 year mortality* (%)	12 (20.3)
1 year creatinine (μmol/L)	153.8 (113.6)
Metformin usage on 1 year follow-up*	11

Results shown as mean±SD unless otherwise specified. *n (%); ¥Median (inter-quartile range). BMI: Body mass index; eGFR: Estimated glomerular filtration rate by modified diet in renal disease study equation; RRT: Renal replacement therapy; APACHE: Acute Physiology and Chronic Health Evaluation; SOFA: Sequential organ failure assessment; ICU: Intensive Care Unit; MALA: Metformin-associated lactic acidosis; CVVH: Continuous veno-venous hemofiltration; CVVHDF: Continuous veno-venous hemodiafiltration; PF: PaO$_2$ to FiO$_2$ ratio; SD: Standard deviation

median time from hospital admission to commencement of renal replacement therapy (RRT).

The receiver operating characteristics curve for the time from admission to RRT with the outcome of mortality had an area under curve of 0.776 ($P = 0.043$). Sensitivity and specificity would both be 80% if the cutoff was set at 765.5 min from admission to RRT [Figure 1].

When comparing patients with other precipitating factors, patients with sepsis were found to have higher heart rates ($P = 0.016$), PaCO$_2$ levels ($P = 0.017$), APACHE IV risk ($P = 0.02$), sequential organ failure assessment score ($P = 0.001$), and maximum nor-adrenaline infusion dosages ($P = 0.001$), with higher rates of mechanical ventilation ($P = 0.013$) and ICU mortality ($P = 0.001$).

Patients with intentional self-inflicted overdose had higher pH ($P = 0.009$) and bicarbonate ($P < 0.001$); and lower serum creatinine level ($P < 0.001$), APACHE IV predicted mortality risk ($P = 0.02$), maximum noradrenaline infusion dosages ($P = 0.043$), and rate of RRT ($P < 0.001$). None of the patients died in the ICU but there is no significant difference in ICU mortality.

Septic patients and patients with higher serum creatinine level had a longer duration of RRT dependence [Figures 2 and 3; $P = 0.026$ and 0.005, respectively].

RRT would be theoretically beneficial in MALA by the elimination of metformin and lactate, correction of acidosis and electrolyte abnormalities and as a support for impaired kidney function. Our study is the first study to demonstrate a longer time from hospital admission to RRT in nonsurvivors, suggesting a beneficial effect of early RRT. The benefits of early RRT in critically ill patients have been debated. In 2016, there were two randomized controlled trials published on
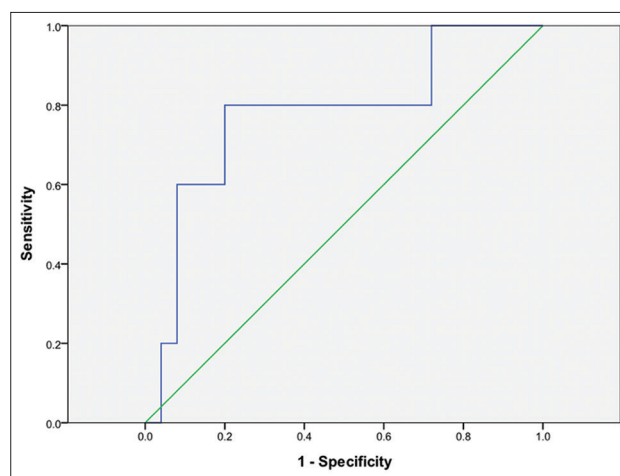

Figure 1: Receiver operating characteristics curve of time from admission to renal replacement therapy commencement for predicting mortality. Area under curve = 0.776 ($P = 0.043$*)
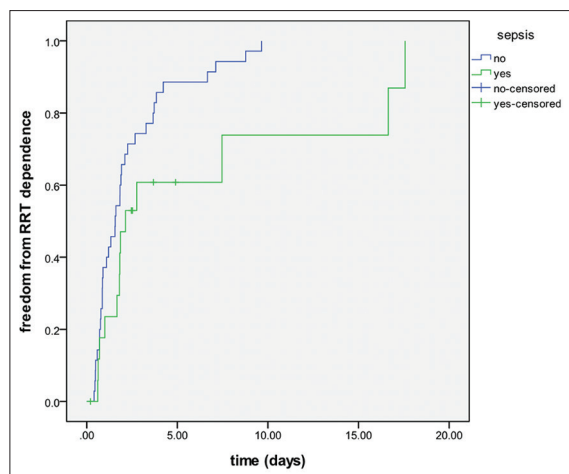
Figure 2: Time to freedom from renal replacement therapy dependence in septic and nonseptic metformin-associated lactic acidosis patients ($P = 0.026$)
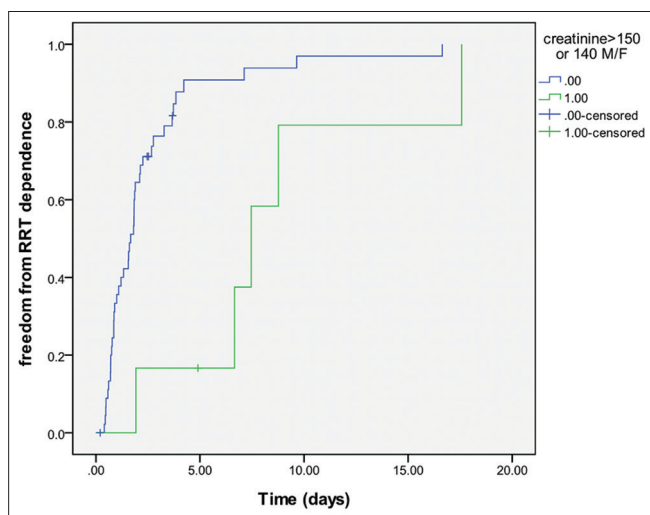

Figure 3: Time to freedom from renal replacement therapy dependence in patients with or without serum creatinine >150 μmol/L in male or 140 μmol/L in female ($P = 0.005$)

early versus late RRT in critically ill patients with different results.[4,5]

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Conflicts of interest
There are no conflicts of interest.

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