Long-Term Kidney Outcomes in Diabetic Patients with Severe Lactic Acidosis:

Interim Analysis of a Multicenter Observational Study

Sorawit Wihakhaphirom[1]
Jirawat Phuphanitcharoenkun[2],
Nopparat Sanyakeun[3], Prit Kusirisin[1]

Division of Nephrology, Department of Internal Medicine, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand
Department of Medicine, Nakornping Hospital, Chiang Mai, Thailand
Department of Medicine, Jomthong Hospital, Chiang Mai, Thailand

Introduction

- Metformin, the first-line oral antidiabetic agent, may offer renoprotective benefits through its glucose-lowering effects but carries a risk of lactic acidosis.
- Several studies suggest that metformin users who develop severe lactic acidosis are more likely to require kidney replacement therapy (KRT).[1,2]
- However, data on both short-term and long-term kidney outcomes remain limited.

1. Posma RA, et al. Prognostic impact of elevated lactate levels on mortality in critically ill patients with and without preadmission metformin treatment: a Danish registry-based cohort study. Ann Intensive Care. 2020.
2. Doenyas-Barak K, et al.. Lactic acidosis and severe septic shock in metformin users: a cohort study. Crit Care. 2016.

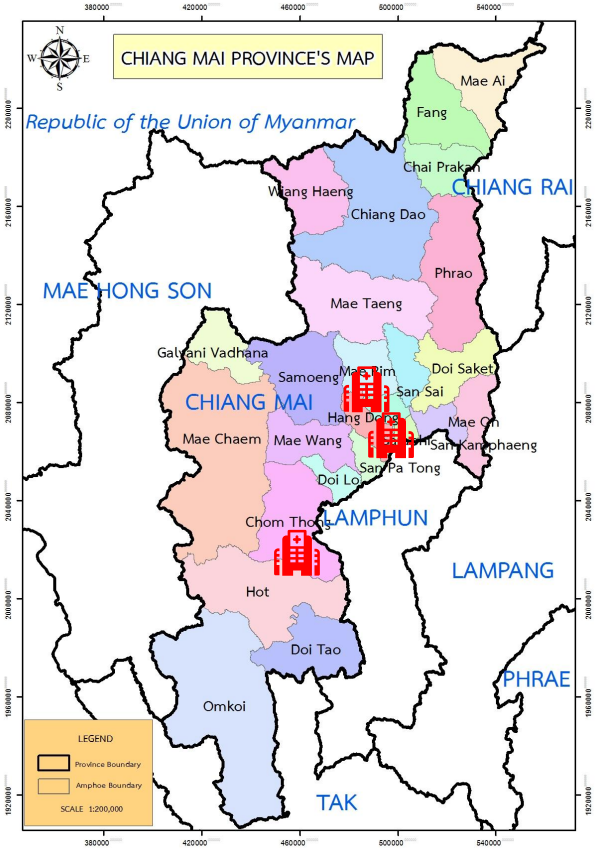
Objective

- This study aimed to investigate these kidney outcomes in this specific population.
- **Our hypothesis** is that metformin users may have a higher prevalence of severe acidosis, resulting in **more severe disease** and an **increased incidence of the rate of acute KRT** and also **an incidence of MAKE at 30, 60, and 90 days** compared to non-users.

Method

- A multicenter retrospective observational study at three medical centers in Northern Thailand (Chiang Mai University Hospital, Jomthong Hospital, and Nakornping Hospital) between 2006 and 2023.

- This study planned to enroll a total of 220 participants, comprising 155 in the experimental group and 65 in the control group



Method

Inclusion criteria	Exclusion criteria
• Age ≥20 years • Diagnosis with diabetes • Elevate serum lactate level (>4 mmol/L) within 12 hours before and after admission • High anion gap metabolic acidosis	• CKD stages 4 and 5 • No document baseline creatinine within 365 days • Death within 24 hours after admission • Other causes of metabolic acidosis • Admission due to trauma • Receiving immunosuppressive drug (eg. Prednisolone ≥15 mg/day) • Pregnancy • Kidney transplant status

Outcome measurement

- **Primary outcome:** the rate of acute kidney replacement therapy (KRT) during admission compared between metformin users and non-users.

- **Secondary outcome:** an incidence of major adverse kidney events (MAKE), defined as mortality, dialysis dependence, or doubling of serum creatinine at 30, 60, and 90 days.

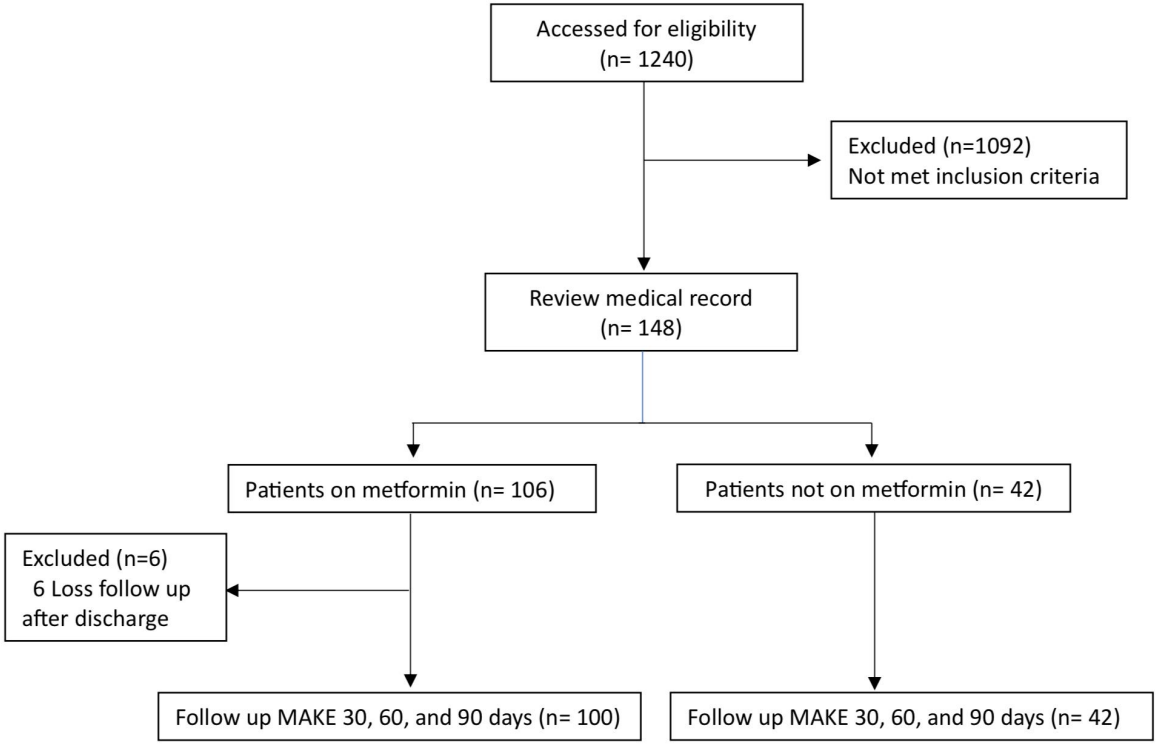
Data collection

- We aimed to collect all these data in this study
    1. **Baseline demographic data**: age, gender, Underlying disease, Baseline creatinine within 1 year before admission, and current medication
    2. **Clinical presentation at admission:** vital signs at presentation, primary diagnostic category
    3. **Admission investigation:** CBC, BUN, Creatinine, electrolyte, lactate level, arterial pH
    4. **Severity of disease at admission:** APACHE II score, SOFA score, the requirement of a ventilator at admission, the requirement of a vasopressor at admission, hospital length of stay
    5. **Clinical outcome in admission:** kidney replacement therapy rate
    6. **Long term clinical outcome:** MAKE at 30, 60, and 90 days after the diagnosis of severe lactic acidosis

Statistic method

- All data will be expressed as mean ± standard deviation (SD) for continuous variables and as percentage (%) for categorical variables.
- The chi-square test was used to analyze categorical variables. Student's t-test or Mann-Whitney U-test was used to compare the mean between the two groups depending on the distribution of data.
- Statistical significance was considered as $p<0.05$, and all reported probability tests were two-sided.
- The data will be analyzed with the program Stata (Version 16.0, StataCorp LLC, Texas, USA)

STROBE flow chart

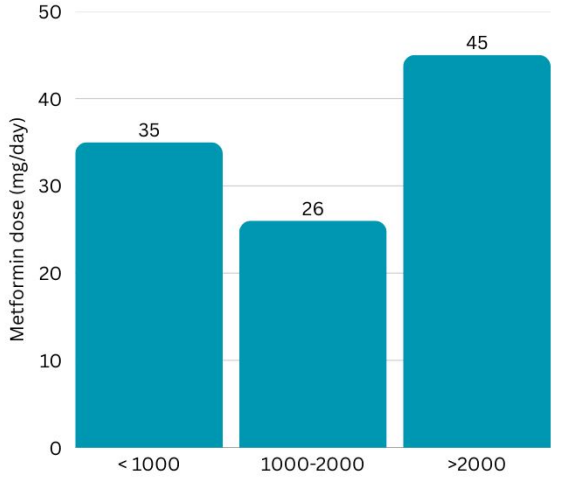


Baseline characteristic

Characteristics	Metformin (n= 106)	Non metformin (n= 42)	P value
Age (years) †	66.81 ± 12.74	69.4 ± 14.73	0.29
Male*	55 (51.9)	27 (64.3)	0.17
Underlying			
Hypertension*	92 (86.7)	33 (78.5%	0.21
Dyslipidemia*	82 (77.3)	32 (76.1)	0.87
Chronic kidney disease*	22 (20.8)	11 (26.2)	0.47
Cardiovascular disease*	29 (27.3)	15 (35.7)	0.32
Cirrhosis*	9 (8.5)	7 (16.7)	0.14
Solid cancer*	11 (10.4)	13 (30.9)	0.002
Current medication			
Sulfonylurea*	46 (43.4)	7 (16.7)	0.002
Thiazolidinediones*	13 (12.3)	0 (0)	0.02
SGLT2 inhibitor*	9 (8.5)	3 (7.1)	0.78
DPP4 inhibitor*	22 (20.8)	5 (11.9)	0.21
Insulin*	18 (16.9)	14 (33.3)	0.03
ACEI*	40 (37.7)	6 (14.3)	0.006
ARB*	27 (25.5)	7 (16.7)	0.25
CCB*	52 (49.1)	10 (23.8)	0.005
Furosemide*	7 (6.6)	11 (26.2)	0.001
Baseline Kidney function			
Creatinine (mg/dl) †	1.00 ± 0.36	1.13 ± 0.45	0.067
eGFR (mL/min/1.73 m²) †	73.16 ± 23.19	67.46 ± 29.49	0.22

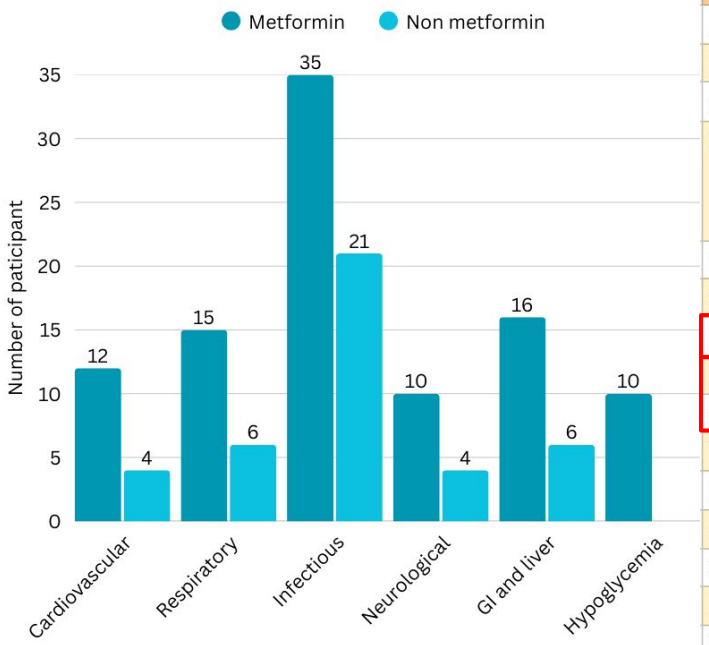
* N (%), † Mean ± SD

Average Metformin dose:
1850 ± 762 mg/day



Admission profile

Admission diagnosis



Admission profile

Admission profile	Metformin (n= 106)	Non metformin (n= 42)	P value
Initial investigation			
BUN (mg/dl) ‡	36 [17,67]	20 [17, 43]	0.13
Creatinine (mg/dl) ‡	1.74 [1, 5.58]	1.37 [1.05, 2.35]	0.07
Stage of acute kidney injury * - Stage 1 - Stage 2 - Stage 3	 20 (18.9) 6 (5.7) 40 (37.7)	 12 (28.6) 4 (9.5) 3 (7.1)	 0.06
WBC (10^3 cell/mm3) ‡	13.17 [9, 16.88]	11.61 [7.81, 16.25]	0.13
Sodium (mmol/L) †	134.55 ± 8.5	133.67 ± 8.50	0.16
Potassium (mmol/L) †	4.6 ± 1.29	4.23 ± 0.99	0.02
Bicarbonate (mmol/L) †	12.44 ± 5.78	15.29 ± 4.68	0.005
pH ‡	7.21 [7.17, 7.25]	7.34 [7.26, 7.41]	0.003
Lactate (mmol/L) ‡	8.69 [5.94, 13.88]	7.43 [5.48, 10.99]	0.08
Disease severity			
APACHE II †	20.56 ± 7.86	19.02 ± 7.47	0.28
SOFA ‡	6 [3, 9]	5 [3, 8]	0.39
Mechanical ventilator *	48 (45.3)	17 (40.5)	0.59
Vasopressor required *	47 (44.3)	14 (33.3)	0.22
Length of stay (days) ‡	7 [4, 15]	10 [4.25, 18.25]	0.337

* N (%), † Mean ± SD, ‡ Median [IQR1, IQR3]

Primary outcome

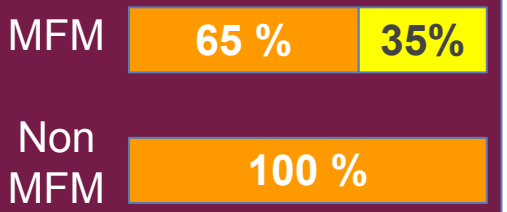
KRT in admission

MFM: 27.36%
vs
Non MFM: 9.52%

RR 2.87

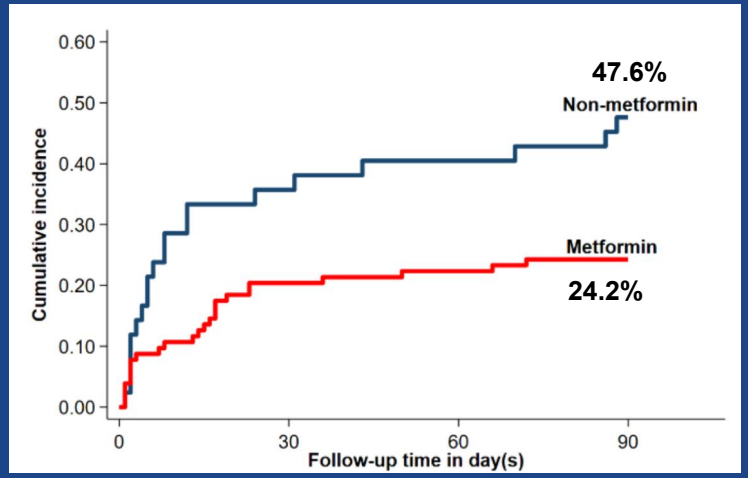
P value	95% CI
0.018	1.08-7.67

Mode of KRT in admission



No peritoneal dialysis was observed in both group

Secondary outcome

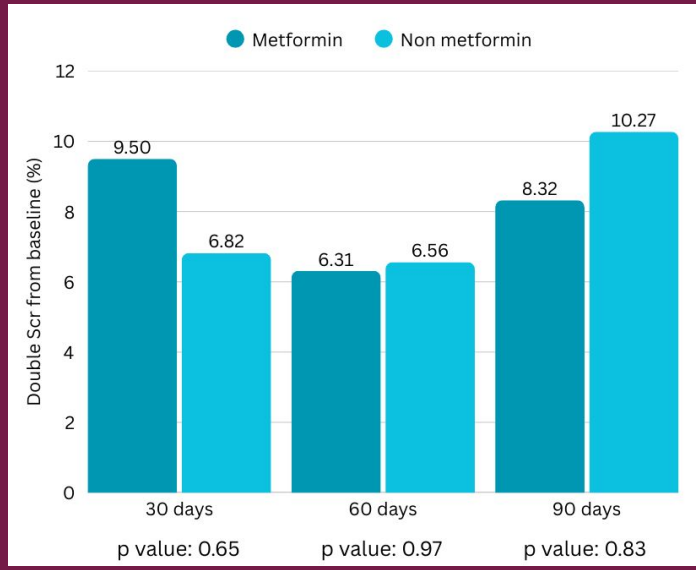


Mortality rate

HR 0.44

P value 0.006

95% CI 0.24-0.79



Doubling serum creatinine (%)

Dialysis dependence was not observed in either group

Discussion

- Our interim analysis supports previous findings that metformin users had lower mortality rates than non-users, with this benefit persisting up to 90 days post-event, despite a higher rate of in admission kidney replacement therapy.[1,2]

- Moreover, our findings provide additional long-term data on kidney outcomes, showing no higher risk of doubling serum creatinine, or dialysis dependence.

1. Doenyas-Barak, K., Beberashvili, I., Marcus, R. et al. Lactic acidosis and severe septic shock in metformin users: a cohort study. Crit Care 20, 10 (2016).
2. Posma RA, et al. Prognostic impact of elevated lactate levels on mortality in critically ill patients with and without preadmission metformin treatment: a Danish registry-based cohort study. Ann Intensive Care. 2020.

Discussion

- Prior studies indicate that lactic acidosis due to severe sepsis is associated with mortality rates of 30–45%, and that septic AKI progresses to AKD in up to 30% of cases[1,2,3]

- In our study, despite higher rates of kidney replacement therapy on admission, the metformin group had a 90-day mortality of 24% and a doubling of serum creatinine is only 8–9% of patients.

- This paradox may be explained by differences in the underlying pathophysiology in the metformin group, lactic acidosis is more likely attribute to drug-induced type B lactic acidosis rather than severe tissue hypoxia.

1. Hernández G, et al. Effect of a Resuscitation Strategy Targeting Peripheral Perfusion Status vs Serum Lactate Levels on 28-Day Mortality Among Patients With Septic Shock: The ANDROMEDA-SHOCK Randomized Clinical Trial. JAMA. 2019;321(7):654–664.
2. Paul R. Mouncey, et al. Trial of Early, Goal-Directed Resuscitation for Septic Shock. N Engl J Med 2015;372:1301-1311.
3. Chiang HY, et l. Sepsis-Associated Acute Kidney Disease Incidence, Trajectory, and Outcomes. Kidney Med. 2024 Dec 27;7(3):100959.

Discussion

- **Strength of this study**
  - **Multi-center design:** Conducting the study across multiple hospitals increases the generalizability of findings and reduces selection bias.
  - **Extended follow up period:** Monitoring outcome upto 90 days post-event provides a comprehensive assessment of the true impact of the risk factor

- **Limitation of this study**
  - **Preliminary analysis:** As this is an initial analysis, the results are subject to change and will require validation after complete data collection and further analysis.
  - **The lack of serum metformin level testing:** This limitation makes it difficult to confirm that the lactic acidosis was metformin-induced.

Conclusion

- In diabetic patients, metformin use may be associated with a higher incidence of kidney replacement therapy (KRT) during hospitalization following severe lactic acidosis. However, it appears to reduce 90-day mortality without significantly increasing the risk of major adverse kidney events.

- Further data collection and analysis are necessary to validate these findings, which will be finalized in the full study.

Thanks

Do you have any questions?

Sorawit.wih@gmail.com