**Supplemental Digital Content**

**Metformin Associated Lactic Acidosis with Acute Kidney Injury: Results of a French Observational Multicenter Study**

Anthony Corchia, MD; Alain Wynckel, MD; Julien Journet, MD; Julie Moussi Frances, MD; Nihel Skandrani, MD; Alexandre Lautrette, MD, PhD; Lara Zafrani, MD; Elisabeth Lewandowski, MD; Pascal Reboul, MD; Laurence Vrigneaud, MD; Zoubir Djerada, MD; Philippe Rieu, MD, PhD

**INDEX**

SUPPLEMENTAL METHODS Page 2

SUPPLEMENTAL STATISTICAL ANALYSIS Page 3

SUPPLEMENTAL RESULTS Page 5

SUPPLEMENTAL ACKNOWLEDGMENTS Page 14

**Methods**

**Medical record**

* We contacted 126 nephrology units including all the French university hospital
* When a centre had >10 cases, one of the authors went to the unit to collect the medical records. Otherwise, the documents were returned by email or post.

**Bicarbonate level**

We estimated the bicarbonate level using the arterial blood gases (pH, PaO2, PaCO2).

**Statistical analysis**

To avoid computational issues (model convergence failure due to sparse data), only covariate with at least five cases were considered in the model. Univariate analysis was performed to screen potential variables for inclusion in the final multivariate model. Potential covariates were: age (years), sex (female: 0, male: 1), body mass index (kg/m2), daily dose of metformin (g), systolic blood pressure (mmHg), heart rate (bpm), temperature (degrees Celsius), shock defined by the requirement of vasopressor agents (no: 0, yes: 1), exposure to renin angiotensin aldosterone system inhibitors (no: 0, yes: 1), exposure to diuretics (no: 0, yes: 1), exposure to proton pump inhibitors (no: 0, yes: 1), digestive disorders (no: 0, yes: 1), plasma creatinine (µmol/L), plasma metformin concentration (mg/L), mechanical ventilation (no: 0, yes: 1), type and intensity of renal support, exposure to renin angiotensin aldosterone system inhibitors (no: 0, yes: 1), Glasgow coma score (GCS), pH, partial oxygen pressure (PaO2, mmHg), partial carbon dioxide pressure (PaCO2, mmHg), arterial or venous blood lactates (mmol/l), urea levels (mmol/L), plasma metformin concentration (mg/L), kalemia (mmol/L), prothrombin index (%), and total bilirubin (µmol/L), Bicarbonate level (mmol/L), anticoagulant (no :0, yes : 1), acute heart failure (no : 0, yes: 1), sepsis (no: 0, yes: 1), exposure to iodinated contrast (no: 0, yes: 1) or chemotherapy agents (no: 0, yes: 1), voluntary intoxication (no: 0, yes: 1), exposure to nonsteroidal anti-inflammatory drugs (no: 0, yes: 1), Chronic kidney disease (no: 0, yes: 1).

Among the variable selection procedures, backward elimination is preferred as it starts with the assumed unbiased global model (Heinze G, Wallisch C, Dunkler D. Variable selection - A review and recommendations for the practicing statistician. Biom J. 2018 May;60(3):431-449.

doi: 10.1002/bimj.201700067). Most statisticians prefer backward elimination over forward selection, especially when collinearity is present (Mantel, [1970](https://www-ncbi-nlm-nih-gov.gate2.inist.fr/pmc/articles/PMC5969114/)). Thus, we proposed this procedure. For sensitivity, all identified associated covariate in different model were also identified using appropriate high dimensional procedure as random forest (package randomForest) and Sparse partial least squares discriminant analysis (package mixomics).

Variables significant at P = .05 at final multivariate analysis were retained as independent predictive factors. The Wald test was used for hypothesis testing. The stability and robustness of the model were validated using the technique of ‘bootstrap’ resampling.

The goodness-of-fit and appropriateness of the logistic regression model were evaluated using the Nagelkerke R squared values and Hosmer-Lemeshow value, and by the overall correct percentage of prediction. Multicolinearity was checked for all analyses.

The association between metformin plasma concentration and pH or lactate level as assessed by multiple linear regression analysis controlling for the other covariates for confounding effects. A stepwise method, with a threshold of p < 0.05 for entry and p < 0.01 for exit, was used for predictor selection. To test the validity of the linear regression model three assumptions were checked on the residues: 1) no outliers: the minimum and maximum values of standardized residual are within [-3, + 3] values; 2) the data points must be independent using the Durbin-Watson test; 3) the distribution of the standardized residuals should be normal with mean = 0 and a constant variance not different from 1 and graphically by mean of histogram, scatterplot, QQplot and normal probability plot (scatter plot of standardized residual vs. standardized predicted value or QQplot) and finally by scatter plot of observed value vs. predicted valuea. Multicollinearity was also checked using collinearity statistics (Variance inflation factor around 1). Adjusted β coefficients (βadj) were estimated for all significant associations. All P values were two-tailed, and a p-value <0.05 was considered statistically significant.

**Results**

**Supplemental table 1: Univariate comparison of clinical characteristics between shocked and non-shocked patients.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Non shocked N=103 | Shocked N=70 | p.overall |
| Age | 71.0 (16) | 71.0 (14) | 0.981 |
| BMI | 27.7 (11) | 27.7 (7.4) | 0.444 |
| Dose of metformin | 2.00 (1.4) | 2.00 (1.3) | 0.353 |
| ACE-ARA drug | 74 (73.3%) | 50 (71.4%) | 0.928 |
| Diuretic | 64 (62.7%) | 37 (52.9%) | 0.256 |
| Proton pump inhibitors | 41 (40.2%) | 25 (36.2%) | 0.717 |
| Digestive disorders | 75 (73.5%) | 35 (50.0%) | 0.003 |
| Acute heart failure | 6 (5.88%) | 8 (11.4%) | 0.306 |
| Sepsis | 15 (14.7%) | 33 (47.1%) | <0.001 |
| Anterior Creatinine | 90.0 (37) | 87.5 (39.5) | 0.642 |
| CKD | 23 (26.4%) | 18 (30.0%) | 0.775 |
| Creatinine discharge | 99.0 (47) | 101 (44) | 0.904 |
| PH | 7.24 (0.14) | 7.01 (0.31) | <0.001 |
| Mechanical ventilation | 4 (3.88%) | 38 (55.9%) | <0.001 |
| Potassium plasma level | 6.15 (2.3) | 6.00 (1.9) | 0.996 |
| HCO3 | 11.0 (6.4) | 7.00 (6) | <0.001 |
| Urea | 29.1 (14) | 28.1 (16) | 0.703 |
| Creatinine | 598 (401) | 580 (631) | 0.531 |
| Bilirubin | 7.00 (6.45) | 7.10 (8) | 0.527 |
| LACTATE | 7.02 (5.55) | 11.9 (11.19) | <0.001 |
| Metformin plasma level | 15.0 (22.46) | 22.0 (28.65) | 0.138 |
| Prothrombin index | 72.0 (22.5) | 53.0 (35.2) | <0.001 |
| Exposure to anticoagulant | 10 (12.7%) | 16 (25.4%) | 0.083 |
| Dialysis: | 69 (67.0%) | 64 (91.4%) | <0.001 |
| Duration of dialysis | 11.5 (9.12) | 35.0 64.5 | <0.001 |
| SAPS2 | 51.0 (10.8) | 74.5 (31.6) | <0.001 |
| Glasgow | 15.0 (0.5) | 11.0 (8) | <0.001 |
| Death: | 4 (3.88%) | 21 (30.0%) | <0.001 |
| Lactate>5 | 68 (66.0%) | 62 (88.6%) | 0.001 |

**Supplemental Table 2: Multivariate comparison of clinical characteristics between shocked patients and non shocked patients**

|  |
| --- |
| **Multivariate analysis** |
|  | **Non shocked (N=103)** | **Shocked (N= 70)** | **P** | **OR** |
| Digestive disorders, n (%) | 75 (73) | 35 (50) | p=0.003 | 0.18[0.06-0.55] |
| Sepsis, n (%) | 15 (15) | 37 (53) | p=0.007 | 4.35[1.5-13] |
| Prothrombin index (%) | 72 (23) | 53 (35) | p<0.001 | 0.97[0.95-0.99] |
| pH | 7.24 (0.14) | 7.01 (0.31) | p=0.02 | 2.8e-5[4e-7-9e-4] |

**Supplemental table 3: Comparison of clinical characteristics between survivors and non-survivors in the 132 patients with lactatemia higher than 5mmol/L**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | SurvivorsN = 110 | Non survivorsN = 22 | Univariate analysis | Multivariate analysis |
|  |  | P | P | AdjustedOR |
| Kalemia (mmol/L), (IQR) | 6.2 (2.1) | 5.2 (1.4) | < 0.01 | NS |  |
| Baseline plasma creatinine (µmol/L), (IQR) | 643 (478) | 295 (395) | < 0.01 | NS |  |
| Prothrombin index, (IQR) | 68 (26) | 53 (39) | 0.024 | NS |  |
| Total bilirubin (µmol/L), (IQR) | 6 (6) | 14.0 (17) | 0.035 | NS |  |
| Glasgow coma score, (IQR)  | 15 (4) | 12 (5) | 0.038 | NS |  |
| RAAS inhibitors, n (%) | 78 (71) | 11 (50) | 0.03 | 0.04 | 0.33[0.11-0.97] |
| Digestive disorders, n (%) | 77 (70) | 8 (36) | < 0.01 | 0.04 | 0.33[0.11-0.93] |
| Mechanical ventilation, n (%) | 25 (23) | 13 (59) | 0.003 | NS |  |
| Shock, n (%) | 44 (40) | 18 (82) | <0.001 | <0.001 | 9.48[2.80-44.58] |

Data are presented as mean ± standard deviation for quantitative variables; and percentages for qualitative variables.

**Supplemental table 4: Comparison of clinical characteristics between MILA and MALA in patients with lactatemia higher than 5mmol/L**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variable | MALAN = 52 | MILAN = 80 | Univariate analysis | Multivariate analysis |
|  |  | P | P | Adjusted OR |
| Glasgow coma score, (IQR) | 11 (8) | 15 (2) | < 0,0001 | NS |  |
| PaCO2 (mmHg), (IQR) | 26 (14) | 22 (13) | 0.03 | NS |  |
| Baseline plasma creatinine (µmol/L), (IQR) | 440 (470) | 699 (525)  | < 0.0001 | 0.0001 | 1.003[1.001-1.004] |
| Previous plasma creatinine (µmol/L), (IQR) | 78 (30) | 96 (40) | < 0.01 | NS |  |
| Blood urea level (mmol/L), (IQR) | 23 (13) | 32 (12) | < 0.0001 | NS |  |
| Prothrombin index (%), (IQR) | 53 (39) | 70 (26) | < 0.001 | NS |  |
| Digestive disorder, n (%) | 19 (36) | 66 (82) | < 0.001 | 0.0001 | 7.38[2.82-20.90] |
| Mechanical Ventilation, n (%) | 21 (40) | 17 (21) | < 0.05 | NS |  |
| Shock, n (%) | 38 (73) | 24 (30) | < 0.0001 | < 0.0001 | 0.132[0.047-0.334] |

Data presented as median (IQR) for quantitative variables; and percentages for qualitative variables.

**Supplemental table 5: Univariate comparison of clinical characteristics between patients with lactatemia higher than 5mmol/L and those < 5mmol/L.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | Lactate< 5 N=43 | Lactate ≥ 5 N=130 | p.overall |
| Age | 72.0 (16) | 70.5 (15) | 0.719 |
| BMI | 27.6 (12.3) | 27.7 (8) | 0.559 |
| Dose of metformin | 2.00 (0.85) | 2.00 (1.3) | 0.128 |
| Systolic blood pressure | 120 (34) | 110 (46) | 0.067 |
| Shock | 8 (18.6%) | 62 (47.7%) | 0.001 |
| ACE-ARA drug | 36 (85.7%) | 88 (68.2%) | 0.045 |
| Diuretic | 30 (69.8%) | 71 (55.0%) | 0.128 |
| Proton pump inhibitors | 18 (42.9%) | 48 (37.2%) | 0.638 |
| Digestive disorders | 25 (58.1%) | 85 (65.9%) | 0.463 |
| Acute heart failure | 4 (9.30%) | 10 (7.75%) | 0.752 |
| Exposure to iodinated contrast | 1 (2.33%) | 4 (3.10%) | 1.000 |
| Exposure chemotherapy agents | 5 (11.6%) | 4 (3.10%) | 0.044 |
| Sepsis | 8 (18.6%) | 40 (31.0%) | 0.169 |
| Anterior Creatinine | 95.0 (39) | 88.0 (40) | 0.152 |
| CKD | 14 (36.8%) | 27 (24.8%) | 0.223 |
| Creatinineat discharge | 100 (53) | 99.0 (44) | 0.652 |
| PH | 7.30 (0.09) | 7.13 (0.25) | <0.001 |
| PaO2 | 88.0 (24.6) | 115 (66.5) | <0.001 |
| PaCO2 | 29.3 (9.8) | 23.0 (12.9) | 0.001 |
| Mechanical ventilation | 4 (9.76%) | 38 (29.2%) | 0.020 |
| Potassium plasma level | 5.80 (2.4) | 6.15 (2.12) | 0.224 |
| HCO3 | 15.0 (6.7) | 8.78 (7.75) | <0.001 |
| Urea | 30.5 (17.7) | 28.4 (14.8) | 0.665 |
| Creatinine | 594 (363) | 590 (588) | 0.721 |
| Bilirubine | 8.05 (7.23) | 6.00 (7.4) | 0.104 |
| LACTATE | 3.76 (1.05] | 9.75 (7.74) | <0.001 |
| Metformin plasma level | 10.0 (16.24) | 26.1 (25.29) | 0.007 |
| Prothrombin index | 70.0 (24) | 64.0 (30) | 0.049 |
| Exposure to anticoagulant | 6 (18.8%) | 20 (18.2%) | 1.000 |
| Dialysis: | 26 (60.5%) | 107 (82.3%) | 0.006 |
| Duration of dialysis | 13.5 (38.5) | 15.0 (40.0) | 0.701 |
| IGS2 | 53.0 (16.6) | 58.0 (17) | 0.560 |
| Glasgow | 15.0 (2) | 14.0 (5) | 0.036 |
| Death | 3 (6.98%) | 22 (16.9%) | 0.175 |

**Supplemental table 6: Comparison of clinical characteristics between MILA and MALA patients who underwent dialysis in the whole population (173 patients)**

|  |  |  |
| --- | --- | --- |
|  | **Dialyzed****N = 133** |  |
|  | **MILA N= 81** | **MALA N= 52** | **p.overall** |
| Death, n (%) | 7 (9) | 14 (27) | 0.010 |
| Shock, n (%) | 27 (33) | 37 (71) | <0.001 |
| CKD, n (%) | 18 (17) | 11 (21) | N.S. |
| Sepsis, n (%) | 0 | 40 (77) | <0.001 |
| Acute Heart Failure, n (%) | 0 | 8 (15) | 0.002 |
| Digestive disorders, n (%) | 65 (80) | 18 (34) | <0.001 |
| Duration of dialysis (hours) | 12 (28) | 24 (48) | 0.007 |
| Duration of dialysis > 120 hours | 2 (2) | 7 (14) | 0.13 |

Data presented as median (IQR) for quantitative variables; and percentages for qualitative variables.

**Supplemental figure 1: Univariate correlation between plasma metformin concentration and arterial pH, and lactate in 70 patients for whom plasma metformin concentration was available.**





**Supplemental figure 2: Correlation between arterial pH and lactate**



**Acknowledgments**

We owe a deep debt of gratitude to all the French nephrology and intensive care units who participed in the study, especially the French Intensive Care Renal Network (FIRN) and the following:

Eric Rondeau MD, PhD, nephrology, CHU Tenon, Paris; Ziad Massy, MD, PhD, nephrology, CHU Ambroise Paré, Paris; Alexandre Seidowsky MD, nephrology, CHU Ambroise Paré, Paris; Thomas Robert, MD, nephrology, APHM hôpital de la Conception, CHU Marseille; Stanislas Faguer MD, nephrology, CHU Toulouse; Pierre Bataille MD, nephrology, CH Boulogne sur mer; Catherine Hanrotel MD, nephrology, CHRU Brest; Eric Cardineau MD, nephrology, CH Alençon; Corinne Guibergia, MD, nephrology, CH Aix En Provence; Bernard Painchart MD, nephrology, CH Cambrai; Raymond Azar MD, nephrology, CH Dunkerque; Thierry Vanderlinden MD, intensive care unit, hôpital Saint Philibert, Lomme; Isabelle Landru, MD, nephrology, CH Lisieux; Arnaud Roccabianca MD, nephrology, CHRU Lapeyronie, Montpellier; Delphine Daubin MD, intensive care unit, CHRU Lapeyronie, Montpellier; Vincent Das MD, intensive care unit, CHI André Grégoire, Montreuil; Pierre Filipozzi MD, nephrology, CHRU Nancy; Genevieve Dumont MD, nephrology, CHR Orleans; Philippe Jousset MD, nephrology, CHCB Pontivy; Ekoué Agbonon MD, nephrology, CH Saint Quentin; Philippe Michel MD, nephrology, CH Sens; Ayman Sarraj MD, Clinique Saint Côme, Compiègne; Severine Poulain MD, intensive care unit, CHCB Bayonne; Christine Beauchamp MD, intensive care unit, CH Brive la Gaillarde; Stephane Edet MD, nephrology, CH Dieppe;  Anna Bernard MD, nephrology, CHU Dijon ; Christian Noel MD, PhD, nephrology, CHRU Lille; Maelle Allibe MD, nephrology, CH Mulhouse; Cecile Vigneau MD, PhD, nephrology, CHU Rennes; Joel Cousson MD, intensive care unit, CHU Reims; Pascal Bindi MD, nephrology, CH Verdun; Thierry Krummel MD, nephrology, CHU Strasbourg; Carole Ichai MD, PhD, intensive care unit, CHU Nice; Vincent Audard MD, PhD, nephrology, CHU Henri Mondor, Creteil; Thomas Rimmelé MD, intensive care unit, CHU Lyon;