**SUPPLEMENTARY APPENDIX for "Niacinamide may be Associated with Improved Outcomes in COVID-19 Related Acute Kidney Injury: An Observational Study"**

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**Supplemental Table 1. Baseline characteristics of the B3, Pre-B3, and SH groups**

| | B3 (n = 90) | Pre-B3 (n = 20) | SH (n = 91) |
|---|---|---|---|
| **Age (y) - mean (SD)** | 65.6 (15.2) | 65.9 (14.3) | 74.6 (11.5) |
| **Female - no. (%)** | 40 (44) | 8 (40) | 36 (40) |
| **Race - no (%)** | | | |
| White non-Hispanic | 27 (30) | 11 (55) | 80 (88) |
| Black non-Hispanic | 31 (34) | 3 (15) | 8 (9) |
| Hispanic | 13 (14) | 2 (10) | 3 (3) |
| Asian | 3 (3) | 2 (10) | 0 (0) |
| Other | 16 (18) | 2 (10) | 0 (0) |
| **BMI - mean (SD)** | 32.2 (7.9) | 31.0 (6.9) | 30.3 (8.0) |
| **Baseline Creatinine (mg/dL) - mean (SD)** | 1.20 (0.55) | 0.94 (0.39) | 1.22 (0.48) |
| **GFR <45 at baseline - no (%)** | 22 (25) | 3 (15) | 21 (23) |
| **Comorbid conditions - no (%)** | | | |
| COPD/asthma | 13 (14) | 0 (0) | 30 (33) |
| Diabetes Mellitus | 50 (56) | 6 (30) | 43 (47) |
| Hypertension | 70 (78) | 8 (40) | 86 (95) |
| HF with reduced EF | 5 (6) | 1 (5) | 9 (10) |
| Malignancy | 20 (22) | 5 (25) | 12 (13) |
| Current or former tobacco | 34 (39) | 11 (55) | 51 (56) |
| **Baseline medications - no (%)** | | | |
| Statin | 62 (69) | 8 (40) | 68 (75) |
| ACEi/ARB | 33 (37) | 6 (30) | 42 (46) |
| **In-hospital medications - no (%)** | | | |
| Hydroxychloroquine | 40 (44) | 15 (75) | 65 (71) |
| Azithromycin | 51 (57) | 12 (60) | 61 (67) |
| Remdesivir[a] | 11 (12) | 1 (5) | 1 (1) |
| Sarilumab[a] | 18 (20) | 0 (0) | 0 (0) |
| Tocilizumab | 10 (11) | 5 (25) | 8 (9) |
| **Characteristics at day of eligibility** | | | |

| | | | |
|---|---|---|---|
| Creatinine (mg/dL) - mean (SD) | 2.10 (1.32) | 1.75 (1.16) | 2.09 (1.38) |
| KDIGO AKI stage - n (%) | | | |
| Stage 1 | 68 (76) | 15 (75) | 70 (77) |
| Stage 2 | 13 (15) | 3 (15) | 13 (14) |
| Stage 3 | 8 (9) | 2 (10) | 8 (9) |
| Hemoglobin (g/dL) - mean (SD) | 10.7 (2.2) | 11.4 (2.0) | 11.4 (1.9) |
| WBC count (K/uL) - mean (SD) | 9.4 (5.2) | 10.1 (4.3) | 8.3 (4.1) |
| Platelet count (K/uL) - mean (SD) | 255 (130) | 210 (126) | 217 (104) |
| Bicarbonate (mEq/L) - mean (SD) | 23.5 (5.0) | 22.6 (6.0) | 22.6 (4.7) |
| Potassium (mEq/L) - mean (SD) | 4.38 (0.56) | 4.39 (0.61) | 4.18 (0.61) |
| On vasopressors - n (%) | 52 (58) | 9 (45) | 25 (28) |
| On mechanical ventilation - n (%) | 56 (62) | 11 (55) | 35 (39) |
| In ICU - n (%) | 63 (70) | 12 (60) | 41 (45) |

[a]Patients were enrolled in a clinical trial of remdesivir or sarilumab, and it is unknown if they were receiving study drug or placebo.
Abbreviations: SD, standard deviation; BMI, body mass index; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; HF with reduced EF, heart failure with reduced ejection fraction; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; KDIGO, Kidney Disease Improving Global Outcomes; AKI, acute kidney injury. WBC, white blood cell; ICU, intensive care unit.

**Supplemental Table 2. Associations among B3 group, pre-B3 group, and sister hospital (SH) for composite endpoint of RRT or death, death alone, and RRT alone.**

| | SH (n=91) | Pre-B3 (n=20) | p | B3 (n=90) | p |
|---|---|---|---|---|---|
| **RRT or Death** | 52 (57.1) | 10 (50.0) | | 38 (42.2) | |
| HR (95% CI) Unadjusted | ref | 0.87 (0.44 to 1.72) | 0.70 | 0.61 (0.40 to 0.93) | 0.02 |
| HR (95% CI) adjusted[a] | ref | 0.80 (0.37 to 1.74) | 0.57 | 0.61 (0.38 to 0.98) | 0.04 |
| HR (95% CI) adjusted: | | | | | |
| In patients with KDIGO1[b] | ref | 0.77 (0.48 to 1.50) | 0.57 | 0.83 (0.48 to 1.46) | 0.42 |
| In patients with KDIGO 2 or 3[c] | ref | 0.55 (0.17 to 1.82) | 0.33 | 0.26 (0.11 to 0.60) | 0.002 |
| KDIGO interaction | | | 0.65 | | 0.02 |
| **Death** | 41 (45.1) | 8 (40.0) | | 22 (24.4) | |
| HR (95% CI) Unadjusted | ref | 0.94 (0.44 to 2.01) | 0.88 | 0.44 (0.26 to 0.74) | 0.002 |
| HR (95% CI) adjusted[a] | ref | 1.07 (0.44 to 2.59) | 0.89 | 0.59 (0.33 to 1.09) | 0.09 |
| HR (95% CI) adjusted: | | | | | |
| In patients with KDIGO1[b] | ref | 1.20 (0.38 to 3.79) | 0.76 | 1.05 (0.53 to 2.11) | 0.88 |
| In patients with KDIGO 2 or 3[c] | ref | 0.69 (0.17 to 2.75) | 0.60 | 0.16 (0.05 to 0.52) | 0.002 |
| KDIGO interaction | | | 0.53 | | 0.008 |
| **RRT** | 17 (18.7) | 6 (30.0) | | 23 (25.6) | |
| HR (95% CI) Unadjusted | ref | 1.59 (0.63 to 4.02) | 0.33 | 1.23 (0.66 to 2.31) | 0.52 |
| HR (95% CI) adjusted[a] | ref | 1.26 (0.38 to 4.20) | 0.71 | 1.09 (0.51 to 2.31) | 0.83 |
| HR (95% CI) adjusted: | | | | | |
| In patients with KDIGO1[b] | ref | 1.56 (0.35 to 6.89) | 0.56 | 1.11 (0.45 to 2.75) | 0.82 |
| In patients with KDIGO 2 or 3[c] | ref | 0.68 (0.12 to 3.88) | 0.66 | 0.75 (0.23 to 2.43) | 0.64 |
| KDIGO interaction | | | 0.44 | | 0.58 |

[a]Model adjusted for age; sex; history of diabetes, hypertension, malignancy, and heart failure with reduced ejection fraction; hemoglobin, leukocyte count, platelet count, and serum creatinine, potassium, and bicarbonate on the day of eligibility; pre-admission use of HMG-CoA reductase inhibitors, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers; and intensive care unit requirement on day of eligibility. N = 89 in the SH group, 20 in the pre-B3 group, and 90 in the B3 group.

[b]Model adjusted for same variables as above. N = 68 in the SH group, 15 in the pre-B3 group, and 68 in the B3 group.
[c]Model adjusted for same variables as above. N = 20 in the SH group, 5 in the pre-B3 group, and 21 in the B3 group.

Abbreviations: RRT, renal replacement therapy; HR, hazard ratio; CI, confidence interval; KDIGO, Kidney Disease Improving Global Outcomes.

**Supplemental Table 3. Association between AKI date and primary and secondary outcomes in B3 hospital and sister hospitals.**

| | HR (95% CI) per 1 day increase in date | p |
|---|---|---|
| **B3 Hospital (During B3 Protocol) (n=90)** | | |
| Death or RRT | 1.06 (0.99 to 1.13) | 0.10 |
| Death alone | 1.03 (0.95 to 1.12) | 0.60 |
| RRT alone | 1.04 (0.96 to 1.13) | 0.34 |
| **B3 Hospital (Pre- B3 Protocol) (n=20)** | | |
| Death or RRT | 1.12 (0.92 to 1.36) | 0.25 |
| Death alone | 1.10 (0.89 to 1.37) | 0.38 |
| RRT alone | 1.04 (0.83 to 1.31) | 0.73 |
| **Sister Hospital (n=91)** | | |
| Death or RRT | 0.99 (0.96 to 1.03) | 0.75 |
| Death alone | 1.01 (0.97 to 1.05) | 0.61 |
| RRT alone | 0.96 (0.90 to 1.02) | 0.17 |

Abbreviations: RRT, renal replacement therapy; HR, hazard ratio; CI, confidence interval.

**Supplemental Table 4. Adjusted time-to-event analysis in subset of B3 group receiving one or more doses of niacinamide (per-protocol) compared to non-B3 group**

| | Non-B3 | B3 receiving niacinamide | p |
|---|---|---|---|
| **RRT or Death** | | | |
| All patients - HR (95% CI)[a] | ref | 0.55 (0.34 to 0.89) | 0.02 |
| KDIGO 1 Patients[b] | ref | 0.75 (0.41 to 1.34) | 0.34 |
| KDIGO 2/3 Patients[c] | ref | 0.27 (0.12 to 0.64) | 0.03 |
| KDIGO Interaction | | | 0.06 |
| **Death Alone** | | | |
| All patients - HR (95% CI)[a] | ref | 0.46 (0.24 to 0.86) | 0.02 |
| KDIGO 1 Patients[b] | ref | 0.75 (0.34 to 1.68) | 0.49 |
| KDIGO 2/3 Patients[c] | ref | 0.20 (0.07 to 0.61) | 0.005 |
| KDIGO Interaction | | | 0.07 |
| **RRT Alone** | | | |
| All patients - HR (95% CI)[a] | ref | 0.95 (0.48 to 1.89) | 0.88 |
| KDIGO 1 Patients[b] | ref | 1.13 (0.48 to 2.69) | 0.78 |
| KDIGO 2/3 Patients[c] | ref | 0.57 (0.19 to 1.74) | 0.32 |
| KDIGO Interaction | | | 0.34 |

[a]Model adjusted for age; sex; history of diabetes, hypertension, malignancy, and heart failure with reduced ejection fraction; hemoglobin, leukocyte count, platelet count, and serum creatinine, potassium, and bicarbonate on the day of eligibility; pre-admission use of HMG-CoA reductase inhibitors, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers; and intensive care unit requirement on day of eligibility. N = 109 in the Non-B3 group, 79 in the B3 group.
[b]Model adjusted for same variables as above. N = 83 in the Non-B3 group, 60 in the B3 group.
[c]Model adjusted for same variables as above. N = 26 in the Non-B3 group, 18 in the B3 group.

Abbreviations: RRT, renal replacement therapy; HR, hazard ratio; CI, confidence interval; KDIGO, Kidney Disease Improving Global Outcomes.

**Supplemental Table 5. Additional sensitivity analyses exploring the association between niacinamide use group and primary and secondary endpoints in the entire cohort and among KDIGO subgroups.**

| | Non-B3 | B3 | p |
|---|---|---|---|
| **Adjusted model,[a] with addition of race** | | | |
| Death or RRT, KDIGO 1 patients - HR (95% CI)[b] | ref | 0.77 (0.42 to 1.42) | 0.41 |
| Death or RRT, KDIGO 2/3 patients - HR (95% CI)[c] | ref | 0.25 (0.11 to 0.58) | 0.001 |
| KDIGO Interaction | | | 0.02 |
| Death alone, KDIGO 1 patients - HR (95% CI)[b] | ref | 1.32 (0.63 to 2.77) | 0.47 |
| Death alone, KDIGO 2/3 patients - HR (95% CI)[c] | ref | 0.23 (0.07 to 0.74) | 0.01 |
| KDIGO Interaction | | | 0.01 |
| RRT alone, KDIGO 1 patients - HR (95% CI)[b] | ref | 0.87 (0.34 to 2.25) | 0.78 |
| RRT alone, KDIGO 2/3 patients - HR (95% CI)[c] | ref | 0.52 (0.17 to 1.65) | 0.27 |
| KDIGO Interaction | | | 0.46 |
| **Adjusted model,[a] with addition of BMI** | | | |
| Death or RRT, KDIGO 1 patients - HR (95% CI)[d] | ref | 0.85 (0.48 to 1.49) | 0.56 |
| Death or RRT, KDIGO 2/3 patients - HR (95% CI)[e] | ref | 0.35 (0.15 to 0.81) | 0.01 |
| KDIGO Interaction | | | 0.08 |
| Death alone, KDIGO 1 patients - HR (95% CI)[d] | ref | 0.77 (0.55 to 2.26) | 0.77 |
| Death alone, KDIGO 2/3 patients - HR (95% CI)[e] | ref | 0.17 (0.05 to 0.56) | 0.004 |
| KDIGO Interaction | | | 0.009 |
| RRT alone, KDIGO 1 patients - HR (95% CI)[d] | ref | 1.08 (0.45 to 2.60) | 0.87 |
| RRT alone, KDIGO 2/3 patients - HR (95% CI)[e] | ref | 0.80 (0.26 to 2.42) | 0.69 |
| KDIGO Interaction | | | 0.68 |
| **Adjusted model,[a] with addition ever smoking and COPD/asthma** | | | |
| Death or RRT, KDIGO 1 patients - HR (95% CI)[f] | ref | 0.85 (0.48 to 1.53) | 0.59 |

| | | | |
|---|---|---|---|
| Death or RRT, KDIGO 2/3 patients - HR (95% CI)[g] | ref | 0.30 (0.13 to 0.68) | 0.004 |
| KDIGO Interaction | | | 0.04 |
| Death alone, KDIGO 1 patients - HR (95% CI)[f] | ref | 1.06 (0.52 to 2.19) | 0.87 |
| Death alone, KDIGO 2/3 patients - HR (95% CI)[g] | ref | 0.16 (0.05 to 0.48) | 0.001 |
| KDIGO Interaction | | | 0.006 |
| RRT alone, KDIGO 1 patients - HR (95% CI)[f] | ref | 1.15 (0.45 to 2.93) | 0.77 |
| RRT alone, KDIGO 2/3 patients - HR (95% CI)[g] | ref | 0.75 (0.26 to 2.22) | 0.61 |
| KDIGO Interaction | | | 0.55 |
| **Adjusted model,[a] excluding individuals taking or in trials of remdesivir, sarulimab, or tociluzimab** | | | |
| Death or RRT, KDIGO 1 patients - HR (95% CI)[h] | ref | 0.96 (0.46 to 1.95) | 0.91 |
| Death or RRT, KDIGO 2/3 patients - HR (95% CI)[i] | ref | 0.19 (0.06 to 0.61) | 0.005 |
| KDIGO Interaction | | | 0.02 |
| Death alone, KDIGO 1 patients - HR (95% CI)[h] | ref | 1.17 (0.50 to 2.73) | 0.72 |
| Death alone, KDIGO 2/3 patients - HR (95% CI)[i] | ref | 0.11 (0.02 to 0.62) | 0.01 |
| KDIGO Interaction | | | 0.02 |
| RRT alone, KDIGO 1 patients - HR (95% CI)[h] | ref | 1.10 (0.32 to 3.79) | 0.89 |
| RRT alone, KDIGO 2/3 patients - HR (95% CI)[i] | ref | 1.13 (0.24 to 5.33) | 0.88 |
| KDIGO Interaction | | | 0.98 |

[a]Model adjusted for age; sex; history of diabetes, hypertension, malignancy, and heart failure with reduced ejection fraction; hemoglobin, leukocyte count, platelet count, and serum creatinine, potassium, and bicarbonate on the day of eligibility; pre-admission use of HMG-CoA reductase inhibitors, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers; and intensive care unit requirement on day of eligibility.
[b]N = 83 in the Non-B3 group, 68 in the B3 group.
[c]N = 26 in the Non-B3 group, 21 in the B3 group.
[d]N = 83 in the Non-B3 group, 65 in the B3 group.
[e]N = 25 in the Non-B3 group, 18 in the B3 group.
[f]N = 83 in the Non-B3 group, 66 in the B3 group.
[g]N = 26 in the Non-B3 group, 21 in the B3 group.
[h]N = 73 in the Non-B3 group, 40 in the B3 group.
[i]N = 22 in the Non-B3 group, 11 in the B3 group.

Abbreviations: RRT, renal replacement therapy; HR, hazard ratio; CI, confidence interval; KDIGO, Kidney Disease Improving Global Outcomes; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

**Supplemental Table 6. Association between niacinamide use group and the composite endpoint and mortality in the entire cohort and among KDIGO subgroups adjusted for endpoint-specific prognostic scores.**[a]

| | Non-B3 | B3 | p |
|---|---|---|---|
| **Death or RRT** | | | |
| All patients - HR (95% CI) | ref | 0.71 (0.47 to 1.07) | 0.10 |
| KDIGO 1 patients - HR (95% CI) | ref | 0.91 (0.55 to 1.52) | 0.72 |
| KDIGO 2/3 patients - HR (95% CI) | ref | 0.38 (0.19 to 0.76) | 0.006 |
| KDIGO Interaction | | | 0.047 |
| **Death Alone** | | | |
| All patients - HR (95% CI) | ref | 0.67 (0.40 to 1.12) | 0.13 |
| KDIGO 1 patients - HR (95% CI) | ref | 1.03 (0.55 to 1.94) | 0.93 |
| KDIGO 2/3 patients - HR (95% CI) | ref | 0.25 (0.10 to 0.64) | 0.004 |
| KDIGO Interaction | | | 0.02 |

[a]Prognostic score derived as the linear predictor in proportional hazards models incorporating age; sex; history of diabetes, hypertension, malignancy, and heart failure with reduced ejection fraction; hemoglobin, leukocyte count, platelet count, and serum creatinine, potassium, and bicarbonate on the day of eligibility; pre-admission use of HMG-CoA reductase inhibitors, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers; and intensive care unit requirement on day of eligibility.

**Supplemental Table 7. Characteristics of patients with KDIGO stage 2 or 3 AKI in B3 group and non-B3 groups.**

| | Non-B3 (n=26) | B3 (n = 21) |
|---|---|---|
| **Age (y) - mean (SD)** | 69.7 (12.9) | 65.1 (16.2) |
| **Female - no. (%)** | 10 (39) | 11 (52) |
| **Race - no (%)** | | |
| White non-Hispanic | 20 (77) | 5 (24) |
| Black non-Hispanic | 4 (15) | 5 (24) |
| Hispanic | 1 (4) | 4 (19) |
| Asian | 0 (0) | 2 (10) |
| Other | 1 (4) | 5 (24) |
| **BMI - mean (SD)** | 30.4 (7.6) | 32.5 (8.1) |
| **Baseline Creatinine (mg/dL) - mean (SD)** | 1.19 (0.65) | 1.09 (0.66) |
| **GFR <45 at baseline - no (%)** | 5 (20) | 5 (24) |
| **Past diagnoses - no (%)** | | |
| COPD/asthma | 5 (19) | 2 (10) |
| Diabetes Mellitus | 16 (62) | 12 (57) |
| Hypertension | 21 (81) | 15 (71) |
| HF with reduced EF | 4 (15) | 2 (10) |
| Malignancy | 5 (19) | 5 (24) |
| Current or former tobacco | 15 (58) | 9 (43) |
| **Baseline medications - no (%)** | | |
| Statin | 16 (62) | 13 (62) |
| ACEi/ARB | 13 (50) | 6 (29) |
| **In-hospital medications - no (%)** | | |
| Hydroxychloroquine | 16 (62) | 8 (38) |
| Azithromycin | 18 (69) | 7 (33) |
| Remdesivir[a] | 1 (4) | 1 (5) |
| Sarilumab[a] | 0 (0) | 5 (24) |
| Tocilizumab | 3 (12) | 4 (19) |

| | | |
|---|---|---|
| **Characteristics at day of eligibility** | | |
| Creatinine (mg/dL) - mean (SD) | 3.26 (2.21) | 3.09 (2.21) |
| KDIGO AKI stage - n (%) | | |
| Stage 1 | - | - |
| Stage 2 | 16 (62) | 13 (62) |
| Stage 3 | 10 (38) | 8 (38) |
| Hemoglobin (g/dL) - mean (SD) | 11.3 (2.2) | 10.2 (2.2) |
| WBC count (K/uL) - mean (SD) | 10.5 (5.3) | 13.7 (6.3) |
| Platelet count (K/uL) - mean (SD) | 235 (131) | 271 (122) |
| Bicarbonate (mEq/L) - mean (SD) | 21.7 (5.9) | 22.7 (4.5) |
| Potassium (mEq/L) - mean (SD) | 4.35 (0.85) | 4.29 (0.67) |
| On vasopressors - n (%) | 10 (40) | 16 (76) |
| On mechanical ventilation - n (%) | 13 (50) | 17 (81) |
| In ICU - n (%) | 15 (58) | 20 (95) |

[a]Patients were enrolled in a clinical trial of remdesivir or sarilumab, and it is unknown if they were receiving study drug or placebo.
Abbreviations: SD, standard deviation; BMI, body mass index; eGFR, estimated glomerular filtration rate; COPD, chronic obstructive pulmonary disease; HF with reduced EF, heart failure with reduced ejection fraction; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; KDIGO, Kidney Disease Improving Global Outcomes; AKI, acute kidney injury. WBC, white blood cell; ICU, intensive care unit.

**Supplement 1. Supplemental Methods**

**Study Oversight**

The Institutional Review Board (IRB) at Beth Israel Deaconess Medical Center determined that the niacinamide protocol was considered treatment, not research, and no individual patient consent was required. The IRBs at Beth Israel Deaconess Medical Center and Lahey Hospital approved data collection from the electronic health record (EHR) at each institution. Interim safety and outcome data were evaluated weekly by an independent committee.

**Electronic Medical Record (EMR) Data Extraction**

Data extracted from the EMR included the following: age; sex; self-reported race and ethnic group; historical diagnoses, smoking status, and pre-admission medications; and first body mass index (BMI) documented. Creatinine was documented daily as the closest value to 07:00. On the day that eligibility criteria were met, values closest to 07:00 were extracted for hemoglobin, leukocyte count, and platelet count; serum bicarbonate and potassium; and intensive care requirement. Administered medications, defined as one or more documented events in the EMR, were extracted; remdesivir and sarilumab were administered in clinical trials, so it is not known whether these patients received study drug or placebo.

**Determination of Baseline Creatinine and Glomerular Filtration Rate (GFR), Acute Kidney Injury (AKI), and Creatinine at time of RRT**

Among the B3 group, baseline serum creatinine in 52/90 (58%) individuals was determined by the most recent serum creatinine in the 7-365d prior to admission, 33/90 (37%) by the lowest value in the first 96h. Four out of ninety (4%) required additional chart review including review of creatinine values prior to 365d before admission, and 1/90 could not be determined. Among the

non-B3 group, baseline serum creatinine in 74/111 (66%) individuals was determined by the 7-365d technique, 29/111 (26%) by the first 96h technique, 7/111 (6.3%) through additional chart review, and 1/111 could not be determined. Distributions were not significantly different between B3 and non-B3 groups (chi square, p= 0.26). Baseline eGFR was calculated using the CKD-EPI equation.[1]

AKI was defined based on Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine guidelines:

- **Stage 1 AKI**: Increase in serum creatinine by ≥ 0.3 mg/dL within 48 hours or increase in SCr 1.5 to 1.9 times baseline which is known or presumed to have occurred within the prior 7 days.
- **Stage 2 AKI**: Increase in serum creatinine to 2.0 to 2.9 times baseline.
- **Stage 3 AKI**: Increase in serum creatinine to 3.0 times baseline or increase in serum creatinine to ≥ 4.0 mg/dL or initiation of renal replacement therapy.

Creatinine at time of renal replacement therapy (RRT) was defined as the value preceding 07:00 on the day of initiation of either hemodialysis or continuous renal replacement therapy. There was no significant difference in mean serum creatinine at the time of RRT initiation (4.78mg/dL in the non-B3 group, 5.63mg/dL in the B3 group; t-test, p=0.22).

**Supplemental Statistical Analysis Information**

**Power Analysis**: Based on a two-sided time-to-event analysis with assumptions of a hazard ratio of 0.6 and an event probability of 0.7 (resulting in a sample size requirement of 172, with

50% in the niacinamide group and 50% in the non-niacinamide group), initial analysis was planned when data on 90 individuals in each arm were available.

**Additional Statistical Test Information**: All analyses were performed as two-sided tests. We calculated frequencies for categorical variables and mean +/- standard deviation for continuous variables to examine baseline characteristics among the B3 and non-B3 groups. Differences among groups were evaluated using Fisher's exact tests for categorical variables and t-tests for continuous variables. We tested the proportional hazards assumption with a time to interaction term and observed no significant departures ($p>0.17$).

**Sensitivity analysis**: We adjusted for variables excluded initially from the primary analysis due to modest degrees of missing data using Cox Proportional Hazards Models as described in the main text. We also used Cox Proportional Hazards Models to examine the association of calendar date with outcome. To ensure our results were robust to the number of predictor variables used, we performed an analysis including B3 group and an endpoint-specific prognostic score derived as the linear predictor from a separated Cox model using the variables from the primary multivariable model for both the composite outcome and mortality,[2] excluding individuals at both disjoint extremes of the distribution of the prognostic score to further reduce uncontrolled confounding.[3]

**Supplement 2. Study Protocol**

**Sponsor:** None

**Protocol Title:** Treatment of acute kidney injury associated with COVID-19 disease using Niacinamide

**Study Objectives:**
**Primary Objective:** To assess the safety and efficacy of oral niacinamide at 1 gm/day for 7 days in patients hospitalized with novel SARS-CoV-2 (COVID 19) disease for reducing the composite outcome of mortality and renal replacement therapy (RRT).
**Secondary Objective:** To assess the effects of niacinamide on (1) mortality alone, (2) RRT alone, and (3) creatinine trajectory over the 10 days following AKI.

**Study Outcomes:**

Primary Efficacy Outcomes:

1. Composite of mortality and RRT within a single hospitalization

Primary Safety Outcome:

1. Proportion of subjects developing acute liver injury defined as a rise of 3x in alanine aminotransferase (ALT) from the time of meeting eligibility criteria
2. Proportion of subjects developing other complications associated with niacinamide use

Secondary Efficacy Outcomes:

1. Mortality alone within a single hospitalization
2. RRT alone within a single hospitalization
3. Creatinine trajectory over 10 days following eligibility

**Study Population**: Hospitalized adult patients with COVID-19 disease and AKI at two tertiary care hospitals in Boston

**Study Design**:
This is an open-label elective treatment protocol to prescribe niacinamide in COVID-19 patients affected by AKI. Eligible patients will have clinically suspected COVID-19 or PCR-confirmed SARS-CoV-2 infection, be hospitalized, and have AKI as defined by field-standard KDIGO criteria. Patients with end-stage renal disease, and patients with AST or ALT greater than 5x the upper limit of normal will be excluded. Pregnant patients can be considered on a casewise basis, as there are minimal adverse effects in models but it does cross the placenta. Kidney transplant recipients are eligible.

Hospitalized COVID-19 patients not meeting exclusion criteria will be monitored daily for development of AKI based on laboratory values drawn as part of their routine clinical care. Should they develop AKI, we will contact the primary team caring for the patient by page and templated electronic medical record note to report their eligibility for niacinamide and discuss potential risks and benefits of commencing niacinamide. Patients identified as potentially benefitting will receive 1g PO niacinamide daily, starting as close to time of enrollment as possible and continuing for up to 7 days (7 total doses), administered by the nursing staff responsible for the participating patient's routine care. Laboratory assessments, which include creatinine, BUN, and ALT, will be collected daily by their primary medical team for the length of

their hospitalization, unless otherwise indicated. Treatment will be discontinued if ALT rises to greater than 3x their baseline at time of study eligibility, or at the discretion of their primary medical team.

Data on outcomes will be collected by retrospective chart review of the electronic medical record.

**Number of Subjects Planned:** Initial analysis to be conducted after the first 90 patients are found to be eligible for niacinamide and have been followed for primary and secondary outcomes for at least 10 days.

**Duration of Treatment**: 7 days

**Duration of Participation:** 7 days

**Eligibility Criteria:**

Inclusion Criteria:

1. COVID-19 disease, as defined by as positive SARS-CoV-2 test
2. AKI, defined as an increase in creatinine by 0.3mg/dL from their previously established baseline OR a 50% increase from their previously established baseline, NOT INCLUDING patients with AKI on their initial labs which resolved without to their previous baseline within 96h of an initial fluid bolus WITHOUT any non-negative interval changes in creatinine.

Exclusion Criteria:

1. Patients with End Stage Renal Disease or stage 5 chronic kidney disease
2. Patients with ALT greater than 5x the upper limit of normal (200IU/L)
3. Patient with documented allergy to the study medication
4. Pregnant patients (to be considered on a case-by-case basis)

**General Statistical Methods and Types of Analyses:**

**Sample size power calculation:**
Based on a two-sided time-to-event analysis with assumptions of a hazard ratio of 0.6 and an event probability of 0.7 (resulting in a sample size requirement of 172, with 50% in the niacinamide group and 50% in the non-niacinamide group), initial analysis was planned when data on 90 individuals in each arm were available.

**Primary endpoint analysis:**
Differences among groups in time to event analysis primary outcome will be conducted using Kaplan-Meier curves with log rank test used to calculate hazard ratios. Cox proportional-hazards regression models will be used to estimate the adjusted association between B3 group and the primary composite endpoint, with adjustments planned for the following variables pending evaluation for factors such as co-linearity and missing data:

- Age
- Sex
- Body mass index (BMI)
- The following comorbidities:

    - Diabetes
    - Hypertension
    - Chronic obstructive pulmonary disease or asthma
    - Systolic heart failure
    - Malignancy
    - Liver disease or cirrhosis
- Former or current tobacco smoking
- Pre-admission use of the following medications:
    - HMG-CoA reductase inhibitors
    - Angiotensin converting enzyme inhibitors or angiotensin receptor blockers
- Use during hospitalization of the following medications
    - Hydroxychloroquine
    - Azithromycin
    - Remdesivir (or trial enrollment)
    - Sarilumab (or trial enrollment)
    - Tocilizumab
- Laboratory values at time of study eligibility
    - Leukocyte count
    - Platelet count
    - Hemoglobin
    - Serum creatinine
    - Serum potassium
    - Serum bicarbonate
- Intensive care unit (ICU) requirement
    - Pressor requirement (if not too colinear with ICU requirement)
    - Mechanical ventilation requirement (If not too colinear with ICU requirement)

Additionally, an *a priori* subgroup analysis by severity of AKI with individuals with Kidney Disease Improving Global Outcomes (KDIGO) stage 2 or 3 AKI analyzed separately from individuals with KDIGO stage 1 AKI is planned, as is an *a priori* subgroup analysis by ICU requirement.

Analyses will be performed with two-sided tests.

**Secondary endpoint analysis:**
Differences among groups in time to event analysis for RRT alone and death alone will be conducted using the same protocol as above for the composite outcome. A generalized estimating equation (GEE) model with an exchangeable correlation matrix will be used to evaluate the secular trend in serum creatinine in the 10 days following the day of eligibility.

Similar to the primary analysis, stratified analysis by KDIGO stage and ICU requirement are planned.

**Other analyses**
Comparisons among groups of baseline variables will be conducted using Fisher's exact tests for categorical variables and t-tests for continuous variables. Sensitivity analysis for the impact of secular trends on outcomes are also planned with models evaluating the association of calendar date with the primary outcome within each treatment group.

**Study Medication:** Niacinamide 500 mg tablet supplied by Rugby Pharmaceuticals

**Dose and Regimen**: Two tablets (1000mg total) Niacinamide once daily for up to 7 days per oral.

**Early Cessation of Therapy**:
Niacinamide will be halted if:

1. ALT rises to greater than 3x their baseline at time of niacinamide eligibility
2. At the discretion of their primary medical team

## SUPPLEMENTAL REFERENCES

1. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604-12.
2. Hansen BB. The prognostic analogue of the propensity score. Biometrika 2008;95:481-8.
3. da Costa BR, Gahl B, Juni P. Tools & techniques--statistics: propensity score techniques. EuroIntervention 2014;10:761-7.