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Niacinamide may be Associated with Improved Outcomes in COVID-19 Related Acute Kidney Injury: An Observational Study

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ABSTRACT

Background: Acute kidney injury (AKI) is a significant complication of Coronavirus Disease 2019 (COVID-19), with no effective therapy. Niacinamide, a vitamin B3 analog, has some evidence of efficacy in non-COVID-19-related AKI. The objective of this study is to evaluate the association between niacinamide therapy and outcomes in patients with COVID-19-related AKI.

Methods: We implemented a quasi-experimental design with non-random, prospective allocation of niacinamide in 201 hospitalized adult patients, excluding those with baseline estimated glomerular filtration rate <15 ml/min/1.73m^2 on or off dialysis, with COVID-19-related AKI by Kidney Disease Improving Global Outcomes (KDIGO) criteria, in two hospitals with identical COVID-19 care algorithms, one of which additionally implemented treatment with niacinamide for COVID-19-related AKI. Patients on the niacinamide protocol (B3 patients) were compared against patients at the same institution before protocol commencement and contemporaneous patients at the non-niacinamide hospital (collectively, non-B3 patients). The primary outcome was a composite of death or renal replacement therapy (RRT).

Results: 38/90 B3 patients and 62/111 non-B3 patients died or received RRT. Using multivariable Cox proportional hazard modeling, niacinamide was associated with a lower risk of RRT or death (HR 0.64, 95% CI 0.40 to 1.00, p=0.05), an association driven by patients with KDIGO stage 2/3 AKI (HR 0.29, 95% CI 0.13 to 0.65, p=0.03; p interaction with KDIGO stage 0.03). Total mortality also followed this pattern (HR 0.17, 95% CI 0.05-0.52 in KDIGO 2/3 patients, p=0.002). Serum creatinine following AKI increased by 0.20 (SE 0.08) mg/dL/day among non-B3 patients with KDIGO 2/3 AKI but was stable among comparable B3 patients (+0.01 (SE 0.06) mg/dL/day; p interaction 0.03).

Conclusions: Niacinamide was associated with lower risk of RRT/death and improved creatinine trajectory among patients with severe COVID-19-related AKI. Larger randomized studies are necessary to establish a causal relationship.

INTRODUCTION

Coronavirus Disease 2019 (COVID) has led to over 1,250,000 deaths worldwide and affects a host of organs including the kidneys. The etiology of COVID-related AKI is likely multifactorial, but most often exhibits an acute tubular injury pattern.[1] Acute tubular injury arises from inflammatory, ischemic, or nephrotoxic stressors. Consequences of COVID-related AKI include severe shortages of dialysis machines and fluids, strained nursing resources, and increased mortality.[2,3]

Previous work links non-COVID AKI arising in the context of renal ischemia and acute tubular necrosis to an acquired renal deficiency of the energy metabolism intermediate nicotinamide adenine dinucleotide (NAD+), a rate limiting substrate for oxidative metabolism in mitochondria, through accelerated hydrolysis and decreased biosynthesis.[4,5] In the mitochondria-rich renal tubule, stress-induced NAD+ shortage curtails ATP production, which if unchecked, can culminate in tubular dysfunction and cell death.[5] A pilot randomized, placebo-controlled trial suggested that oral niacinamide could safely increase NAD+ and potentially prevent AKI among perioperative patients, but it has not been tested in COVID-related AKI.[4] There are no therapies for AKI prevention approved by the US Food and Drug Administration (FDA).

Niacinamide, the base form of vitamin B_3, is an FDA “generally recognized as safe” (GRAS) nutritional supplement whose safety at chronic high doses has been established in trials for other indications.[4,5] Given its safety, immediate availability, and limited but encouraging evidence of efficacy in non-COVID AKI, we implemented a niacinamide protocol for patients with AKI at a single hospital in Boston designed to prevent progression of AKI and development of related complications.

In this report, we compare rates of progression to renal replacement therapy and death and trends in serum creatinine among patients with COVID-related AKI on the niacinamide protocol against patients both admitted at the niacinamide hospital prior to implementation and contemporaneously admitted at a non-intervention hospital. We hypothesized that administration of oral niacinamide would prevent progression and reduce complications associated with COVID-related AKI.

METHODS

Setting

We conducted this study at two large tertiary acute care teaching hospitals within the Beth Israel Lahey Health System (BILH) that admitted comparable numbers of COVID-19 patients during the study period (**Figure 1**). One hospital implemented the niacinamide protocol as a routine part of clinical care on the basis of data in post-operative AKI.[4] Both hospitals otherwise utilized a single COVID-19 care algorithm common to BILH.

Study design and oversight

We employed a quasi-experimental design, chosen for its ability to be rapidly implemented using existing resources and preserve eligibility for other potential life-saving therapies available only through clinical trials.[6] Oversight is described in **Supplemental Methods**.

Eligibility criteria

We included hospitalized patients who developed persistent AKI, were at least 18 years old, had laboratory-confirmed positive SARS-CoV-2 PCR test from a nasopharyngeal swab, and were admitted to either hospital between March 15 - April 20, 2020. “Persistent AKI” was defined as 0.3 mg/dL or greater increase in serum creatinine over baseline, excluding individuals with AKI on admission that resolved to baseline with routine supportive care within 96 hours. These AKI criteria were employed to enable implementation in a pragmatic fashion, with a 96-hour cutoff chosen to decrease the likelihood of including patients with prerenal azotemia. Individuals with baseline estimated glomerular filtration rate (eGFR) <15 ml/min/1.73m^2 both on and off dialysis or those who elected to receive comfort measures only (CMO) up to 48 hours after development of AKI were excluded. Given the hepatic metabolism of niacinamide, individuals with ALT > 5 times the upper limit of normal (200 IU/L) were excluded.

Protocol implementation

The dose of niacinamide was informed by trials with long-term exposure in patients without kidney disease[7-9] and in patients with advanced kidney disease[10,11] that affirmed its safety. Beginning April 2, 2020, nephrologists at the niacinamide protocol hospital performed daily chart review of all COVID-19+ inpatients to determine whether they met eligibility criteria. Once a patient became eligible, care teams were contacted with a templated note and by pager with the elective recommendation to begin oral niacinamide, 1 g once daily, for a 7-day course; patients could receive doses through orogastric or nasogastric feeding tubes if needed. A total of 79/90 eligible patients (87.8%) received one or more niacinamide doses. Niacinamide was stopped in patients whose ALT rose > 3 times their value on the day of eligibility. Care teams could also discontinue niacinamide at their discretion.

Data sources and variables assessed

Data were obtained by review of the electronic medical record (EMR). Baseline creatinine was defined as the most recent serum creatinine in the 7 – 365 days prior to admission; when none was available, the lowest creatinine value within the first 96 hours of hospitalization was used. Severity of AKI was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) creatinine-based criteria.[12] Further details are provided in **Supplemental Methods.**

Exposure and comparison group designation

Eligible patients developing AKI on or after April 1, 2020 in the niacinamide protocol hospital were designated the “B3" group; those who developed AKI before April 1 were designated the “pre-B3” group. Eligible patients at the sister hospital not implementing the niacinamide protocol were designated the “SH” group. The pooled pre-B3 group and SH group was designated the “non-B3” group.

Endpoints

The primary endpoint was the time in days from date of eligibility to RRT or death, whichever occurred first, during the hospitalization.[13] Data collection was censored at time of hospital discharge or on May 1, 2020; censoring events are reported in **Figure 2**. Secondary endpoints were time in days from date of eligibility to death alone and RRT alone and change in serum creatinine over the 10 days following the date of eligibility, with censoring at time of RRT, death, or discharge.

Statistical analysis

Multivariable Cox proportional-hazards regression models were used to estimate the adjusted association between B3 group and the primary composite endpoint, as well as secondary endpoints of death alone and RRT alone. Models included age, sex, comorbid conditions, medications taken prior to admission, laboratory values on day of eligibility, and whether individuals received ICU level care. Variables included in the multivariate model were selected based on biological plausibility and clinical relevance. Laboratory measurements were taken from distinct samples. Analyses were performed on an intention to treat basis. Two patients missing one or more covariates were excluded from multivariate analyses.

We designed one *a priori* subgroup analysis, comparing individuals with KDIGO stage 1 versus KDIGO stage 2 or 3 AKI using a multiplicative interaction term. One additional patient with missing baseline creatinine was excluded from these analyses.

Our secondary analysis employed a generalized estimating equation (GEE) model with an exchangeable correlation matrix to evaluate the secular trend in serum creatinine in the 10 days following the day of eligibility. Similar to the primary analysis, we evaluated patients in KDIGO stages 2 and 3 separately from stage 1 patients. Additional details including sensitivity analyses are reported in **Supplemental Methods**. Statistical analyses were performed with SAS software, version 9.4.

RESULTS

Characteristics of cohorts

A total of 441 patients with COVID-19 were admitted to the intervention hospital and 412 to the non-intervention hospital between March 15 – April 19, 2020 (**Figure 1**). Of these,

approximately one-quarter developed persistent AKI at each hospital. Following exclusions, 90 patients were included in the B3 group and 111 in the non-B3 group, of which 20 were pre-B3 group and 91 were from the SH.

Baseline creatinine and the proportion of patients with a baseline eGFR < 45 ml/min/1.73m^2 were similar between the B3 and non-B3 groups (**Table 1**). The frequency of AKI and distribution of AKI severity at the time of eligibility were also similar. Groups differed according to age, race, COPD/asthma, smoking history, and administration of other COVID-19-targeted therapies during the same hospitalization. On the date of meeting eligibility, creatinine and AKI stage were similar across groups. Groups differed by hemoglobin, platelet count, potassium level, requirement for ICU level care, and vasopressor medication support. **Supplemental Table 1** shows baseline characteristics with the pre-B3 and SH groups separated.

Primary Endpoint

Over a median follow up of 11 days following the date of eligibility (13 days in the B3 group, 9 days in the non-B3 group), 71 of 201 patients (35.3%) died and 46 of 201 (22.9%) received renal replacement therapy across all groups. **Table 2** reports the proportion of patients meeting the primary endpoint as well as each component separately in each group. Unadjusted time-to-event analysis demonstrated significantly lower hazard for the composite endpoint of RRT or death in the B3 group compared with the non-B3 group, with particularly lower risk in the subset of patients with KDIGO AKI stage 2 or 3 (hazard ratio [HR] 0.62, 95% confidence interval [CI] 0.42 to 0.94 among all patients, HR 0.29 95%CI 0.13 to 0.65 among KDIGO 2/3 patients, **Table 2, Figure 2**). The corresponding multivariable HR for all patients was 0.64 (95% CI 0.40 to 1.00, **Table 2**).

The adjusted association between risk of RRT or death and niacinamide implementation was significantly modified by KDIGO stage at the time of eligibility (p interaction = 0.03). Among patients with KDIGO 1 AKI, we observed no reduced hazard for death or RRT. In contrast, niacinamide was associated with lower risk of the primary outcome among patients with more severe AKI (**Table 2**)**.**

Secondary Endpoints

When components of the composite endpoint were analyzed separately, the association with death was similar to that for the combined endpoint. As with the primary outcome, the association of niacinamide with mortality was significantly modified by KDIGO stage (p interaction = 0.008), with no significant association among patients in KDIGO stage 1 AKI, but approximately 80% lower hazard among KDIGO stage 2/3 patients in the B3 group compared to the non-B3 group. The corresponding estimates for RRT alone were all non-significant.

Creatinine on the day of eligibility was similar between the B3 and non-B3 groups (**Table 1**). Over the 10 days following eligibility, we did not observe an overall significant difference in creatinine trends between the B3 and non-B3 groups (p = 0.54). However, like the primary composite endpoint and mortality, there were apparent differences based on AKI severity.

Among patients with KDIGO 2/3 AKI, creatinine values were similar in both groups on the day of eligibility (3.16 mg/dL in B3, 3.17 in non-B3, p=0.99). These values increased significantly over the ensuing 10 days in the non-B3 group by an average of 0.20 (SE 0.08) mg/dL/day, while they remained flat in the B3 group (change of 0.01 (SE 0.06) mg/dL/day, p = 0.89). The adjusted difference in these trends was statistically significant (p = 0.03). In contrast, creatinine demonstrated no significant linear trend over 10 days among patients with KDIGO stage 1 AKI,

regardless of treatment group (change of 0.003 (SE 0.04) mg/dL/day in the non-B3 group, 0.007 (SE 0.02) in the B3 group, p = 0.93).

Safety

Nine of 79 (11.4%; 95% CI 5.3 to 20.5%) individuals receiving niacinamide in the B3 group had the medication stopped because of a threefold increase in ALT compared to the first day they received niacinamide. Transaminitis (ALT >200 IU/L) occurred in 13/88 individuals (14.8%; 95% CI 7.4 to 22.2%) in the B3 group who had at least 1 ALT value measured post-AKI. No other adverse events were reported in the B3 group. Whereas ALT was measured within 24 hours of the day of eligibility and at least once in the 10d afterward in 88/90 (98%) of B3 group, these data were available in only 49/91 (54%) of the SH group.

Sensitivity analyses

Supplemental Table 2 repeats the time-to-event analyses in **Table 2**, but with the pre-B3 and SH groups analyzed separately. We observed no significant difference between the pre-B3 and SH groups for any outcome.

We examined the association of calendar date with outcome in each treatment group and found no confounding by ongoing secular trends (**Supplemental Table 3**).

Analysis of the 79 patients within the B3 group who actually received niacinamide showed similar reduced hazard for the primary endpoint in the adjusted time-to-event analysis when compared with the non-B3 group (**Supplemental Table 4)**.

Repeated primary analyses with additional adjustment or exclusions to ensure robustness yielded highly concordant results (**Supplemental Table 5**), as did analyses using a single prognostic score covariate in place of separated covariates in the model **(Supplemental Table 6).** Baseline characteristics of the B3 and non-B3 groups in the subset of individuals with KDIGO AKI stage 2/3 are shown in **Supplemental Table 7.**

DISCUSSION

In this quasi-experimental study conducted in two large hospitals, implementation of a niacinamide protocol among COVID-19 AKI patients was associated with lower risk for the composite of RRT or death, driven primarily by a lower risk among the subset of patients with KDIGO stage 2 or 3 AKI. Secondary endpoint analysis showed that the difference in composite outcome was driven by mortality and not RRT. Patients with KDIGO 2/3 AKI in the B3 group demonstrated stable creatinine in the 10 days after diagnosis, whereas those in the non-B3 group had increasing creatinine by an average of 0.2 mg/dL/day.

COVID-19 AKI affected 27% of patients hospitalized with COVID-19 across the two institutions in this study. This proportion is between the 22% and 36% described among hospitalized patients in reports from New York City.[14,15] Given the substantial increase in mortality reported with AKI in hospitalized COVID-19 patients, the high frequency of AKI represents a profound risk among already vulnerable patients.

The renal tubule is a known target of non-COVID-19 AKI, requiring constant energy from mitochondria for active solute transport. Ischemic, inflammatory, and toxic stressors reduce renal NAD+, compromising transport function.[5,16] Part of this shortfall may result from a local decrease of niacinamide and other biosynthetic precursors.[4,5,17] If this energetic deficit persists, acute tubular injury arises. Our results demonstrate that niacinamide supplementation had no significant association with measured outcomes in patients with KDIGO stage 1 AKI. On average these individuals had no net increase in serum creatinine after meeting eligibility regardless of niacinamide administration, suggesting that they were likely to recover on their own regardless of therapy. Although speculative, individuals with mild AKI may not be sufficiently NAD+ deficient to benefit from NAD+ boosting. Consistently, experimental AKI

models exhibit a proportional relationship between renal NAD+ reduction and AKI severity.[5] Of note, results from the RECOVERY trial demonstrate a similar trend for dexamethasone and mortality, with benefit seen only among sicker patients.[18]

The absence of association between niacinamide and RRT is notable. Three potential factors that may have contributed to this finding. First, all patients in our study have AKI, and hence mortality among patients with AKI essentially is a test of AKI prognosis. Second, as we discuss in our limitations below, timing of RRT may be less objective than mortality. Third, while we observed a strong association with mortality, we also observed a statistically significant association with improved creatinine trend. Creatinine trend and death may provide objective 'bookend' indicators of the true effect, which is likely to be moderate.

Experimental results suggest that NAD+ augmentation may not only protect the kidney, but also fortify brain, heart, lung, liver, and even vasculature against disease.[19] Safety analyses showed that, despite the subset of patients with AKI being sicker than the overall hospitalized COVID-19 patient population, rates of transaminitis in individuals receiving niacinamide were comparable to those reported previously, although true rates of liver injury from COVID-19 remain poorly understood.[20] While this study was focused on renal outcomes, the association of niacinamide with a reduction in mortality among severely ill patients supports further investigation of NAD+ augmentation in preventing and treating extrarenal complications of COVID-19.

Until an effective vaccine for COVID-19 is available, modulating host susceptibility to adverse outcomes will also remain important. Compared to pharmacologic modulation of host susceptibility—e.g., with IL-6 inhibition—niacinamide is distinguished by its unique safety profile as a GRAS nutritional supplement and its inexpensiveness. High dose niacinamide has been safely administered for months to patients with advanced CKD.[10] Compared to other NAD+

precursors, niacinamide also has the theoretical advantage of inhibiting stress-induced enzymes such as CD38 and poly-ADP ribose polymerases that hydrolyze NAD+ and may be deleterious to organ function.[19]

Our study has important limitations. Niacinamide outcomes reflect a single center experience. We made a practical decision to offer niacinamide as standard treatment, precluding placebo controls. Our comparators were therefore either historical from the same hospital or contemporary from another hospital. This precludes determination of causality. There was a significant age disparity between the B3 and non-B3 groups, as well as disparity in race, certain comorbidities, concurrent therapies, and rates of intensive care utilization. We performed statistical adjustments to address these differences, and while age and certain comorbidities were significantly associated with outcomes, they did not substantially alter the association between B3 and our composite endpoint, mortality alone, or creatinine trends following AKI. Of note, the age discrepancy was mitigated in the subset of patients with KDIGO 2/3 AKI, among whom the associations were strongest. We also performed separate sensitivity analyses for variables of interest that could not be included in the primary multivariate model, all of which yielded similar results. Unmeasured confounding is nonetheless still likely to have affected our results; the majority of patients in the non-B3 group were not at the same hospital as the B3 group, introducing different processes of care despite the use of the same COVID-19 care algorithm. Availability of prior creatinine values to determine an accurate baseline was variable, and may have led to misclassification of AKI, particularly in the KDIGO 1 group. Furthermore, while KDIGO guidelines support the use of a baseline creatinine against which to evaluate in-hospital changes, we acknowledge that application of a 0.3 mg/dl change could include too many individuals with modest creatinine elevation that is not consistent with AKI. However, inclusion of such individuals is balanced between the groups and would tend to bias the results toward the null. Timing of RRT initiation can be subjective, which in the context of an open-label

trial introduces the potential for bias. However, mean serum creatinine at the time of RRT initiation was indistinguishable between the groups. Moreover, mortality was the primary driver of the composite endpoint rather than time to RRT initiation, which did not significantly differ between institutions. The large effect size on the composite outcome and mortality alone we report in the KDIGO 2/3 group should not be considered definitive evidence of the magnitude of niacinamide's effect in this group. Finally, the number of patients was relatively small, increasing the likelihood that the large differences observed here may not hold when applied to a broader population. Only a large randomized trial can establish whether niacinamide positively affects outcomes in COVID-related AKI.

This quasi-experimental study found that niacinamide administered for the prevention of COVID-19-related AKI progression was safe and associated with reduced estimated risk of death or the need for RRT compared to historical controls and contemporaneous patients from a sister hospital. The association was strongest in severe AKI. Creatinine levels also stabilized among patients with severe AKI receiving niacinamide. Larger randomized studies of niacinamide in COVID-19 patients are needed to confirm these apparent benefits.

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Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author SMP, pending approval from our institutional review board. The data are not publicly available as they contain information that could compromise research participant privacy.

SUPPLEMENTAL MATERIALS TABLE OF CONTENTS

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Table 1. Characteristics of patients in the B3 group and non-B3 group.

	Non-B3 (n = 111)	B3 (n = 90)
Age (y) - mean (SD)	73.1 (12.4)	65.6 (15.2)
Female - no. (%)	44 (40)	40 (44)
Race - no (%)		
White non-Hispanic	91 (82)	27 (30)
Black non-Hispanic	11 (10)	31 (34)
Hispanic	5 (5)	13 (14)
Asian	2 (2)	3 (3)
Other	2 (2)	16 (18)
BMI - mean (SD)	30.4 (7.8)	32.2 (7.9)
Baseline Creatinine (mg/dL) - mean (SD)	1.17 (0.47)	1.20 (0.55)
eGFR < 45 ml/min/1.73m^2 at baseline - no (%)	24 (22)	22 (25)
Past diagnoses - no (%)		
COPD/asthma	30 (27)	13 (14)
Diabetes Mellitus	49 (44)	50 (56)
Hypertension	94 (85)	70 (78)
HF with reduced EF	10 (9)	5 (6)
Malignancy	17 (15)	20 (22)
Current or former tobacco	62 (56)	34 (39)
Baseline medications - no (%)		
Statin	76 (69)	62 (69)
ACEi/ARB	48 (43)	33 (37)
In-hospital medications - no (%)		
Hydroxychloroquine	80 (72)	40 (44)
Azithromycin	73 (66)	51 (57)
Remdesivir[a]	2 (2)	11 (12)
Sarilumab[a]	0 (0)	18 (20)
Tocilizumab	13 (12)	10 (11)
Characteristics at day of eligibility		
Creatinine (mg/dL) - mean (SD)	2.02 (1.35)	2.10 (1.32)

KDIGO AKI stage - n (%)		
Stage 1	85 (77)	68 (76)
Stage 2	16 (14)	13 (15)
Stage 3	10 (9)	8 (9)
Hemoglobin (g/dL) - mean (SD)	11.4 (1.90)	10.7 (2.19)
WBC count (K/uL) - mean (SD)	8.62 (4.16)	9.41 (5.20)
Platelet count (K/uL) - mean (SD)	216 (108)	255 (130)
Bicarbonate (mEq/L) - mean (SD)	22.6 (4.93)	23.5 (4.97)
Potassium (mEq/L) - mean (SD)	4.22 (0.61)	4.38 (0.56)
On vasopressors - n (%)	34 (31)	52 (58)
On mechanical ventilation - n (%)	46 (41)	56 (62)
In ICU - n (%)	53 (48)	63 (70)

[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.

Table 2. Association between Niacinamide Use Group and Primary and Secondary Endpoints in the Entire Cohort and among KDIGO Subgroups.

	Non-B3 (n = 111)	B3 (n = 90)	p
RRT or Death	62 (55.9)	38 (42.2)	
HR (95% CI) Unadjusted	Ref	0.62 (0.42 to 0.94)	0.02
HR (95% CI) Adjusted[a]	Ref	0.64 (0.40 to 1.00)	0.05
HR (95% CI) Adjusted:			
In patients with KDIGO1[b]	Ref	0.88 (0.51 to 1.53)	0.66
In patients with KDIGO 2/3[c]	Ref	0.29 (0.13 to 0.65)	0.003
KDIGO interaction			0.03
Death Alone	49 (44.1)	22 (24.4)	
HR (95% CI) Unadjusted	Ref	0.45 (0.27 to 0.74)	0.002
HR (95% CI) adjusted[a]	Ref	0.59 (0.33 to 1.05)	0.07
HR (95% CI) adjusted:			
In patients with KDIGO 1[b]	Ref	1.06 (0.53 to 2.11)	0.87
In patients with KDIGO 2/3[c]	Ref	0.17 (0.05 to 0.52)	0.002
KDIGO interaction			0.008
RRT Alone	23 (20.7)	23 (25.6)	
HR (95% CI) Unadjusted	Ref	1.11 (0.62 to 1.99)	0.72
HR (95% CI) adjusted[a]	Ref	1.02 (0.52 to 2.02)	0.95
HR (95% CI) adjusted:	Ref		
In patients with KDIGO1[b]	Ref	1.09 (0.46 to 2.78)	0.84
In patients with KDIGO 2/3[c]	Ref	0.73 (0.25 to 2.16)	0.57
KDIGO interaction			0.56

[a]Model adjusted for age; sex; history of diabetes, hypertension, malignancy, and heart failure with reduced ejection fraction; hemoglobin, leukocyte count, platelet count, 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, 90 in the B3 group.
[b]Model adjusted for same variables as above. N = 83 in the Non-B3 group, 68 in the B3 group.
[c]Model adjusted for same variables as above. N = 26 in the Non-B3 group, 21 in the B3 group.

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

Figure 1: Patient flow at niacinamide protocol hospital (A) and sister hospital (B).

Figure 2: Freedom from composite endpoint of RRT or death in all patients and in the subset with KDIGO stage 2 or 3 AKI.

Figure 1

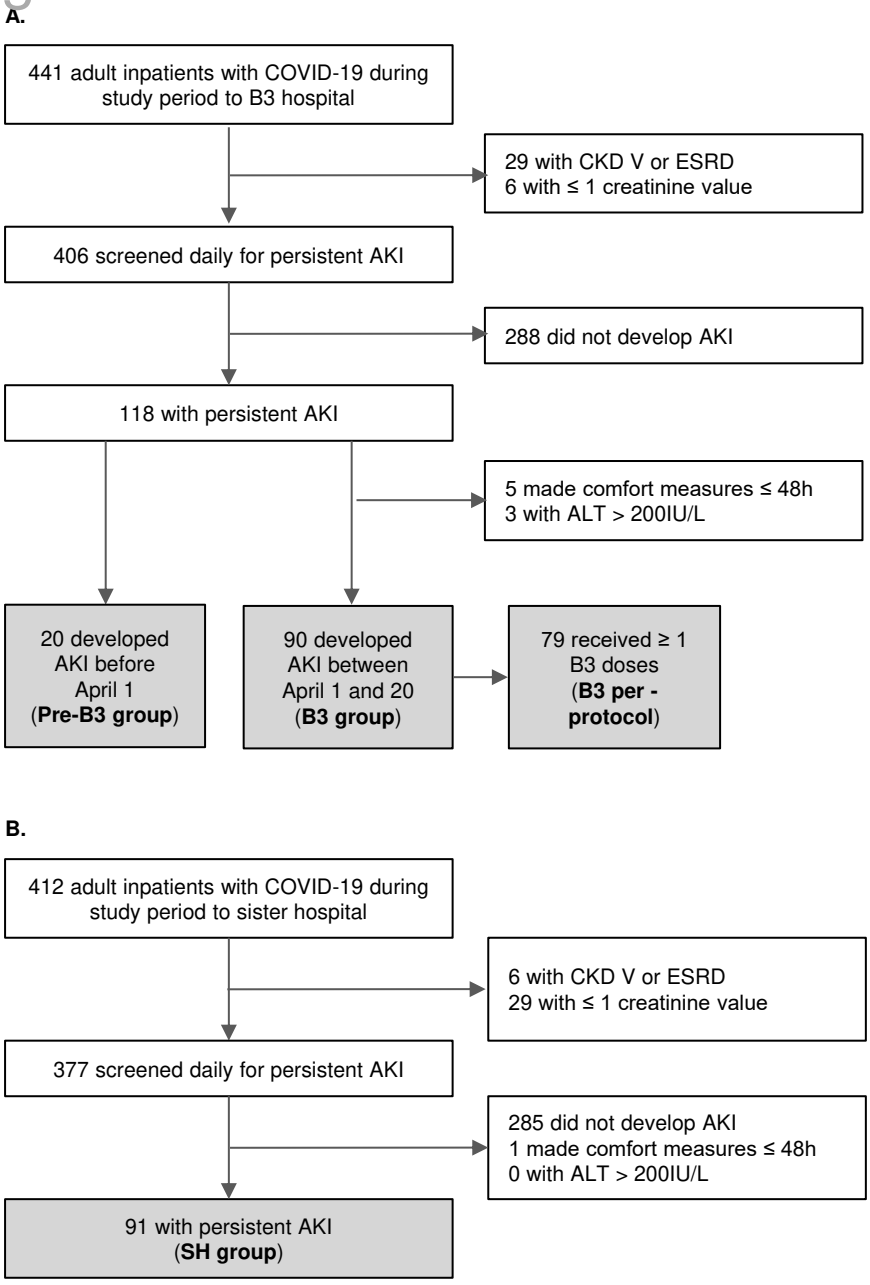
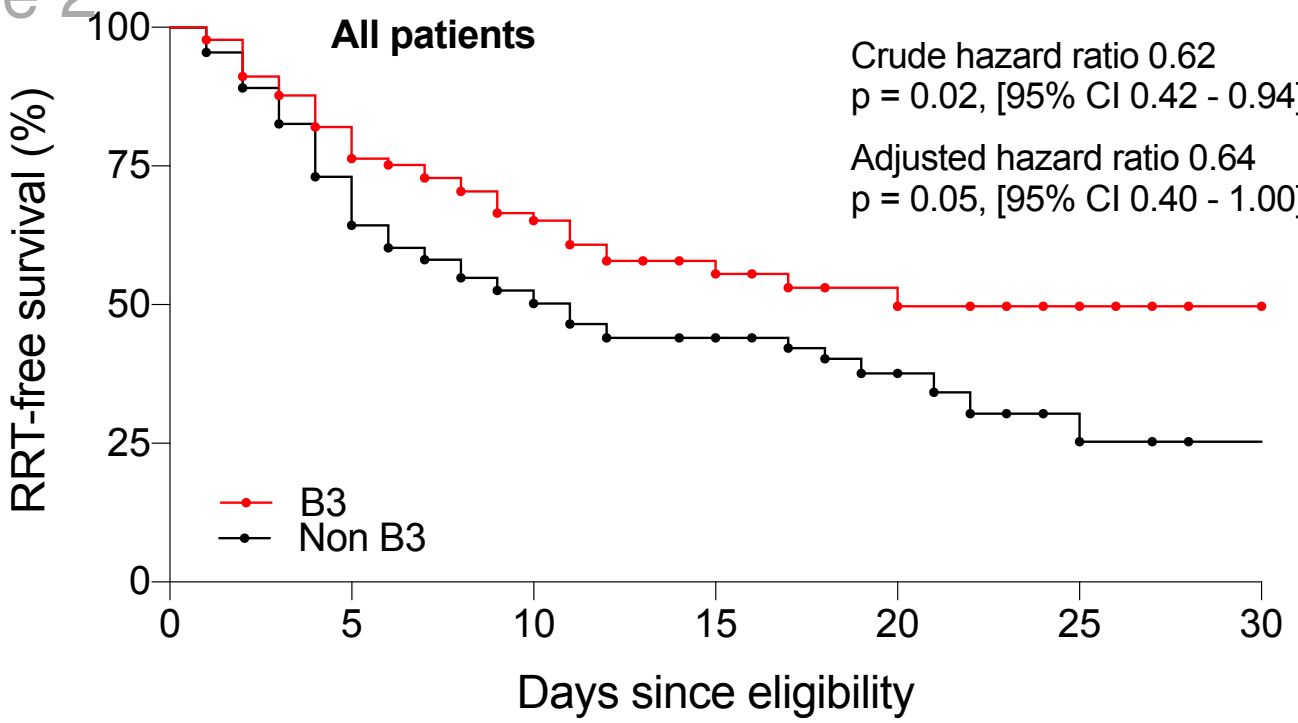
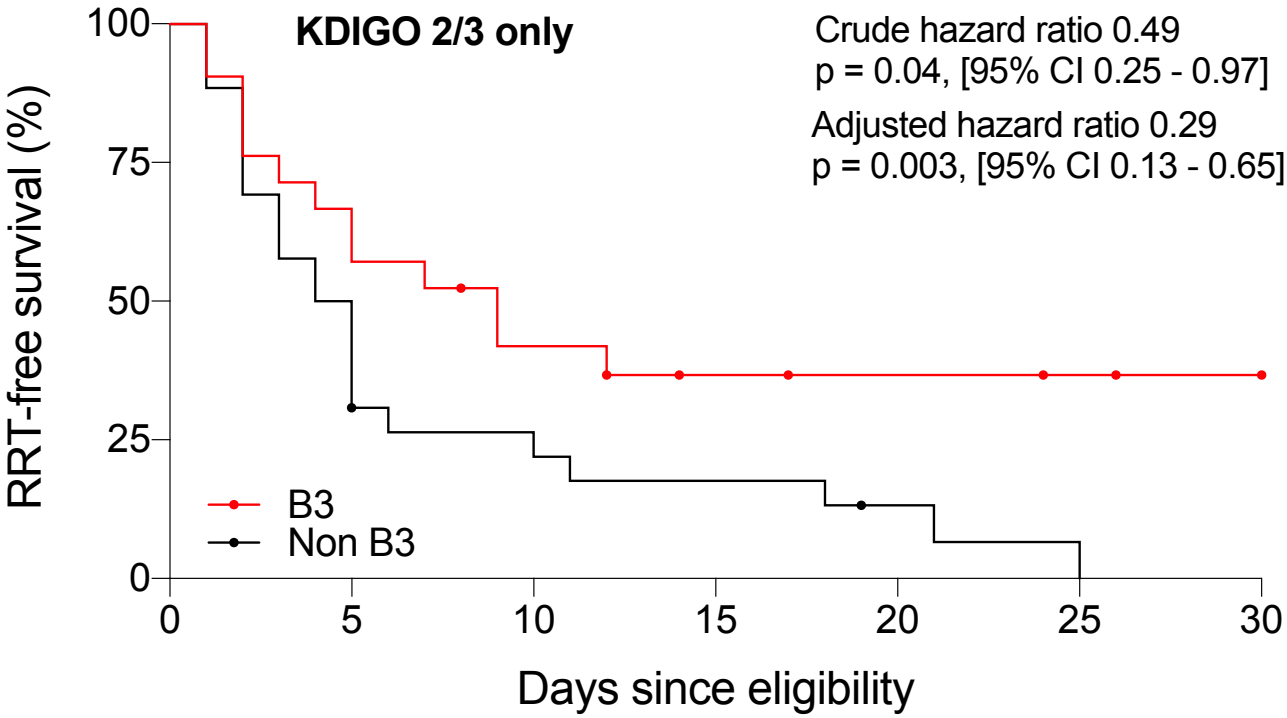

A.
441 adult inpatients with COVID-19 during study period to B3 hospital
29 with CKD V or ESRD
6 with ≤ 1 creatinine value
406 screened daily for persistent AKI
288 did not develop AKI
118 with persistent AKI
5 made comfort measures ≤ 48h
3 with ALT > 200IU/L
20 developed AKI before April 1 (Pre-B3 group)
90 developed AKI between April 1 and 20 (B3 group)
79 received ≥ 1 B3 doses (B3 per - protocol)
B.
412 adult inpatients with COVID-19 during study period to sister hospital
6 with CKD V or ESRD
29 with ≤ 1 creatinine value
377 screened daily for persistent AKI
285 did not develop AKI
1 made comfort measures ≤ 48h
0 with ALT > 200IU/L
91 with persistent AKI (SH group)

Figure 2



No. at risk

B3	90	72	50	25	16	9	1
Non B3	111	75	45	26	12	6	3



No. at risk

B3	21	14	10	6	5	3	1
Non B3	26	13	6	5	3	1	0