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ORIGINAL ARTICLE

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Incidence and risk factors for hyperkalaemia in patients treated for COVID-19 with nafamostat mesylate

Kentaro Kodama[1] | Toru Imai PhD[1] | Yasuo Asai MD, PhD[2] | Yutaka Kozu MD, PhD[2] | Kentaro Hayashi MD, PhD[2] | Tetsuo Shimizu MD, PhD[2] | Yasuhiro Gon MD, PhD[2] | Susumu Ootsuka PhD[1]

[1]Department of Pharmacy, Nihon University Itabashi Hospital, Itabashi-ku, Japan

[2]Division of Respiratory Medicine, Department of Internal Medicine, Nihon University School of Medicine, Itabashi-ku, Japan

Correspondence
Toru Imai, Department of Pharmacy, Nihon University Itabashi Hospital, 30-1 Oyaguchi-kamimachi, Itabashi-ku, Tokyo 173-8610, Japan.
Email: imai.toru@nihon-u.ac.jp

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Abstract

What is known and objective: Nafamostat mesylate (NM) is used clinically in combination with antiviral drugs to treat coronavirus disease (COVID-19). One of the adverse events of NM is hyperkalaemia due to inhibition of the amiloride-sensitive sodium channels (ENaC). The incidence and risk factors for hyperkalaemia due to NM have been studied in patients with pancreatitis but not in COVID-19. COVID-19 can be associated with hypokalaemia or hyperkalaemia, and SARS-CoV-2 is thought to inhibit ENaC. Therefore, frequency and risk factors for hyperkalaemia due to NM may differ between COVID-19 and pancreatitis. Hyperkalaemia may worsen the respiratory condition of patients. The objective of this study was to determine the incidence and risk factors for hyperkalaemia in COVID-19 patients treated with favipiravir, dexamethasone and NM.

Methods: This retrospective study reviewed the records of hospitalized COVID-19 patients treated with favipiravir and dexamethasone, with or without NM, between March 2020 and January 2021. Multivariable logistic regression analysis was performed to identify the risk factors for hyperkalaemia.

Results and Discussion: Of 45 patients who received favipiravir and dexamethasone with NM for the treatment of COVID-19, 21 (47%) experienced hyperkalaemia. The duration of NM administration was a significant predictor of hyperkalaemia (odds ratio: 1.55, 95% confidence interval: 1.04–2.31, $p = 0.031$). The receiver-operating characteristic curve analysis determined that the cut-off value for predicting the number of days until the onset of hyperkalaemia was 6 days and the area under the curve was 0.707.

What is new and conclusion: This study revealed that the incidence of hyperkalaemia is high in patients treated for COVID-19 with NM, and that the duration of NM administration is a key risk factor. When NM is administered for the treatment of COVID-19, it should be discontinued within 6 days to minimize the risk of hyperkalaemia.

KEYWORDS
amiloride-sensitive sodium channel, COVID-19, hyperkalaemia, nafamostat mesylate

1 | WHAT IS KNOWN AND OBJECTIVE

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a *Betacoronavirus* that causes severe pneumonia similar to that caused by severe respiratory syndrome coronavirus and Middle East respiratory syndrome coronavirus.[1,2] It is highly contagious, with more than 276 million cases worldwide and more than 5.37 million deaths as of 23 December 2021.[3] SARS-CoV-2 infection causes coronavirus disease (COVID-19),[4] and antiviral drugs and steroids are used as therapy.[5] However, their therapeutic effect is limited, and various drug screening systems are being used to search for new therapeutic agents.

It has been suggested that the spike protein expressed on the surface of SARS-CoV-2 is primed by transmembrane protease serine 2 (TMPRSS2) and enters host cells via angiotensin-converting enzyme 2 receptors.[6] In order to inhibit the entry of SARS-CoV-2 into the host, screening of inhibitors targeting TMPRSS2 has been conducted, and nafamostat mesylate (NM) has been identified as a candidate.[7,8] Basic studies suggest that NM inhibits SARS-CoV-2 entry into lung epithelium-derived calu-3 cells by inhibiting TMPRSS2.[7,9] In addition, NM has been reported to be effective against COVID-19 in clinical practice,[10,11] and its use in combination with antiviral drugs may improve the therapeutic outcome because of its ability to inhibit the entry of SARS-CoV-2 into host cells.[10]

Nafamostat mesylate inhibits proteolytic enzymes[12] and has been used for treating acute pancreatitis and disseminated intravascular coagulopathy (DIC).[13,14] Although NM is generally safe,[13,14] it can cause hyperkalaemia due to inhibition of the amiloride-sensitive sodium channel (ENaC).[15] SARS-CoV-2 may inhibit the activation of ENaC,[16] and hyperkalaemia is a common complication of COVID-19.[17] Conversely, SARS-CoV-2 may increase the activity of the renin-angiotensin system, resulting in hypokalaemia,[18] and hypokalaemia has also been reported as a complication of COVID-19.[18–20] As SARS-CoV-2 infection may affect serum potassium regulation, the incidence of hyperkalaemia due to NM may differ in COVID-19 patients from that in patient with other conditions. NM has been reported to be a risk factor for hyperkalaemia in patients with acute pancreatitis.[21] There have been two case reports of NM-induced hyperkalaemia in patients with COVID-19,[22,23] but the incidence and risk factors for NM-induced hyperkalaemia in patients with COVID-19 are unknown.

It is important to prevent hyperkalaemia because fluctuations in serum potassium levels may increase the risk of respiratory failure requiring ventilator management.[24] Thus, clarification of the frequency and risk factors of NM-induced hyperkalaemia in COVID-19 would be beneficial for patient management. Therefore, in this study, we investigated the incidence and risk factors of hyperkalaemia in COVID-19 patients who were treated with NM.

2 | METHODS

We conducted a retrospective study using electronic medical records.

2.1 | Patients and setting

Patients hospitalized with COVID-19 at Nihon University Itabashi Hospital in Tokyo, Japan, between March 2020 and January 2021 were included in the study.

2.2 | Inclusion and exclusion criteria

In our institution, the standard treatment for patients hospitalized with COVID-19 was a combination of favipiravir and dexamethasone. Patients who received favipiravir (3600 mg/day on the first day, and 1600 mg/day on the second and subsequent days) for up to 14 days and dexamethasone (6.6 mg/day) for up to 10 days were included in the standard treatment group. Patients who received favipiravir and dexamethasone in the same doses as the standard treatment group and NM were included in the combination treatment group. NM was administered at a dose of 0.2 mg/kg/hour by continuous intravenous infusion. The combination treatment group included patients who were treated with NM because of persistent fever or no reduction in oxygen demand within 3 days after starting standard treatment. In patients with COVID-19, non-invasive positive pressure ventilation and ventilator management are risk factors for acute kidney injury,[25] and are considered to be risk factors for hyperkalaemia. In addition, it has been reported that the incidence of hyperkalaemia is higher in patients with fatal COVID-19 than in patients who recover.[17] For these reasons, patients who received positive pressure ventilation (nasal high flow or ventilator); patients who died during drug treatment; and patients with hyperkalaemia before the start of treatment were excluded. Hyperkalaemia was defined as a serum potassium level of ≥5 mEq/L, according to the definition of the American Heart Association.[26]

2.3 | Data collection

The following data were extracted from electronic medical records: patient background: age, sex, weight, body mass index and body temperature; dosing parameters: duration of NM administration (days) and dose (mg/kg/day); laboratory parameters on admission: blood urea nitrogen, serum creatinine, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), sodium, potassium, lactate dehydrogenase, ferritin and C-reactive protein levels; white blood cell count and eGFR. In addition, serum potassium levels during drug administration, history of present illness, medical history and concomitant medications were recorded. Creatinine clearance was calculated using the Cockcroft–Gault equation.

2.4 | Statistical methods

We compared the characteristics of the patients in the standard and combination therapy groups before the start of treatment. Next, we

compared the incidence of hyperkalaemia from the start of treatment and the number of days of hyperkalaemia from the onset of infection to the end of treatment in each group. In addition, we compared the pre-treatment backgrounds of the patients who did not have hyperkalaemia and those who had hyperkalaemia in the combination treatment group. The groups were compared using Fisher's exact test for comparison of categorical variables, and the Mann–Whitney U-test or Student's t-test for comparison of continuous variables.

Among patients in the combination treatment group, risk factors for hyperkalaemia were identified using multivariable logistic regression. The independent variables were factors that have been suggested as independent risk factors in previous studies (age, presence of fever, duration of NM administration and serum potassium level before NM administration).[21] In addition, Pearson's correlation coefficient was used to screen variables for multicollinearity. If two factors showed a strong correlation ($r > 0.8$), one of the two factors was excluded from the model. The receiver-operating characteristic (ROC) curve was used to calculate the cut-off value for predicting hyperkalaemia for factors with a p value < 0.05 in the univariate analysis, using multivariable logistic regression analysis. Two-sided p-values < 0.05 were considered statistically significant. JMP 14 (SAS Institute Inc.) was used for the analyses.

2.5 | Ethics statement

This study protocol complied with the Japanese ethical guidelines for medical research involving human subjects and was approved by the Nihon University Itabashi Hospital Institutional Ethics Committee (approval number: RK-210608-06).

3 | RESULTS AND DISCUSSION

3.1 | Comparison of clinical characteristics between the standard and the combination treatment groups

Of the 96 patients who received standard or combination therapy during the study period, 82 were eligible for inclusion in the analysis. Of these, 37 patients were in the standard treatment group and 45 patients were in the combination treatment group. Fourteen patients were excluded because they had received positive pressure ventilation, died during the drug treatment period and had a serum potassium level of ≥5 mEq/L before the start of treatment (Figure 1). The clinical characteristics of the patients in the standard treatment and combination treatment groups before the start of treatment are shown in Table 1. There were significantly more males ($p = 0.004$) in the combination treatment group, and patients in the combination treatment group had significantly higher ALT ($p = 0.043$) levels than patients in the standard treatment group.

3.2 | Incidence and number of days to onset of hyperkalaemia

Four of the 37 patients (11%) in the standard treatment group and 21 of the 45 patients (47%) in the combination treatment group developed hyperkalaemia. The incidence of hyperkalaemia was significantly higher in the combination treatment group than in the standard treatment group ($p < 0.001$). The time from the onset of infection to development of hyperkalaemia was 11.5 (8.0–14.3) days in

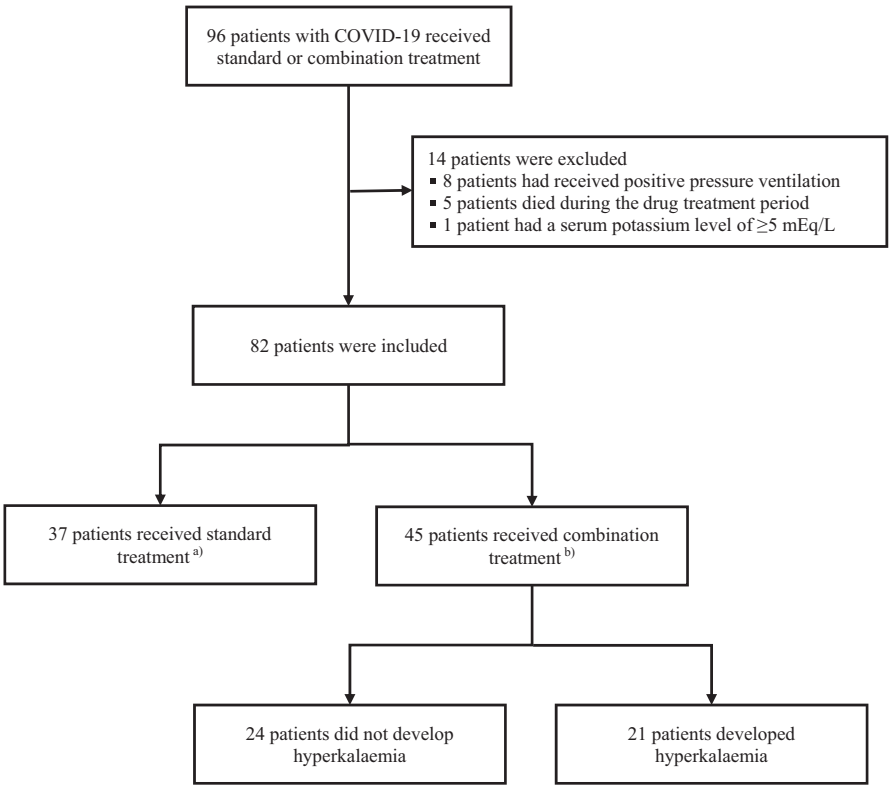

FIGURE 1 Flow chart of selection patient. (A) The standard treatment group was treated with favipiravir and dexamethasone. (B) The combination treatment group was treated with favipiravir, dexamethasone and nafamostat mesylate

TABLE 1 Comparison of clinical characteristics of the standard treatment group and the combination treatment group

	Standard treatment group [a] (*n* = 37)	Combination treatment group [b] (*n* = 45)	*p*
Patient background			
Age	65.1 ± 15.5	61.8 ± 14.6	0.328 [c]
Sex (male)	16 (43.2)	34 (75.6)	0.004 [d]
Body weight (kg)	63.5 ± 19.9	68.9 ± 22.1	0.259 [c]
BMI	24.7 ± 6.1	24.8 ± 6.3	0.916 [c]
Fever (≥38°C)	11 (29.7)	19 (42.2)	0.260 [d]
Pre-administration laboratory values			
BUN (mg/dl)	14.1 (11.3–17.5)	13.7 (11.5–16.4)	0.773 [e]
Scr (mg/dl)	0.81 (0.72–1.13)	0.89 (0.70–1.02)	0.933 [e]
BUN / Scr	16.6 (14.5–20.9)	16.3 (13.0–22.1)	0.579 [e]
Ccr (ml/min)	61.3 (46.2–97.2)	82.9 (64.4–99.4)	0.078 [e]
eGFR (ml/min/1.73 m^2)	62.5 (49.9–73.8)	66.6 (56.7–78.0)	0.071 [e]
T-Bil (mg/dl)	0.56 (0.34–0.75)	0.49 (0.38–0.72)	0.944 [e]
AST (U/L)	28.0 (23.0–37.0)	34.0 (25.5–44.5)	0.102 [e]
ALT (U/L)	19.0 (14.5–36.5)	31.0 (18.5–49.0)	0.043 [e]
Sodium (mEq/L)	139.0 (137.0–141.0)	138.0 (136.0–141.0)	0.626 [e]
Potassium (mEq/L)	3.9 (3.6–4.2)	4.0 (3.7–4.3)	0.252 [e]
WBC (cells/μl)	5100.0 (4400.0–5950.0)	5300.0 (3700.0–6555.0)	0.911 [e]
LDH (U/L)	259.0 (200.0–306.0)	235.0 (197.0–293.0)	0.532 [e]
Ferritin (ng/ml)	312.8 (128.7–499.8)	339.2 (145.2–650.8)	0.496 [e]
CRP (mg/dl)	3.6 (0.98–5.7)	2.8 (1.4–5.4)	0.989 [e]
Medical history			
Hypertension	10 (27.0)	13 (28.9)	>0.999 [d]
Ischaemic heart disease	3 (8.1)	1 (2.2)	0.323 [d]
Heart failure	1 (2.7)	1 (2.2)	>0.999 [d]
Diabetes mellitus	5 (13.5)	11 (24.4)	0.269 [d]
Malignant tumour	2 (5.4)	8 (17.8)	0.105 [d]
COPD	3 (8.1)	6 (13.3)	0.503 [d]
Concomitant medications			
ACE inhibitor or ARB	12 (32.4)	13 (28.9)	0.811 [d]
Potassium-sparing diuretics	2 (5.4)	2 (4.4)	>0.999 [d]
Thiazide diuretics	0 (0.0)	1 (2.2)	0.499 [d]
Loop diuretics	1 (2.7)	2 (4.4)	>0.999 [d]
TMP/SMX	0 (0)	2 (4.4)	0.499 [d]

Note: Qualitative variables are expressed as the number of cases (%) and continuous variables as mean ± standard deviation or median (interquartile range). [a]The standard treatment group was treated with favipiravir and dexamethasone; [b]The combination treatment group was treated with favipiravir, dexamethasone and nafamostat mesylate; [c]Student's *t*-test; [d]Fisher's exact test; and [e]Mann–Whitney U-test.

Abbreviations: ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; and WBC, white blood cell; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; Ccr, creatinine clearance; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; Scr, serum creatinine; SMX, sulfamethoxazole; T-Bil, total bilirubin; TMP, trimethoprim.

the standard treatment group and 13.0 (10.0–15.5) days in the combination treatment group, a non-significant difference ($p = 0.412$) (Table 2).

3.3 | Comparison of clinical characteristics of patients with and without hyperkalaemia in the combination treatment group

Of the 45 patients in the combination treatment group, 21 developed hyperkalaemia. The patients who developed hyperkalaemia were significantly older ($p = 0.027$) and had a significantly longer NM administration period ($p = 0.016$) than the patients without hyperkalaemia (Table 3).

3.4 | Multivariable logistic regression analysis of risk factors for hyperkalaemia

Pearson's correlation coefficient was 0.273, 0.224 and −0.007 for the correlation between serum potassium level on admission and age, duration of treatment and age, and duration of treatment and serum potassium level on admission respectively. Multivariable logistic regression analysis showed that the occurrence of hyperkalaemia was significantly associated with the duration of NM administration (odds ratio: 1.55, 95% confidence interval: 1.04–2.31, $p = 0.031$), but there were no strong correlations between the independent variables (Table 4).

3.5 | Receiver-operating characteristic curve analysis

Receiver-operating characteristic curve analysis of the relationship between the duration of NM treatment and the occurrence of hyperkalaemia revealed that the area under the curve was 0.707. The optimal cut-off value for predicting the time to the onset of hyperkalaemia was 6 days, with a sensitivity of 85.7% and the specificity of 45.8% (Figure 2).

4 | DISCUSSION

Nafamostat mesylate inhibits SARS-CoV-2 entry into the body and is expected to be effective in COVID-19 when used in combination with antiviral drugs.[10] We investigated the incidence of hyperkalaemia and risk factors for hyperkalaemia in COVID-19 patients treated with NM. The results showed that the incidence of hyperkalaemia was higher in the combination treatment group using NM and suggested that the duration of NM administration was an independent risk factor.

In this study, the incidence of hyperkalaemia in the standard treatment group (10.8%) was similar to that reported in a meta-analysis investigating the incidence of hyperkalaemia in patients with COVID-19 (0.22%–13.23%).[27] In contrast, the incidence of hyperkalaemia in the combination treatment group was 46.7%. According to the manufacturer, the incidence of hyperkalaemia in patients with DIC treated with NM is 4.53%,[28] which is far lower than that observed in COVID-19 patients treated with NM in this study. It has been reported that NM inhibits the secretion of prostasin, a serine protease, inhibits the activity of ENaC in renal collecting ducts,[15] inhibits Na^+-K^+ ATPase in renal collecting ducts and inhibits aldosterone secretion,[29,30] resulting in hyperkalaemia. Viruses invade and proliferate by utilizing various functions of the cells that make up the body. Cleavage of the S protein is necessary for SARS-CoV-2 to enter host cells. Furin, a serine protease, has been reported to be involved in this cleavage.[31] As furin cleaves the common amino acid sequence in the extracellular domain of S protein and ENaC, infection with SARS-CoV-2 may cause competition with furin and inhibit the activity of ENaC.[16] ENaC exists in the apical membrane of the distal renal tubules and collecting ducts and reabsorbs sodium, and the renal outer medullary potassium channel, located in the same region, secretes potassium into the tubular lumen for urinary excretion.[32] Therefore, when the activity of ENaC is decreased, urinary excretion of potassium is prevented, and hyperkalaemia occurs as a result.[15] In addition, concomitant dexamethasone use degrades muscle proteins by increasing catabolism.[33] In muscle tissue, the potassium: nitrogen ratio is 2.7 mEq of potassium per gram of nitrogen.[34] Dexamethasone increases urea nitrogen excretion by degrading

TABLE 2 Comparison of the incidence and duration of hyperkalaemia between the standard treatment group and the combination treatment group

	Standard treatment group [a] ($n = 37$)	Combination treatment group [b] ($n = 45$)	p
Incidence of hyperkalaemia	4 (10.8)	21 (46.7)	<0.001 [c]
Time from onset of infection to development of hyperkalaemia (days)	11.5 (8.0–14.3)	13.0 (10.0–15.5)	0.412 [d]

Note: The number of patients is reported as the frequency (%), and the time to development of hyperkalaemia is reported as the median (interquartile range). [a]The standard treatment group was treated with favipiravir and dexamethasone; [b]The combination treatment group was treated with favipiravir, dexamethasone and nafamostat mesylate; [c]Fisher's exact test; and [d]Mann–Whitney U-test.

TABLE 3 Comparison of clinical characteristics of patients in the combination group with and without hyperkalaemia

	Without hyperkalaemia [a] (*n* = 24)	Hyperkalaemia [b] (*n* = 21)	*p*
Patient background			
Age	57.3 ± 15.2	66.9 ± 12.4	0.027 [c]
Sex (male)	16 (66.7)	18 (85.7)	0.177 [d]
Body weight (kg)	67.2 ± 17.7	70.8 ± 26.6	0.583 [c]
BMI	24.3 + 5.3	25.4 ± 7.3	0.589 [c]
Fever (≥38°C)	9 (37.5)	10 (47.6)	0.555 [d]
Dosing parameters			
Dose of NM (mg/kg/day)	4.7 ± 0.1	4.8 ± 0.1	0.706 [c]
Duration of NM administration (days)	6.5 (5.0–8.0)	8.0 (6.5–10.0)	0.016 [e]
Time from onset of infection to start of NM administration (days)	9.0 (8.0–10.8)	9.0 (6.0–10.0)	0.351 [d]
Pre-administration laboratory values			
BUN (mg/dl)	13.1 (9.1–17.1)	14.6 (12.7–16.0)	0.219 [e]
Scr (mg/dl)	0.91 (0.62–0.99)	0.86 (0.79–1.09)	0.322 [e]
BUN / Scr	15.7 (12.5–21.2)	16.3 (13.0–23.6)	0.724 [e]
Ccr (ml/min)	85.6 (67.0–118.4)	74.2 (62.6–95.4)	0.322 [e]
eGFR (ml/min/1.73 m^2)	67.9 (58.0–78.2)	66.2 (53.8–77.1)	0.488 [e]
T-Bil (mg/dl)	0.56 (0.39–0.75)	0.42 (0.37–0.67)	0.311 [e]
AST (U/L)	35.5 (24.3–45.8)	29.0 (25.5–40.0)	0.322 [e]
ALT (U/L)	38.0 (18.3–51.3)	26.0 (18.5–43.5)	0.412 [e]
Sodium (mEq/L)	138.5 (136.3–140.0)	138.0 (136.0–142.0)	0.515 [e]
Potassium (mEq/L)	3.9 (3.5–4.2)	4.1 (3.9–4.3)	0.063 [e]
WBC (cells/μL)	4850.0 (3700.0–6575.0)	5600.0 (4100.0–6450.0)	0.785 [e]
LDH (U/L)	236.0 (209.5–311.0)	220.0 (191.0–333.5)	0.856 [e]
Ferritin (ng/ml)	287.6 (135.4–657.0)	371.9 (193.4–599.6)	0.577 [e]
CRP (mg/dl)	2.7 (1.7–5.0)	3.1 (1.4–7.1)	0.733 [e]
Medical history			
Hypertension	4 (16.7)	9 (42.3)	0.098 [d]
Ischaemic heart disease	0 (0.0)	1 (4.8)	0.467 [d]
Heart failure	0 (0.0)	1 (4.8)	0.467 [d]
Diabetes mellitus	5 (20.8)	6 (28.6)	0.730 [d]
Malignant tumour	5 (20.8)	3 (14.3)	0.705 [d]
COPD	2 (8.3)	4 (19.1)	0.396 [d]
Concomitant medications			
ACE inhibitor or ARB	5 (20.8)	8 (38.1)	0.323 [d]
Potassium-sparing diuretics	1 (4.2)	1 (4.8)	>0.999 [d]
Thiazide diuretics	0 (0.0)	2 (9.5)	0.212 [d]
Loop diuretics	1 (4.2)	1 (4.8)	>0.999 [d]
TMP/SMX	1 (4.2)	1 (4.8)	>0.999 [d]

Note: Qualitative variables are expressed as the number of cases (%) and continuous variables as mean ± standard deviation or median (interquartile range). [a]The non-hyperkalaemia group had serum potassium levels persistently <5 mEq/L; [b]The hyperkalaemia group had serum potassium levels ≥5 mEq/L; [c]Student's *t*-test; [d]Fisher's exact test; and [e]Mann–Whitney U-test.

Abbreviations: ACE, angiotensin-converting enzyme; ALT, alanine aminotransferase; and WBC, white blood cell; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; Ccr, creatinine clearance; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; LDH, lactate dehydrogenase; Scr, serum creatinine; SMX, sulfamethoxazole; T-Bil, total bilirubin; TMP, trimethoprim.

TABLE 4 Multivariable logistic regression of risk factors associated with hyperkalaemia

	OR	95% CI	*p*
Age	1.07	1.00–1.14	0.053
Fever (≥38˚C)	4.05	0.69–23.9	0.123
Duration of NM administration (days)	1.55	1.04–2.31	0.031
Potassium on admission (mEq/L)	7.07	0.85–58.8	0.070

Abbreviations: CI, confidence interval; OR, odds ratio.

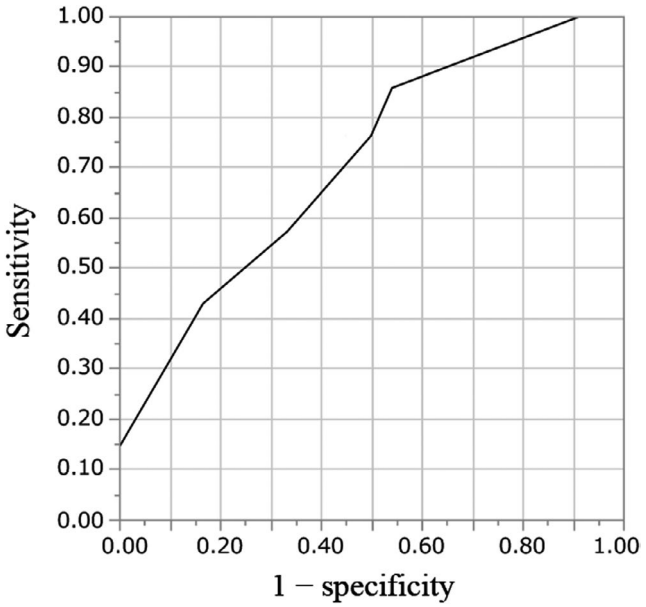

FIGURE 2 Receiver-operating characteristic curve of the risk of hyperkalaemia as a function of the duration of nafamostat mesylate therapy. AUC, 0.707; cut-off value, 6 days; sensitivity, 85.7%; specificity, 45.8%

muscle proteins.[35] Therefore, the release of potassium, a component of muscle protein, is expected to be released with urea nitrogen; however, there have been no reports of hyperkalaemia in patients treated with dexamethasone alone. This is because various physiological functions compensate for serum potassium levels during steroid monotherapy. However, the combination of ENaC-inhibiting trimethoprim-sulfamethoxazole (TMP/SMX) and corticosteroids has been reported to increase the incidence of hyperkalaemia more than the administration of TMP/SMX alone.[36] In other words, corticosteroids may cause potassium elevation, and ENaC inhibition by TMP/SMX interferes with the compensatory function and increases the incidence of hyperkalaemia. In this study, we speculated that the administration of dexamethasone as the standard treatment for COVID-19 may have increased potassium-releasing protein catabolism, and the combined use of NM may have inhibited potassium excretion from the tubules, contributing to the increased incidence of hyperkalaemia. Furthermore, in the case series of combination treatment of COVID-19 with NM and favipiravir, the incidence of hyperkalaemia due to NM was 9% (1/11),[10] which was lower than in the present study. In the present study, NM was combined with dexamethasone, and this may have contributed to the development of hyperkalaemia. Based on the above, we consider that the increased incidence of hyperkalaemia is due to a combination of factors, such as potassium release by protein catabolism induced by dexamethasone, in addition to suppression of ENaC activity due to SARS-CoV-2 infection and NM. However, as we did not measure ENaC activity in each patient in this study, we believe that pharmacological studies are warranted to determine the detailed mechanism by which NM induces hyperkalaemia in patients with COVID-19.

In the comparison of patient characteristics in this study, there were differences between the standard treatment group and the combination treatment group, in the percentage of males and ALT levels. Although it has been suggested that COVID-19 causes electrolyte abnormalities,[27] it has been reported that the incidence of electrolyte abnormalities does not differ by sex.[18,37] In addition, NM is metabolized by hydrolysis in hepatic microsomes and cytosol.[38,39] Although the liver is partially involved, the dependence on liver function is low, and mild liver damage is not thought to cause an increase in blood concentration. Therefore, the differences in clinical characteristics between groups are unlikely to have led to the higher incidence of hyperkalaemia in the combination therapy group.

Based on the results of the increased incidence of hyperkalaemia in COVID-19 patients treated with NM, we examined the risk factors for hyperkalaemia. In the combination treatment group, hyperkalaemia was associated with older age and a longer duration of treatment. A previous study also found the age and duration of treatment were risk factors for hyperkalaemia in patients treated for acute pancreatitis with NM.[21] Basic research suggests that the ENaC expression level decreases with age in rats.[40] In addition, it has been suggested that the ability to secrete aldosterone in response to elevated potassium is reduced in older adults.[41] NM is known to inhibit the activity of ENaC and aldosterone secretion,[15,29,30] so hyperkalaemia may be more likely to occur in the older adults treated with NM than in younger individuals. In addition, NM has been reported to inhibit ENaC activity from the day after administration,[15] and the gradual increase in K-releasing protein catabolism by steroids may lead to a situation where hyperkalaemia is more likely to occur as the duration of administration is prolonged.

We examined the use of NM for treating COVID-19 to clarify the risk factors for hyperkalaemia. We performed multivariable logistic regression analysis using the presence of hyperkalaemia as the dependent variable and the presence of fever and serum potassium level before NM administration, which have been shown to influence the increase in serum potassium level in previous studies,[21] and age and duration of NM administration, which were significantly

associated with hyperkalaemia in the univariate analysis as independent variables. The analysis showed that prolonged NM administration was a risk factor for the development of hyperkalaemia. The duration and timing of administration of NM for COVID-19 have not been clearly defined, and discontinuation of NM before the onset of hyperkalaemia is important as a therapeutic strategy. In the ROC analysis performed in this study, the cut-off value was calculated to be 6 days. Therefore, we suggest that NM administration should be ended after approximately 6 days in order to avoid the onset of hyperkalaemia.

This study had several limitations. First, this retrospective study was a single-centre study and used medical records; therefore, the findings might not be generalizable. Second, this study did not include patients with diseases other than COVID-19 as a control group; therefore, it was not possible to evaluate whether the incidence of hyperkalaemia in patients treated with NM is higher in COVID-19 patients than with other conditions, such as pancreatitis and DIC. Third, the balance of potassium input and output, considering factors such as infusion, diet, vomiting and urinary potassium level, was not evaluated, and factors affecting serum potassium levels, such as renin and aldosterone, were not evaluated. Therefore, it is not possible to determine whether all hyperkalaemia in the NM group was attributable to NM use. Fourth, serum potassium was not measured daily, so there may be some error in the measurement of the time to the onset of hyperkalaemia. However, there are few effective therapeutic agents for COVID-19, the global incidence currently remains very high, so it is important to use existing drugs to control the severity of the disease. Therefore, even considering these limitations, we believe that this study, which suggests a guideline for the duration of NM administration to patients with COVID-19, contains important findings.

Currently, the mainstream drugs for COVID-19 treatment are antivirals and anti-inflammatory drugs that are used after the mid-term post-infection period when oxygen demand is needed,[42,43] but NM is one of the few drugs that are effective when administered in the early phase of the disease in order to inhibit entry of SARS-CoV-2 into the cells of the body. Based on the results of this study, we recommend that NM should be administered only for a short period of time in order to avoid the development of hyperkalaemia. Further studies are needed to determine the optimal timing and duration of administration to maximize the effectiveness of NM for treating patients with COVID-19.

5 | WHAT IS NEW AND CONCLUSION

This study revealed that the incidence of hyperkalaemia is high in COVID-19 patients treated with NM, and that the duration of NM administration is a key risk factor. SARS-CoV-2 infection and steroid treatment may have had a synergistic effect and exacerbated the development of hyperkalaemia. NM administration should be discontinued within 6 days in patients with COVID-19, in order to avoid the onset of hyperkalaemia.

CONFLICT OF INTEREST

No conflicts of interest have been declared.

PATIENT CONSENT

The requirement for consent was waived because of the retrospective study design.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Kentaro Kodama https://orcid.org/0000-0003-3617-8233
Toru Imai https://orcid.org/0000-0002-8648-7571

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