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Evaluation of risk factors for uric acid elevation in COVID-19 patients treated with favipiravir

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ABSTRACT

The objective of this retrospective study was to identify the clinical risk factor associated with uric acid elevation in coronavirus disease (COVID-19) patients treated with favipiravir. Uric acid elevation was defined as an unexplained increase of ≥1.5 times in the patient's uric acid level from baseline. Twenty-nine COVID-19 patients were included in the study. Uric acid elevation developed during favipiravir therapy in 12 (41.4%) patients and the median onset time was 4.5 days after starting favipiravir. In multiple logistic regression analysis, the favipiravir dosage (adjusted OR = 1.69 [1.02–2.81], P = 0.044) and younger patient age (adjusted OR = 0.91 [0.83–0.99], P = 0.040) were significant clinical risk factors for uric acid elevation. No significant between-group difference was noted in the uric acid elevation and non-elevation groups in the clinical recovery after favipiravir therapy. The uric acid levels of patients administered with favipiravir should be monitored closely.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense single-stranded RNA virus that is closely related to bat-derived SARS-like coronaviruses [1]. Since its outbreak in Wuhan, China in December 2019, the virus has rapidly spread worldwide and has caused the respiratory illness, coronavirus disease (COVID-19). However, as definitive therapies for established COVID-19 remain to be defined, there is significant interest in repurposing existing antiviral agents for use against COVID-19.

Favipiravir, a pyrazine carboxamide derivative, is a novel antiviral drug that was originally approved in Japan for epidemics caused by influenza virus infections. Favipiravir acts as a prodrug which is converted intracellularly into its ribofuranosyl 5′-triphosphate active metabolite (favipiravir-RTP) [2]. The favipiravir-RTP molecule can inhibit a broad range of other RNA viruses. The exact mode of action is unknown, although it is theorized that favipiravir-RTP could be

mis-incorporated into a growing viral RNA chain or could bind to conserved polymerase domains, thereby preventing viral RNA replication [3, 4]. The incorporation of favipiravir-RTP in the nascent viral RNA could result either in lethal mutagenesis by ambiguous base-pairing or in chain termination. Due to its activity against RNA viruses, the efficacy of favipiravir against several RNA viruses including SARS-CoV-2, Influenza A virus subtype H1N1, Ebola virus, etc., has been tested [5–9].

Nonetheless, favipiravir exhibits a number of common adverse effects, including the elevation of serum uric acid, liver and kidney injury, diarrhea, and neuropsychiatric symptoms. Among these adverse effects, hyperuricemia exhibits the highest incidence, occurring in 5 of 6 volunteers (83.3%) who undergo favipiravir administration (1800 mg on day 1 followed by 1200 mg on days 2−6) in phase 1 safety studies (Study JP111) [10]. In a phase 3 clinical study comparing the treatment efficacy of favipiravir (1600 mg on day 1 followed by 800 mg on days 2−5) and oseltamivir for patients with influenza, the favipiravir group (5.6%, 21/378) had a higher incidence of elevated blood uric acid levels than the oseltamivir group (0.3%, 1/380) [10]. This finding has raised justifiable concerns that the currently recommended higher dosing strategy (3600 mg on day 1 followed by 1600 mg on subsequent days; maximum administration period, 14 days) in COVID-19 patients excessively increases the risk of this

adverse effect [11]. However, there is no consensus regarding the clinical risk factors for uric acid elevation developed during favipiravir therapy. In addition, few reports have examined details such as the frequency of occurrence and onset time of this adverse event.

In this study, we aimed to identify the clinical risk factors associated with uric acid elevation in COVID-19 patients treated with favipiravir.

2. Materials and methods

2.1. Study design and patients

This single-center retrospective cohort study was conducted after the study protocol was approved by the Institutional Review Board of Toho University Omori Medical Center (Tokyo, Japan). Given the retrospective study design, we obtained tacit informed consent from every patient by using an opt-out option through a notice that was displayed on the institutional webpage, whereby all eligible patients could deny participation. This investigation was carried out between February, and June 2020, and the study enrolled adult patients (age ≥18 years) with SARS-CoV-2 infection that was confirmed on nasopharyngeal swab sample testing and were orally administered favipiravir. The presence of SARS-CoV-2 was detected by the real-time reverse transcription-polymerase chain reaction using the BD MAX System (BD Diagnostic Systems, Franklin Lakes, NJ, USA). Patients were excluded if they had recently received agents that interact with favipiravir, had data missing for the clinical information evaluated in this study, and did not survive for ≥1 week after the completion of favipiravir therapy. We retrieved data regarding the following characteristics for each eligible patient: demographic parameters, medical history, previous treatment for hyperuricemia, favipiravir dosage, treatment duration, admission to the intensive care unit (ICU), and biochemical and hematological indices from electronic medical records. All study participants were followed up until the termination of favipiravir therapy.

2.2. Evaluation of uric acid elevation

Changes in the patients' biochemical and hematological parameters were assessed after ≥3 days of favipiravir treatment. Serum uric acid elevation was defined as an unexplained increase of the patient's uric acid level ≥1.5 times from baseline, with reference to several well-known criteria for abnormal laboratory findings for parameters such as aspartate aminotransferase, creatinine, and amylase based on the Common Terminology Criteria for Adverse Events (CTCAE version 5.0) [12]. The measurements of the uric acid level were performed in the hospital using the uricase-peroxidase method in a solution using Detamina-L UA as the reagents (Hitachi Chemical Diagnostics Systems Corporation, Tokyo, Japan) and analyzed on LABOSPECT 008α as the apparatus (Hitachi High-Technologies Corporation, Tokyo, Japan). The primary endpoints included the incidence and time of onset of uric acid elevation developed during favipiravir therapy, and multiple logistic regression analysis was performed to identify the predictors of this adverse effect.

To confirm the efficacy profile, we compared the post-favipiravir therapy clinical recovery of the uric acid elevation group with that of the non-uric acid elevation group, after excluding patients treated in the ICU. The clinical recovery was evaluated as follows: time to defervescence (i.e., axillary temperature <37.0°C for more than 48 hours and C-reactive protein CRP level <30% of the baseline value). Furthermore, we evaluated the time to achieving negative results on the nasopharyngeal SARS-CoV-2 nucleic acid test.

Table 1
Baseline characteristics of study participants.

Parameter	n (%) or median (interquartile range)
Number of cases	29
Age (years)	51.0 (39.0, 63.0)
Weight (kg)	66.2 (52.6, 73.7)
Body mass index (kg/m^2)	24.0 (21.3, 27.1)
Initial dosage of favipiravir (mg/12 h)	1800 (1800, 1800)
Maintenance dosage of favipiravir (mg/12 h)	800 (800, 800)
Duration of favipiravir therapy (days)	12.0 (9.0, 14.0)
Intensive care unit admission	4 (13.8)
Physical findings	
Maximum body temperature (°C)	38.3 (37.4, 38.6)
Heart rate (bpm)	84.0 (80.0, 94.0)
Respiratory rate (bpm)	19.0 (17.0, 24.0)
Systolic blood pressure (mmHg)	122.0 (118.0, 128.0)
Medical history	
Hypertension	9 (31.0)
Diabetes mellitus	7 (24.1)
Hyperlipidemia	4 (13.8)
Heart failure	3 (10.3)
Hyperuricemia	2 (6.9)

2.3. Statistical analysis

Data are expressed as median [interquartile range (IQR)], unless otherwise specified. Continuous variables were analyzed using the Wilcoxon signed-rank or Mann−Whitney U test, whereas categorical variables were analyzed using the chi-square or Fisher exact test. The time from the initiation of favipiravir therapy to the development of uric acid elevation was estimated using the Kaplan−Meier method. Univariate and multivariate logistic regression analyses using a forward stepwise approach were subsequently conducted to determine the odds ratios (OR) for uric acid elevation post-favipiravir therapy. Then, the variables that exhibited P-values <0.1 in univariate analysis were entered as independent variables in multivariate logistic regression analysis, to establish the regression model. Because of a variable potentially associated with uric acid excretion, the estimated glomerular filtration rate (eGFR) was also included regardless of statistical significance. All statistical analyses were performed with SPSS for Windows version 24.0 (SPSS Japan Inc., Tokyo, Japan). P-values <0.05 were considered to be statistically significant.
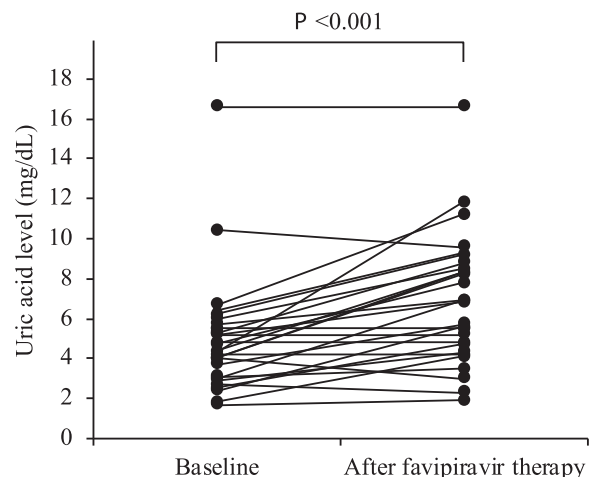

Fig. 1. Changes of the serum uric acid level after the initiation of favipiravir therapy. The median uric acid level increased significantly to 6.8 (4.7, 8.5) from 4.4 (3.1, 5.5) mg/dL at baseline in all patients.

3. Results

3.1. Study subjects

During the study period, 31 patients received favipiravir therapy against COVID-19. Of these, 1 patient died during favipiravir therapy due to disease deterioration, and 1 patient had missing clinical data. Thus, 29 patients were included in the study. All enrolled patients received the same dosage of favipiravir (3600 mg on day 1 followed by 1600 mg on the subsequent days) and completed the therapy within 14 days. The median (IQR) duration of favipiravir therapy was 12.0 (9.0, 14.0) days, and 26 patients received favipiravir for ≥7 days. None of the patients were treated with drugs that interact with favipiravir. Table 1 presents the baseline characteristics of participants.

3.2. Evaluation of uric acid elevation

Uric acid elevation developed during favipiravir therapy in 12 of 29 (41.4%) COVID-19 patients. Of these, in 6 (50.0%), 4 (33.3%), and 2 (16.7%) patients, the uric acid level increased 1.5–2.0, 2.0–2.5, and ≥2.5 times from baseline, respectively. Fig. 1 shows the changes in the uric acid level after starting favipiravir in all patients, and the median (IQR) uric acid level increased significantly to 6.8 (4.7, 8.5) from 4.4 (3.1, 5.5) mg/dL at baseline ($P < 0.001$). Eleven patients (37.9%) met the diagnostic criteria for hyperuricemia (>7.0 mg/dL) [13], although none showed any common symptoms and signs of hyperuricemia. In the uric acid elevation group, the median (IQR) dosage of favipiravir was 14.3 (12.0, 15.8) mg/kg/12 h, which was significantly higher than 11.9 (10.5, 13.6) of the non-uric acid elevation group ($P = 0.043$; Table 2). The median (IQR) onset time of uric acid elevation was 4.5 (4.0, 7.0) days after starting favipiravir. Kaplan−Meier analysis estimates of the time from the initiation of therapy to the development of uric acid elevation are shown in Fig. 2. After 14 days of follow-up, the cumulative incidence of uric acid elevation was 6.9% at 3 days, 27.9% at 6 days, and 44.2% at 9 days after favipiravir therapy. Favipiravir therapy was discontinued due to uric acid elevation by >11 mg/dL in one patient (3.4%). However, after the cessation of favipiravir therapy, the uric acid levels returned to the baseline value in all patients.

The five variables that exhibited *P*-values <0.1 in the univariate analyses were chosen as independent variables for inclusion in the multivariate logistic regression analysis. As a result, the dosage of favipiravir (adjusted OR = 1.56 [1.03−2.37], $P = 0.037$) and younger patient age (adjusted OR = 0.93 [0.87−0.99], $P = 0.027$) were significant clinical risk factors for uric acid elevation (Table 2). Moreover, Fig. 3 shows the relationship between clinical risk factors and uric acid elevation based on the univariable logistic regression analysis (absence, 0; presence, 1). The dosage of favipiravir was a significant predictor of uric acid elevation according to the following equation:

$$Probability \, 1/[1 + exp(-(-4.764 + 0.336 \times Dose/Bodyweight))]$$

A 50% risk of developing uric acid elevation was found to be correlated with a favipiravir dosage of 14.2 mg/kg/12 h. In addition, younger patient age was a significant predictor of uric acid elevation according to the following equation:

$$Probability = 1/[1 + exp(-(2.395 - 0.056 \times Age))]$$

A 50% risk of developing uric acid elevation was found to be correlated with the age of 42.8 years.

3.2. Comparison of clinical recovery

Among the 29 patients included in this study, four patients were excluded from the clinical recovery analysis group due to need for ICU care. In the uric acid elevation group, the median (IQR) duration to negative results with the SARS-CoV-2 nucleic acid test tended to be shorter than that of the non-uric acid elevation group (11.0 (10.5, 14.0) vs 16.0 (13.0, 18.0) days; $P = 0.063$), although there was no significant difference. Similarly, no significant between-group difference was observed for the uric acid elevation and non-elevation groups in time to return of body temperature to <37.0°C for 2 consecutive days (6.0 (3.0, 8.0) vs 5.5 (5.0, 8.5) days; $P = 0.559$), and CRP level <30% of the baseline (7.5 (7.0, 8.0) vs 6.5 (4.8, 7.3) days; $P = 0.151$).

4. Discussion

This study showed a high incidence of uric acid elevation, with regard to the established standards, in COVID-19 patients who received favipiravir therapy. The typical signs and symptoms such as gout and urinary stones were not observed in this study; however, uric acid levels increased more than 2.0-fold in 50% of these patients, and uricemia of moderate to severe intensity was recorded. In addition, the median onset time of uric acid elevation was 4.5 days. Previously, in a randomized control trial among COVID-19 patients to compare the efficacy and safety of favipiravir and arbidol, the incidence of uric acid elevation was significantly higher in the favipiravir group (13.8%) than in the arbidol group (2.5%) [5]. In an interim report of a multicenter observational study of favipiravir in COVID-19 patients in Japan, 17.6% (524/2970) of the patients showed hyperuricemia or uric acid elevation with favipiravir therapy, and 0.30% (9/2970) presented with gout [14]. Thus, favipiravir can increase uric acid levels in COVID-19 patients; however, these studies did not report data concerning detailed uric acid levels and onset time of uric acid elevation. Based on the results from our study, we suggest that the COVID-19 patients receiving favipiravir therapy should receive appropriate uric acid level monitoring to aid the early detection of this adverse effect, and the decision to continue or discontinue favipiravir after the development of this adverse effect should be made based on the clinical risk−benefit assessment for the individual.

Using multivariate analyses, we identified two potential risk factors for uric acid elevation in patients receiving favipiravir therapy against COVID-19: (1) the dosage of favipiravir, and (2) younger patient age. This study, to the best of our knowledge, is the first report of clinical risk factors of uric acid elevation post-favipiravir therapy. The mechanism responsible for uric acid elevation is unclear, although it is thought to result from the decreased urinary excretion of uric acid induced by favipiravir [10]. Favipiravir and its metabolite, favipiravir hydroxide, inhibit the organic anion transporters (OAT) 1 and OAT3, leading to the decreased tubular secretion of uric acid, and favipiravir hydroxide enhances uric acid reabsorption mediated by a urate transporter, collectively resulting in decreased uric acid excretion. Thus, favipiravir therapy may induce a dose-dependent increase in uric acid levels. Indeed, in this study, wherein the COVID-19 patients were administered a higher dose of favipiravir than the approved favipiravir regimen for influenza, the incidence rate of uric acid elevation was markedly higher than in some previous studies [5, 10]. Therefore, we consider that the dosage of favipiravir is closely related to uric acid elevation. As described herein, the dosage of favipiravir in the uric acid elevation group was significantly higher than that in the non-elevation group. However, there was no significant difference in the post-favipiravir therapy clinical recovery between the uric acid elevation and non-elevation groups. Nonetheless, it may be difficult to ensure the safety of favipiravir therapy with the currently recommended uniform dosing strategy in COVID-19 patients, whose dosage was 3600 mg on day 1 followed by 1600 mg on the subsequent days (maximum administration period, 14 days). In particular, if the same dose is given to all patients, we consider that the risk of developing uric acid elevation might exceed 50% in patients weighing less than 56 kg, as derived from the following equations: a body weight threshold = 1600 (mg/day) / [14.2 (mg/kg/12 h) × 2].

Table 2
Clinical risk factors associated with uric acid elevation in patients COVID-19 patients with treated with favipiravir.

Risk factor	Univariate analysis			Multivariate analysis		
	UA-elevatate (*n* = 12)	Non-UA-elevate (*n* = 17)	*P*-value	Adjusted odds ratio	95%CI	*P*-value
Age (years)	38.0 (28.3, 57.0)	53.0 (47.0, 65.0)	0.043	0.93	0.87−0.99	0.027
Male sex (no. [%])	4 (33)	13 (76)	0.020			
Duration of favipiravir therapy (days)	12.0 (9.0, 12.5)	13.0 (9.0, 14.0)	0.777			
Dosage of favipiravir (mg/kg/12 h)	14.3 (12.0, 15.8)	11.9 (10.5, 13.6)	0.048	1.56	1.03−2.37	0.037
Laboratory data at the baseline						
Creatinine (mg/dL)	0.7 (0.6, 0.8)	0.7 (0.6, 0.9)	0.283			
eGFR (mL/min/1.73m^2)	85.9 (72.8, 96.4)	73.7 (64.3, 87.2)	0.263			
Aspartate aminotransferase (IU/L)	28.0 (19.8, 34.3)	37.0 (26.0, 48.0)	0.211			
Alanine aminotransferase (IU/L)	25.5 (12.3, 43.0)	36.0 (23.0, 41.0)	0.303			
Total bilirubin (mg/dL)	0.6 (0.4, 0.7)	0.5 (0.4, 0.7)	0.517			
Uric acid (mg/dL)	4.5 (3.4, 5.5)	5.1 (4.0, 6.0)	0.116			
Concomitant medications						
Penicillins	0 (0)	2 (12)	0.218			
Cephems	4 (33)	11 (65)	0.099			
Carbapenems	1 (8.3)	4 (24)	0.293			
Macrolides	3 (25)	8 (47)	0.228			
Antihyperuricemic drugs[a]	1 (8)	1 (6)	0.798			
Ciclesonide	11 (91.7)	13 (76)	0.293			
Nafamostat mesilate	0 (0)	3 (18)	0.124			

Values are n (%) or median (interquartile range).
UA = uric acid; eGFR = estimated glomerular filtration rate.
[a] Antihyperuricemic drugs included allopurinol, febuxostat, topiroxostat, benzbromarone, and probenecid.

Accordingly, we should consider that a target dosage strategy based on the body weight could minimize the risk of uric acid elevation while maintaining the clinical efficacy of favipiravir therapy. A recent in vitro study by Wang et al. reported favipiravir has half-maximal effective concentration of 61.88 mM, half-cytotoxic concentration >400 mM against SARS-CoV-2 infection [15]. In addition, favipiravir is capable of boosting its own concentration by dose- and time-dependent self-inhibition of aldehyde oxidase. The self-inhibition of metabolism and formation of favipiravir−inactive metabolite in the liver after continuous use may increase the circulating favipiravir and/or inactive metabolite ratio [16]. Hence, the use of a population

pharmacokinetic (PK) model based on its concentration profiles could have established an exposure-response relationship for uric acid elevation post-favipiravir therapy. Unfortunately, we did not obtain any data about the patients' plasma favipiravir and favipiravir hydroxide concentrations, and further studies are necessary to determine whether the incidence of uric acid elevation could be reduced by adjusting the favipiravir dose according to the patient's body weight, for which there is currently no specific recommendation. Regarding younger patient age, one of the identified risk factors, 2 Phase 1 studies (Studies JP103 and JP106) in healthy adult participants reported no large differences in the plasma concentration profiles or PK
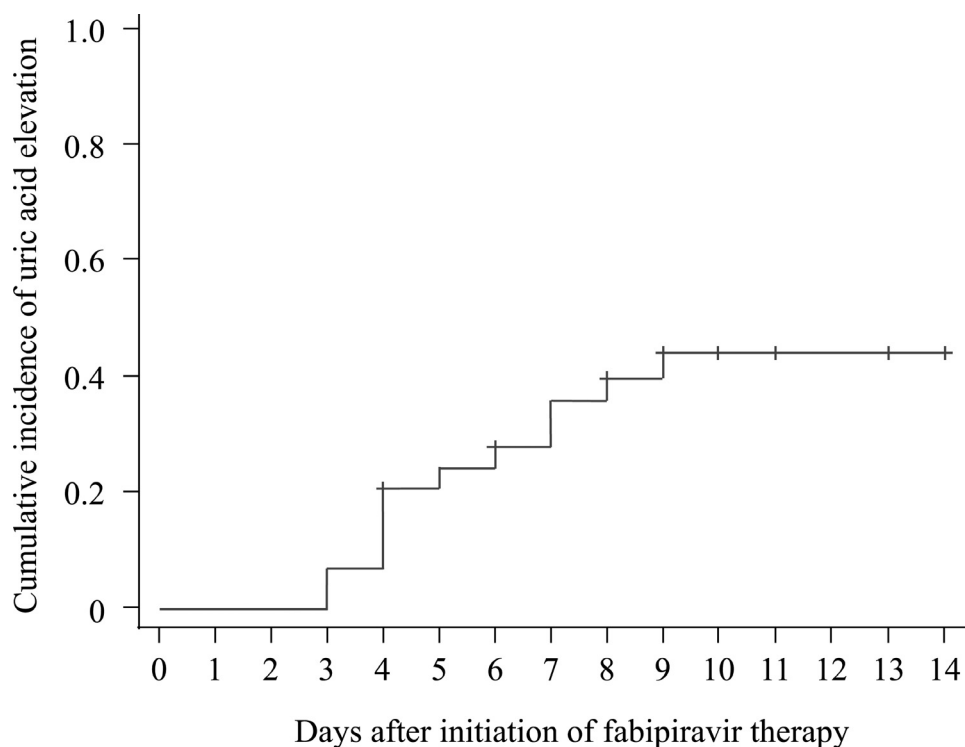

Fig. 2. Kaplan−Meier curve of the onset of uric acid elevation after the initiation of favipiravir therapy.
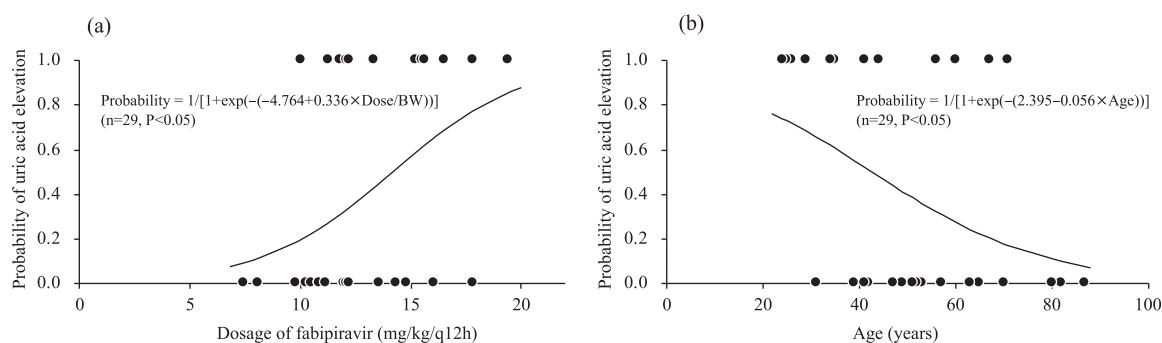
Fig. 3. Univariable relationships between the probability uric acid elevation post-favipiravir therapy and each of dosage of favipiravir (A) and younger patient age (B) The relationship between the clinical risk factors and uric acid elevation (absence, 0; presence, 1), and the dosage of favipiravir and the younger patient age were significant predictors of uric acid elevation.

parameters of favipiravir between young and older adult participants. These data suggest that the difference in age distribution is unlikely to affect the PK of favipiravir [10]. However, there is limited experience with the use of favipiravir in older adults at the present time, and further research is necessary to confirm the relationship between age and the efficacy and safety of favipiravir for COVID-19 patients.

This study had several limitations. First, owing to the limited number of patients with COVID-19 at the single study center, this study did not classify the patients according to their renal function such as eGFR. Patients with kidney dysfunction generally manifest higher blood uric acid levels and decreased urinary uric acid clearance [17]. Thus, in patients with moderate to advanced kidney dysfunction, favipiravir may result in hyperuricemia more frequently due to the exposure to higher plasma concentrations of favipiravir hydroxide, although direct evidence for this aspect has not been gathered. Second, the uric acid elevation in this study was defined as an unexplained increase ≥ 1.5 times the patient's uric acid level from the baseline. This may have limited the evaluation of the incidence rate of uric acid elevation. However, of the 12 patients who developed uric acid elevation, 8 patients (67.7%) met the diagnostic criteria for hyperuricemia (> 7.0 mg/dL) [13], thus, providing support for the definition of elevated uric acid levels used in this study. Third, the study had a retrospective design and, therefore, might have limited generalizability of the conclusions. Therefore, a prospective study should be carried out to validate the preliminary findings of this study.

5. Conclusions

Uric acid elevation observed in COVID-19 patients treated with favipiravir was associated with the dosage of favipiravir administered and younger patient age. The median onset time to elevated uric acid level was 4.5 days after initiation of favipiravir. Therefore, the uric acid levels of patients with the abovementioned risk factors for uric acid elevation should be monitored closely throughout the duration of favipiravir therapy. As this study may have limited generalizability, further prospective studies incorporating more cases are needed to confirm our findings.

Ethical approval

The study protocol adhered to the ethical guidelines for epidemiological studies and was approved by the Ethics Committee of Toho University Omori Medical Center (approval number M20059).

Author contributions

Conceptualization, Y.H., Y.S. and K.T.; sample collection and methodology, Y.H., T.M., K.N., T.M. and H.O.; formal analysis, Y.H.; writing-

original draft preparation, Y.H., Y.S. and K.M.; writing-review and editing, Y.H., Y.S., S.U., Y.I. and T.Y.; supervision K.N. All authors meet the ICMJE authorship criteria and have approved the final version of the manuscript.

Declaration of competing interest

The authors report no conflicts of interest relevant to this article.

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