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The safety profile of favipiravir in COVID-19 patients with severe renal impairment

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Abstract

Objective: The safety profile of favipiravir in patients with severe renal impairment has not been investigated and available data are insufficient. The study aimed to compare the incidence of favipiravir-associated adverse events amongst patients with varying renal function statuses.

Methods: Records of 921 patients who were hospitalised for COVID-19 and had received at least 5 days of favipiravir treatment were retrospectively evaluated and 228 patients were included in the study. Patients' age, sex, comorbidities, estimated glomerular filtration rate (eGFR) and haematological and biochemical values were recorded. The incidence of adverse events was compared with the age, sex, comorbidities and eGFR of the patients.

Results: The mean age of the patients was 59.3 ± 15.6 years, and 38.2% of the patients were women. One hundred and thirty-one (57.5%) patients had experienced adverse events. These adverse effects consisted of ALT elevation (35.5%), AST elevation (21.5%), anaemia (16.2%), hyperuricaemia (10.5%), hepatocellular injury (9.2%), neutropenia (3.5%) and thrombocytopenia (2.6%). The incidence of adverse events was not significantly different when patients had eGFR >60 mL/min/1.73 m^2 or eGFR 30-60 mL/min/1.73 m^2 ($P > .05$), but significantly increased when the eGFR dropped to <30 ($P < .05$). The differences seen with hyperuricaemia and anaemia were significant ($P < .05$).

Conclusion: Even though favipiravir appeared to be well tolerated in the individuals with renal failure in this study, its use in this population remains a challenge that requires more research and analysis.

1 | INTRODUCTION

The coronavirus disease-2019 (COVID-19) pandemic has posed a significant challenge to health systems all over the world. Favipiravir is one of the pharmacological treatment alternatives for COVID-19.[1] Generally, favipiravir has a good safety profile and no serious adverse drug events have been reported. Hyperuricaemia, diarrhoea, neutropenia and increased liver transaminases have been reported as the most common adverse drug events. Although favipiravir has been used in many countries for some time, worldwide clinical studies of its safety profile are still ongoing.[2] Its pharmacokinetic data show that it has a short half-life and is rapidly excreted in

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the hydroxylated form via renal elimination.[3] Chronic kidney disease is frequently seen in the general population and is a risk factor for increased morbidity and mortality in COVID-19. The study aimed to compare the incidence of favipiravir-associated total and significant adverse events amongst patients having different estimated glomerular filtration rates (eGFRs).

What's known

- In COVID-19 patients, chronic renal disease is linked to an increase in morbidity and mortality.
- Despite the lack of safety data for favipiravir in patients with renal failure, the emergence of COVID-19 justifies its usage in this population.
- Favipiravir-related side effects (eg, hepatocellular injury) are well known, although the risk factors that lead to these side effects are unknown.

What's new

- Favipiravir increased the incidence of anaemia and hyperuricaemia in COVID-19 patients with severe renal impairment compared with those without renal impairment. However, these differences were not seen in severe adverse events (grades 3 and 4).
- The hepatocellular injury seems to be duration-dependent, as it was observed more frequently in patients treated with favipiravir for ≥10 days than in those treated for <10 days.

2 | MATERIAL AND METHODS

A retrospective observational study was conducted at Inonu University Turgut Ozal Medical Center between July 2020 and December 2020. Ethical approval for the study was granted by the Health Sciences Non-Interventional Ethics Committee of Inonu University (No: 2021/1541). Nine hundred and twenty-one patients with moderate to severe COVID-19 who had received favipiravir for at least five days participated in the study. Patients under the age of 18, patients who had received hydroxychloroquine or favipiravir before hospitalisation, patients using hydroxychloroquine and favipiravir concomitantly, patients who had received chemotherapy in the previous 3 weeks, patients with haematological disease and patients who had been treated in the intensive care unit at any stage of hospitalisation were excluded.

Favipiravir was administered to all patients orally as a 2 × 1600 mg loading dose on the first day and 2 × 600 mg maintenance dose on the following days for a maximum of 14 days. The age, sex, comorbid diseases and eGFR levels (calculated via the CKD-EPI method) of the patients were evaluated. Biochemical and haematological parameters of patients who had received favipiravir were compared before and after treatment.

2.1 | Grade of adverse events

The liver enzyme elevation grade, anaemia, neutropenia and thrombocytopenia were classified using the Common Terminology Criteria for Adverse Events (CTCAE v5.0).

Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than the upper limit of normal (ULN) but <3 × ULN were considered grade-1 liver enzyme elevation. A 3-5-fold rise in AST or ALT compared with ULN was classified as grade 2, a 5-20-fold increase as grade 3 and a > 20-fold increase as grade 4.

Normal ALT levels were identified as 19-25 IU/L for female patients and 29-33 IU/L for male patients,[4] whereas the normal AST levels were identified as 10-40 IU/L for female patients and 9-32 IU/L for male patients, and the normal alkaline phosphatase (ALP) levels were identified as 45-115 IU/L for male patients and 30-100 IU/L for female patients.

Drug-induced liver injury (DILI) was classified as either hepatocellular, cholestatic or mixed-type on the basis of the ALT and the ALP levels. For example, the hepatocellular injury was defined as an ALT more than three times the ULN and an *R* value of >5, whereas the *R* value was calculated as (ALT/ULN)/(ALP/ULN).[5]

The grade of anaemia was analysed as follows: grade 1 (male patient: 10.0-13.0 g/dL, female patient: 10.0-12.0 g/dL), grade 2 (male/female patient: 8.0-10.0 g/dL) and grade 3 (male/female patient: <8.0 g/dL). The grade of neutropenia was set as follows: grade 1 (male/female patient: 1500-2100 μL), grade 2 (male/female patient: 1000-1500 μL), grade 3 (male/female patient: 500-1000 μL) and grade 4 (male/female patient: <500 μL).

Moreover, the grade of thrombocytopenia was analysed as follows: grade 1 (male/female patient: 75 000-150 000 μL), grade 2 (male/female patient: 50 000-75 000 μL), grade 3 (male/female patient: 25 000-50 000 μL) and grade 4 (male/female patient: <25 000 μL).

Favipiravir-associated hyperuricaemia was defined as a post-treatment serum uric acid value of >6 mg/dL.[6]

2.2 | Statistical analysis

The data were statistically evaluated using the SPSS 20.0 (Statistical Package for Social Sciences) software. The Shapiro-Wilk test was used for normality analysis, and parametric tests such as the independent sample *t* tests were used for quantitative data. Pearson's χ^2 test, Yates continuity correction, or Fischer's exact test were used to analyse the differences of the categorical data. A *P* value of <.05 was considered to be statistically significant.

3 | RESULTS

Two hundred and twenty-eight COVID-19 patients receiving favipiravir therapy were included in this retrospective study. Baseline characteristic features of the patients receiving favipiravir are given in Table 1. Approximately two-thirds of the patients had one or more comorbidities, with the most common comorbidity being hypertension. The patients were given favipiravir for a mean of 7.2 ± 2.4 days. One hundred and forty-two patients had normal renal function (eGFR >60 mL/min/1.73 m^2), 58 had moderate renal impairment (eGFR 30-60 mL/min/1.73 m^2) and 28 had severe renal impairment (eGFR <30 mL/min/1.73 m^2).

Adverse events were seen in 131 (57.5%) COVID-19 patients after receiving favipiravir for an average of 6.5 ± 2.6 days. The observed adverse events included elevation of ALT and AST (35.5% and 21.5%, respectively), grades 1 and 2 anaemia (16.2%), hyperuricaemia (10.5%) and all grades of neutropenia (3.5%) and thrombocytopenia (2.6%). The mixed and cholestatic injury was not seen as DILI types, whereas the hepatocellular injury was seen in 9.2% of all patients.

Although adverse events were observed in 61.3% of male patients and 51.2% of female patients ($P = .135$), ALT elevation was observed in 40.8% and 26.7% of male patients and female patients, respectively. The mean ages of those with and without adverse events were similar ($P = .26$). No association was found between the development of anaemia, thrombocytopenia, neutropenia, hyperuricaemia, ALT or AST elevation, hepatocellular injury or age ($P > .05$).

Hypertension was found in 36.6% of male patients and 57% of female patients ($P = .003$). Diabetes mellitus was found in 25.4% of male patients and 45.3% of female patients ($P = .002$). The relationship between comorbidities and adverse events is given in Table 2. Although the incidence of total adverse events in patients with at least one comorbidity and in those with no comorbidities seemed to be similar ($P = .2$), hyperuricaemia was observed more frequently in patients with at least one comorbidity (13.6% vs 4.1%, $P = .048$). Elevated levels of ALT were more common in non-diabetic subjects than in diabetics ($P = .024$), whereas AST elevation was higher in non-hypertensives than in hypertensives ($P = .005$).

The incidence of favipiravir-associated adverse events in 142 patients with eGFR >60 mL/min/1.73 m^2 and in 58 patients with eGFR of 30-60 mL/min/1.73 m^2 was found to be similar (56.3% vs 48.3%, $P = .299$). The incidence of adverse events was 82.1% in patients with eGFR of <30 mL/min/1.73 m^2, whereas it was 54% in patients with eGFR of >30 mL/min/1.73 m^2 ($P = .008$). Additionally, the rate of favipiravir-associated anaemia and hyperuricaemia was higher in the group with eGFR of <30 mL/min/1.73 m^2 ($P < .05$) (Table 3).

Although the incidence of total adverse events was seen to be similar in patients who received favipiravir for ≥10 days and in those who received favipiravir for <10 days ($P = .354$), hepatocellular injury was observed more frequently in patients treated for ≥10 days (16.9% vs 5.7%, $P = .014$).

4 | DISCUSSION

Favipiravir was developed for the treatment of the neuraminidase inhibitor-resistant new influenza and has been used in the treatment of influenza, ebola and norovirus. Additionally, favipiravir is one of the pharmacological treatment alternatives for COVID-19.[1]

Increased hyperuricaemia[7] and liver enzymes[8] are the most common laboratory changes associated with favipiravir use according to the latest published clinical studies. Increases in liver transaminases have been found in more than 1% of individuals, pointing to probable DILI.[8] One trial demonstrated that patients with severe COVID-19 are predisposed to having abnormal liver function.[9] However, distinguishing between COVID-19-related liver injury and DILI is complicated.[10]

In the present study, liver enzyme-related adverse effects were observed in patients at all grades of ALT (35.5%) and AST elevation (21.5%). Mixed-type and cholestatic-type DILI were not observed, whereas hepatocellular-type DILI was observed in 9.2% of all patients. Acute hepatocellular injury in 90% of toxicity cases has been reported in studies evaluating drug-induced hepatotoxicity with histopathological findings.[11] However, cases of cholestatic DILI developing after a 2-week favipiravir regimen have also been reported in the literature. In one of these cases, acute decompensation of cirrhosis with cholestatic jaundice was observed because of favipiravir

TABLE 1 Characteristics of COVID-19 patients receiving favipiravir therapy

Male/female patients	142/86
Age, mean ± standard deviation (SD)	59.3 ± 15.6 y
eGFR, mean ± SD	68.5 ± 31.9 mL/min/1.73 m^2
Presence of comorbidity, percent	67.5%
Hypertension	44.3%
Diabetes mellitus	32.9%
Coronary artery disease	21.1%
Chronic obstructive pulmonary disease	11.4%
Malignancy	9.2%
Congestive heart failure	6.6%
Asthma	5.3%
Gout	2.2%

TABLE 2 Comparison of adverse events in patients with and without comorbidity

	Hypertension (+) (n = 101)	Hypertension (−) (n = 127)	*P* value
ALT elevation	28.7%	40.9%	.055
AST elevation	12.9%	28.3%	.005
Anaemia	13.9%	19.1%	.494
Hyperuricaemia	13.9%	7.9%	.213
Hepatocellular injury	7.9%	10.2%	.711
Neutropenia	4%	3.1%	.735
Thrombocytopenia	3%	2.4%	1
	Diabetes mellitus (+) (n = 75)	**Diabetes mellitus (−) (n = 153)**	***P* value**
ALT elevation	25.3%	40.5%	.024
AST elevation	17.3%	23.5%	.369
Anaemia	13.3%	17.6%	.523
Hyperuricaemia	12%	9.8%	.781
Hepatocellular injury	6.7%	10.2%	.467
Neutropenia	2.7%	3.9%	1
Thrombocytopenia	2.7%	2.6%	1
	Malignancy (+) (n = 21)	**Malignancy (−) (n = 207)**	***P* value**
ALT elevation	28.6%	36.2%	.646
AST elevation	28.6%	20.8%	.408
Anaemia	23.8%	15.5%	.35
Hyperuricaemia	8.3%	10.6%	1
Hepatocellular injury	9.5%	9.2%	1
Neutropenia	4.8%	3.4%	.544
Thrombocytopenia	0%	2.9%	1
	Gout (+) (n = 5)	**Gout (−) (n = 223)**	***P*-value**
ALT elevation	20%	35.9%	.658
AST elevation	20%	21.5%	1
Anaemia	0%	16.6%	1
Hyperuricaemia	60%	9.4%	.009
Hepatocellular injury	0%	9.4%	1
Neutropenia	0%	3.6%	1
Thrombocytopenia	0%	2.7%	1
	Coronary artery disease (+) (n = 48)	**Coronary artery disease (−) (n = 180)**	***P* value**
ALT elevation	20.8%	39.4%	.026
AST elevation	14.6%	23.3%	.265
Anaemia	18.8%	15.6%	.754
Hyperuricaemia	14.6%	9.4%	.444
Hepatocellular injury	8.3%	9.4%	1
Neutropenia	4.2%	3.3%	.676
Thrombocytopenia	2.1%	2.8%	1
	Congestive heart failure (+) (n = 15)	**Congestive heart failure (−) (n = 213)**	***P* value**
ALT elevation	26.7%	36.2%	.582
AST elevation	13.3%	22.1%	.535
Anaemia	20%	15%	.716

TABLE 2 (Continued)

	Congestive heart failure (+) (n = 15)	Congestive heart failure (−) (n = 213)	*P* value
Hyperuricaemia	0%	11.3%	.378
Hepatocellular injury	0%	9.9%	.372
Neutropenia	0%	3.8%	1
Thrombocytopenia	0%	2.8%	1
	Chronic obstructive pulmonary disease (+) (n = 26)	**Chronic obstructive pulmonary disease (−) (n = 202)**	***P* value**
ALT elevation	30.8%	36.1%	.748
AST elevation	15.4%	22.3%	.581
Anaemia	11.5%	16.8%	.777
Hyperuricaemia	7.7%	10.9%	1
Hepatocellular injury	7.7%	9.4%	1
Neutropenia	7.7%	3%	.228
Thrombocytopenia	0%	3%	1
	Asthma (+) (n = 12)	**Asthma (−) (n = 216)**	***P* value**
ALT elevation	41.7%	35.2%	.758
AST elevation	8.3%	22.2%	.47
Anaemia	0%	17.1%	.223
Hyperuricaemia	8.3%	10.6%	1
Hepatocellular injury	8.3%	9.3%	1
Neutropenia	0%	3.7%	1
Thrombocytopenia	0%	2.8%	1

treatment.[12] In this study, hyperuricaemia was observed in 10.5% of patients receiving favipiravir, although according to the literature, the occurrence of hyperuricaemia has been reported as only 4.79%.[8]

In addition, one of the case reports showed that non-oliguric acute kidney injury had developed 48 hours after favipiravir treatment in two COVID-19 pneumonia patients with normal creatinine clearance at baseline. Acute kidney injury was resolved in these patients 24-48 hours after discontinuing favipiravir.[13] However, data associating-specific organ injury with favipiravir is limited.

The decrease in the neutrophil count is a common haematological adverse event with favipiravir.[8] A decrease in neutrophil and haemoglobin counts was observed after favipiravir treatment in a trial investigating the haematological side effects of the drug. According to the same study, although the white blood cell count did not change after taking favipiravir, the platelet count increased significantly.[14] In this study, anaemia was observed in 16.2%, neutropenia in 3.5% and thrombocytopenia in 2.6% of patients after favipiravir treatment.

One retrospective descriptive study described the results of severe COVID-19 pneumonia patients who received at least 5 days of favipiravir therapy. The laboratory parameters of the patients were evaluated before and after favipiravir treatment. At the end of favipiravir therapy, a statistically significant increase in ALT and lymphocyte levels was found; however, there was no significant change in leukocyte or neutrophil counts. The effects of favipiravir on haematological laboratory parameters appeared to be contradictory to the literature.[15]

In a large cohort study of 1099 COVID-19 patients, 21.3% and 22.2% of the patients, respectively, had elevated levels of ALT and AST. In that study, hepatic enzyme elevation was shown to be more common in patients with severe disease than in those with the non-severe disease. Lymphocytopenia, thrombocytopenia and leukopenia were found in 83.2%, 36.2% and 33.7% of the patients, respectively. Similarly, abnormal haematological laboratory values were more frequent in severe COVID-19 patients than in non-severe patients.[16]

In a study of 4299 individuals, despite all biochemical and haematological adverse effects, favipiravir showed a well-characterised safety profile.[17] It was stated that the incidence of adverse effects could not be directly attributed to the use of favipiravir. This might have been because of the patients' treatment regimens aside from favipiravir.[18]

Adverse events related to favipiravir were observed in 61.3% of male patients and 51.2% of female patients in our study ($P > .05$). Although 40.8% of male patients had elevated ALT levels, this was observed in only 26.7% of female patients ($P < .05$). There was no difference between male and female patients in the occurrence of other adverse events. Likewise, the mean ages of those with and without adverse effects were similar in our study. In a study that analysed all suspected adverse drug events for favipiravir reported in 2015, severe adverse drug events were found to have occurred more frequently in male and elderly patients.[2]

When we looked at comorbidities, hypertension and diabetes were found more frequently in female patients than in male patients (57% vs 36.6% and 45.3% vs 25.4%, respectively). Elevation of ALT

TABLE 3 Comparison of adverse events in patients with eGFR <30 and >30 mL/min/1.73 m^2

	eGFR <30 (n = 28)	eGFR >30 (n = 200)	*P* value
Age, mean ± SD	57 ± 19.7	59.7 ± 15	.401
Duration of favipiravir therapy, mean ± SD	6.8 ± 2.7	7.2 ± 2.4	.327
Grades 1 and 2 anaemia	39.2%	13%	.001
Hyperuricaemia	32.1%	7.5%	.001
ALT elevation (any grade)	25%	37%	.214
Grades 1 and 2	21.4%	34.5%	.168
Grades 3 and 4	3.6%	2.5%	.74
AST elevation (any grade)	17.9%	22%	.617
Grades 1 and 2	13.3%	22%	.348
Grades 3 and 4	4.6%	0%	.123
Drug-induced liver injury	4.8%	10%	.484
Hepatocellular injury	4.8%	10%	.484
Cholestatic injury	0%	0%	—
Mixed type injury	0%	0%	—
Neutropenia (any grade)	0%	4%	.6
Grades 1 and 2	0%	3.5%	.602
Grades 3 and 4	0%	0.5%	1
Thrombocytopenia (any grade)	7.1%	2%	.16
Grades 1 and 2	7.1%	1.5%	.115
Grades 3 and 4	0%	0.5%	1

levels was greater in non-diabetic patients than in diabetic cases. Likewise, the elevation of AST levels was observed more frequently in patients without hypertension than in those with hypertension. The fact that adverse effects were more common in male patients than in female patients and that comorbidities such as diabetes and hypertension were less common in male patients than in female patients might be a contributory cause. Interestingly, patients without coronary artery disease had higher ALT enzyme levels than patients with coronary artery disease. As was expected, hyperuricaemia was more frequent in gout patients than in non-gout patients.

The blood trough concentration of favipiravir in patients with moderate renal impairment had increased 1.5 times compared with that of patients with normal renal function. In addition, because of the lack of available data for severe renal impairment patients, some prescribing protocols consider favipiravir to be contraindicated in these patients.[19]

Adverse events associated with the favipiravir treatment occurred in 43.4% of patients with mild renal insufficiency and in 30.3% of patients with normal creatinine clearance. Overall, the data are insufficient to recommend the use of favipiravir in patients with renal insufficiency.[10]

In a study comparing the effect of chronic kidney disease on clinical and prognostic features amongst hospitalised COVID-19 patients, patients without chronic kidney disease were more commonly administered favipiravir than patients with chronic kidney disease. This problem was observed in this study and was associated with the lack of data on favipiravir use in the early pandemic period. At the same time, it would not have been appropriate to test the safety of favipiravir therapy at this point.[20]

The safety of favipiravir therapy was tested in a trial in paediatric patients with COVID-19, multisystem inflammatory syndrome (MIS-C) and any degree of renal impairment. In that study, nine patients received favipiravir for 5 days, in spite of their renal impairment at the time of admission. In the trial, favipiravir treatment was received in two patients with GFR <30 mL/min/L/1.73 m^2. Favipiravir was administered to patients without dose adjustment, and no remarkable adverse events were observed in these patients as a result of favipiravir treatment. It was suggested that favipiravir may be an appropriate treatment option without dose adjustment in paediatric SARS-CoV-2 patients with renal insufficiency.[21]

In a study in which favipiravir was administered to a haemodialysis patient with COVID-19, the favipiravir blood concentrations were found to be similar to those of non-haemodialysis patients with normal renal function.[22] In another case report, no significant adverse events were observed in a patient on haemodialysis receiving favipiravir therapy, although serum ALP and gamma-glutamyl transferase levels increased during the treatment.[23] However, there are no comprehensive studies in the literature regarding the safety of favipiravir usage in patients with severe renal impairment. The necessary dose adjustments of favipiravir for these patients have thus not been identified. In this study, the incidence of adverse events observed after favipiravir use in patients with severe renal impairment was significantly higher than in patients with eGFRs >30 mL/min/1.73 m^2.

In this study, we looked at changes in laboratory values before and after favipiravir treatment for each patient independently. Anaemia and hyperuricaemia were more common in those with severe renal impairment than in the general population. Likewise, according to the findings of the current study, the incidence of anaemia and hyperuricaemia observed after favipiravir treatment in patients with severe renal impairment was higher than in the other groups. Therefore, regular follow-up monitoring of complete blood counts and biochemical parameters—particularly haemoglobin and uric acid—is needed in COVID-19 patients with severe renal impairment receiving favipiravir treatment.

4.1 | Limitations

The single-centred, retrospective nature of the study may be considered a limitation. Because this study was retrospective, side effects such as nausea, vomiting, diarrhoea and chest pain could not be evaluated.

Although we mainly observed changes in haematological and hepatic laboratory parameters after favipiravir treatment, this does not indicate that changes in these parameters could be completely associated with favipiravir. Haematological and hepatic changes may have been linked to the severity of COVID-19 infection and the use of medications other than favipiravir.

In addition, another limitation of the study was that the long-term laboratory parameters of these patients were not assessed following favipiravir therapy.

5 | CONCLUSION

Favipiravir increased the incidence of anaemia and hyperuricaemia in COVID-19 patients with severe renal impairment. However, after the use of favipiravir, no increased incidence of significant adverse events (grades 3 and 4) was observed in COVID-19 patients with severe renal impairment compared with those without renal impairment. In conclusion, favipiravir appeared to be well tolerated in the renal failure patients in this study. Because there is a lack of information on favipiravir usage in patients with severe renal impairment, we believe that the findings of our study will contribute to the literature. However, favipiravir usage in this population remains a challenge that will require more research and investigation.

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DISCLOSURES

There is no conflict of interest between authors.

AUTHOR CONTRIBUTIONS

Selim Gök: Data curation, methodology, conceptualization, investigation, writing-review & editing, writing of the original draft. Ömer Faruk Bahçecioğlu: Data curation, methodology, conceptualization, investigation, writing-review & editing, writing of the original draft. Mefküre Durmuş: Data curation, investigation, methodology, formal analysis, writing-review & editing. Zeynep Ülkü Gün: Supervision, validation, methodology, formal analysis, visualization. Yasemin Ersoy: Methodology, supervision. Zeynep Ayfer Aytemur: Methodology, supervision. Özkan Ulutaş: Methodology, supervision.

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REFERENCES

1. Wu R, Wang L, Kuo H-CD, et al. An update on current therapeutic drugs treating COVID-19. *Curr Pharmacol Rep*. 2020;6:56-70.
2. Kaur RJ, Charan J, Dutta S, et al. Favipiravir use in COVID-19: analysis of suspected adverse drug events reported in the WHO database. *Infect Drug Resist*. 2020;13:4427.
3. Agrawal U, Raju R, Udwadia ZF. Favipiravir: a new and emerging antiviral option in COVID-19. *Med J Armed Forces India*. 2020;76:370-376.
4. Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: evaluation of abnormal liver chemistries. *Am J Gastroenterol*. 2017;112:18-35.
5. Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug-induced liver injury. *Clin Pharmacol Ther*. 2011;89:806-815.
6. Bardin T, Richette P. Definition of hyperuricemia and gouty conditions. *Curr Opin Rheumatol*. 2014;26:186-191.
7. Chen C, Huang J, Cheng Z, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial. *MedRxiv*. 2020.
8. Avigan Prescribing Information; 2021. https://www.cdc.gov.tw/File/Get/ht8jUiB_MI-aKnlwstwzvw. cited February 6, 2021.
9. Parohan M, Yaghoubi S, Seraji A. Liver injury is associated with severe coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of retrospective studies. *Hepatol Res*. 2020;50:924-935.
10. Fan Z, Chen L, Li J, et al. Clinical features of COVID-19-related liver functional abnormality. *Clin Gastroenterol Hepatol*. 2020;18:1561-1566.
11. Zhang X, Ouyang J, Thung SN. Histopathologic manifestations of drug-induced hepatotoxicity. *Clin Liver Dis*. 2013;17:547-564.
12. Kumar P, Kulkarni A, Sharma M, Rao PN, Reddy DN. Favipiravir-induced liver injury in patients with coronavirus disease 2019. *J Clin Transl Hepatol*. 2021;9:276.
13. Nasa P, Shrivastava P, Kulkarni A, Vijayan L, Singh A. Favipiravir induced nephrotoxicity in two patients of COVID-19. *J Assoc Phys India*. 2021;69:88.
14. Yaylaci S, Dheir H, Şenocak D, et al. The effects of favipiravir on hematological parameters of covıd-19 patients. *Revista Da Associação Médica Brasileira*. 2020;66:65-70.
15. Erdem HA, Ekren PK, Çağlayan D, et al. Treatment of SARS-cov-2 pneumonia with Favipiravir: early results from the Ege University cohort, Turkey. *Turk J Med Sci*. 2021;51:912-920.
16. Guan W-J, Ni Z-Y, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2019;2020:1708-1720.
17. Pilkington V, Pepperrell T, Hill A. A review of the safety of favipiravir–a potential treatment in the COVID-19 pandemic? *J Virus Eradication*. 2020;6:45-51.
18. Shrestha DB, Budhathoki P, Khadka S, Shah PB, Pokharel N, Rashmi P. Favipiravir versus other antiviral or standard of care for COVID-19 treatment: a rapid systematic review and meta-analysis. *Virol J*. 2020;17:1-15.
19. Brief FGPP. Unlocking the Treatment for Mild to Moderate COVID-19 in India; 2021. Available from: https://www.glenmarkpharma.com/sites/default/files/Glenmark-FabiFlu-Press-Brief.pdf. Accessed February 6, 2021.
20. Dirim AB, Demir E, Yadigar S, et al. COVID-19 in chronic kidney disease: a retrospective, propensity score-matched cohort study. *Int Urol Nephrol*. 2021:53:2117-2125.
21. Ozsurekci Y, Oygar PD, Gürlevik SL, et al. Favipiravir use in children with COVID-19 and acute kidney injury: is it safe? *Pediatr Nephrol*. 2021:1-6.
22. Hirai D, Yamashita D, Seta K. Favipiravir for COVID-19 in a patient on hemodialysis. *Am J Kidney Dis*. 2021;77:153.
23. Koshi E, Saito S, Okazaki M, et al. Efficacy of favipiravir for an end stage renal disease patient on maintenance hemodialysis infected with novel coronavirus disease. *CEN Case Rep*. 2019;2020:1-6.

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