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
the hydroxylated form via renal elimination. 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).

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, 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).

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: 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).

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.

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 χ² 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.
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 m²), 58 had moderate renal impairment (eGFR 30-60 mL/min/1.73 m²) and 28 had severe renal impairment (eGFR <30 mL/min/1.73 m²).

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 thrombocytopoenia (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).

| 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 m² |
| 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% |

The incidence of favipiravir-associated adverse events in 142 patients with eGFR >60 mL/min/1.73 m² and in 58 patients with eGFR of 30-60 mL/min/1.73 m² 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 m², whereas it was 54% in patients with eGFR of >30 mL/min/1.73 m² (P = .008). Additionally, the rate of favipiravir-associated anaemia and hyperuricaemia was higher in the group with eGFR of <30 mL/min/1.73 m² (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).

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 hyperuricaemia7 and liver enzymes8 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...
|                         | 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    |
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%. 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. However, data associating specific organ injury with favipiravir is limited.

The decrease in the neutrophil count is a common haematological adverse event with favipiravir. 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. 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 leucocyte or neutrophil counts. The effects of favipiravir on haematological laboratory parameters appeared to be contradictory to the literature.

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.

In a study of 4299 individuals, despite all biochemical and haematological adverse effects, favipiravir showed a well-characterised safety profile. 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.

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 2 (Continued) |
|----------------------|
| **Concentive heart failure (+) (n = 15)** | **Concentive 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    |
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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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/1.73 m\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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\textsuperscript{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.

| TABLE 3 Comparison of adverse events in patients with eGFR <30 and >30 mL/min/1.73 m\textsuperscript{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 |
| Necrotising 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 |
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 Bahçeceoğlu: 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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