Saudi Toxicology Journal (STJ)

Journal home page: https://uqu.edu.sa/s.toxicology.s/S.T.J

Article

Impact of Favipiravir Toxicity on Liver Function in Hospitalized Adult Covid-19 Patients in Taif, Saudi Arabia

Doaa M Johari[1], Abdullah R. Alzahrani[2], Tariq Alpakistany[3], and Mohammad Melebari [4]*

[1]Pharmacy administration department, Taif Health cluster, ministry of Health, Taif, 26254, Saudi Arabia.
[2]Department of Pharmacology and Toxicology, Faculty of Medicine, Umm Al-Qura University, Al-Abidiyah, P.O.Box 13578, Makkah, 21955, Saudi Arabia.
[3]Public health laboratory, Taif 26521, Ministry of health, Saudi Arabia.
[4] Department of Biology, Faculty of Science, Al-Baha University, Al-Baha, 65431, Saudi Arabia.
*Corresponded Author: Mohammad Melebari, e-mail: melebari@bu.edu.sa

Citation: Johari, D. M.; Alzahrani, A. R.; Alpakistany, T. and Melebari, M. (2024). Impact of Favipiravir Toxicity on Liver Function in Hospitalized Adult Covid-19 Patients in Taif, Saudi Arabia. *STJ*,**2024**,1,39-50 https://doi.org/10.70957/uqu.edu.sa/s.toxicology.s/stj.2024.1.5

Received: 10 November 2024

Accepted: 17 December 2024

Published: 24 December 2024

Abstract:

Background: Favipiravir is an antiviral medication for the treatment of coronavirus disease 2019 (COVID-19). There were a limited number of studies investigating the hepatotoxic adverse effects of favipiravir. **Aim of the Study:** The study aimed to assess the potential toxic impact of loading and maintenance doses of favipiravir on liver function through liver function evaluation. **Materials and Methods:** In this cross-sectional retrospective observational study, 476 adult COVID-19 patients hospitalized at King Faisal Medical Complex (KFMC) in Taif City, Saudi Arabia, used favipiravir. Liver functions (aspartate aminotransferase (AST), alanine aminotransferase (ALT), and Free bilirubin) were taken from randomly selected subjects. Pre- and post-treatment liver function results were randomly assigned. **Results:** The age of the patients varied between 18 and 65 years. All participants enrolled in this trial were diagnosed with COVID-19 and received treatment with favipiravir. The majority of patients, treated with favipiravir, exhibited normal liver function test results, with 78.2% showing normal levels of AST and 45% showing normal levels of ALT. A smaller percentage of patients, 20.2% and 48.7% respectively, experienced a modest increase in these enzyme levels. After undergoing favipiravir therapy, the majority of patients (95.59%) showed normal bilirubin levels. A notable disparity was observed in the levels of AST, ALT, and bilirubin before and after favipiravir treatment, with a p-value < 0.001 for all patients included in the study. Conclusion: According to the study, antiviral favipiravir had no major liver side effects; it caused hepatic function elevations but not serious and is reversible after discontinuation.

Keywords: Favipiravir, hepatotoxicity, COVID-19, Pandemic, Saudi MoH.

1. Introduction

As of April 2022, over 500 million COVID-19 confirmed cases had been reported worldwide, with over 400 million infected patients in over 210 countries having confirmed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. Over six million deaths have been related to COVID-19 [1]. Most patients present with mild to moderate symptoms, while others remain asymptomatic during the incubation period and infection. Severe cases can start with shortness of breath and dyspnea, progress to severe pneumonia, multiple organ failure, and even death [2]. The World Health Organization (WHO) reports that most patients with COVID-19 experience symptoms such as pyrexia, cough, fatigue, loss of appetite, dyspnea, muscle aches, headaches, sore throat, diarrhea, nausea, vomiting, and nasal congestion. Additionally, neurological complaints such as dizziness, agitation, muscle weakness, convulsions, and stroke-like symptoms include speech or vision difficulties, balance instability, and gait abnormalities [3]. According to Zhang et al. (2020) [4], those who have elevated counts of neutrophils and leukocytes, in addition to low lymphocytes, are at a higher risk of developing severe COVID-19 pneumonia and need critical care. Severe COVID-19 pneumonia is also indicated by elevated C-reactive protein, α-hydroxybutyrate dehydrogenase activity, D-dimer levels, and decreased total protein levels. All these patients with severe COVID-19 pneumonia should be under mechanical ventilation or artificial respiration [4]. The viral structural spike protein binds to the Angiotensin-Converting Enzyme 2 (ACE2) receptor to let SARS-CoV-2 into cells. Transmembrane protease, serine 2 (TMPRSS2) helps it use host cell receptors and endosomes [5]. Viral particles manufacture polyproteins for the replicase-transcriptase complex system, RNA-dependent RNA polymerase (RdRP), and structural proteins when they enter cells [6, 7].

Real-time reverse-transcription polymerase chain reaction (RT-PCR) is the gold standard for diagnosing COVID-19 infection, using nucleic acid next-generation sequencing and viral-specific primers. The main aim is to detect the envelope protein, nucleocapsid protein, and open reading frame gene sequences in the viral genome [8, 9]. Samples collected include nasal swabs, sputum, lower respiratory tract secretions, blood, and feces [8]. A study by Yang et al. (2020) found that sputum had the highest accuracy, preceding nasal swabs [10]. K. K.-W. et al. (2020) [11] found that COVID-19 RNA sequence was detected in 91.7% of COVID-19 patients' saliva, indicating the accuracy of this molecular diagnostic technique. The study highlights the importance of accurate and reliable testing for COVID-19 infection [11]. Favipiravir is an antiviral agent that disrupts the replication of various RNA viruses, including the influenza virus. Its active form, favipiravir ribofuranosyl-5’-triphosphate (RTP), competes with purine nucleoside and blocks RNA-dependent RNA polymerase, preventing viral transcription and replication [13, 14]. This disruption leads to increased mutations in translation, causing devastating mutagenesis in RNA viruses [15]. Favipiravir is a potent therapeutic agent in COVID-19 treatment, effectively preventing infection spread and removing the virus [16]. It has also been used effectively against Ebola and other RNA viruses responsible for viral hemorrhagic fever [16, 17]. Studies have shown improved survival rates in patients with moderate to high Ebola viral loads by favipiravir, with doses ranging from 6,000 mg on the first day to 2,400 mg on days 2 to 9 [17]. Bai et al.'s study also showed a significant decline in Ebola viral load with favipiravir, with doses of 800 mg twice daily on the first day and 600 mg twice daily on the second day [17]. Moreover, given that the homology of gene sequences in COVID-19 exceeds 90%, it is anticipated that the administration of antiviral medications to patients with COVID-19 will probably enhance or reduce the duration required for viral elimination [18, 19].

According to the Saudi Ministry of Health (MoH) protocol, favipiravir is administered for mild to moderate COVID-19-infected patients, followed by corticosteroid therapy for severe symptoms [20]. Adverse events associated with favipiravir include elevated liver enzymes, uric acid levels, neutropenia, and gastrointestinal issues [21]. Presumably, these unfavorable incidents were self-regulated with discontinuation of the medicine, requiring no further intervention for resolution [22]. The study conducted by Cai, Q. et al. (2020) [21] demonstrated that favipiravir had mild adverse effects, including one case of poor diet, two cases of diarrhea, and one case of liver injury. The administration of favipiravir can be extended for prolonged periods based on the patient's clinical state [22]. Favipiravir was found to have

teratogenic and embryotoxic effects, according to previous findings [23].

Unfortunately, there is not enough information available at this time on the effects of favipiravir on pregnant women [24]. Favipiravir has been found to have a teratogenic effect and should not be prescribed to pregnant females. It is contraindicated for those becoming pregnant, requiring effective contraception during therapy and one week after the last dose [12]. Additional serious side effects of favipiravir included asthma, oropharyngeal pain, rhinitis, nasopharyngitis, blood creatine phosphokinase (CPK) increased, blood in urine, tonsil polyp, pigmentation, dysgeusia, bruise, blurred vision, eye pain, vertigo, supraventricular extrasystole, eczema, and pruritus [25]. In addition, it has been shown that favipiravir can cause testes toxicity, disrupting sperm count and viability through bilateral seminiferous epithelial degeneration and hypoplasia, prompting urgent investigation of potential sequelae in male patients [26]. Favipiravir can cause renal toxicity in patients with high-risk factors like diabetes, heart diseases, hypertension, nephrotoxic medications, or elderly patients with chronic kidney disease. This occurs due to epithelial degeneration and renal tubule dilation. Careful observation and accurate dose adjustment are necessary due to persistent elevation in serum creatinine, without other medical reasons like nephrotoxic drugs, sepsis, hypotension, dehydration, or other medical causes [27].

This study investigates the relationship between loading and maintenance doses of favipiravir in COVID-19 patients and acute liver toxicity. It aims to compare liver enzyme levels before and after treatment to assess the liver toxicity due to favipiravir treatment and identify mild, moderate, or severe elevations.

2. Materials and Methods

The design of the study is a cross-sectional retrospective, hospital-based study, conducted at King Faisal Medical Complex in Taif City (KFMC), which is an 800-bed facility currently accommodating COVID-19-positive patients. The data obtained for this study focused on liver function tests, including AST, ALT, and free bilirubin.

2.1 Population and Study Sample Size

The study included a sample of 476 adult patients who received favipiravir with a loading dose of 1800 mg twice daily for the first day, followed by the maintenance dose of 800 mg twice daily for 7-10 days, between January 2021 and October 2021. The sample size was determined using the Qualtrics online calculator, based on a total of 4265 patients. The study used a 95% confidence interval (CI).

The study included patients who met the following criteria:

• Aged between 18 and 65 years

• Both males and females

• The respiratory sample was diagnosed as positive for COVID-19.

• Hospitalized with mild to moderate symptoms, including fever, without the need for oxygen or presence of pneumonia.

• Administering the favipiravir pill.

• Possessing diverse ethnic backgrounds.

• The onset of symptoms occurred within a week.

The study excluded patients who met the following criteria:

• Patients who were admitted to the hospital with severe symptoms of COVID-19, including pneumonia, severe respiratory distress, a respiratory rate over 30 breaths per minute, and blood oxygen saturation below 90%.

• In cases of liver or renal disorders that have progressed to end-stage.

• Having a prior medical record of allergic reactions to favipiravir.

• Administering additional drugs that have hepatotoxic effects.

• Women who are currently pregnant or breastfeeding.

2.2 Collection of Data

The laboratory test results on liver enzyme function were acquired from the files of COVID-19-positive individuals who met all the specified inclusion criteria. The evaluation of liver enzyme function involved the random division of data acquired from patients' files into stratified random samples. The

samples were stratified based on ALT, AST, and bilirubin levels before and after therapy initiation.

Furthermore, the laboratory results indicated whether the liver enzyme function tests (ALT, AST, and bilirubin) indicated normal or abnormal levels. The elevation or abnormality of liver enzymes (ALT, AST) was classified into three grades: mild, moderate, and severe, while the upper normal limit of serum AST was 42 U/L and ALT was 33 U/L, according to the KFMC reference range. Thus, the upper normal limit of total bilirubin is 1.1 mg/dL, and the AST and ALT are mild at level <210 U/L (<5-fold), moderate at the range of 210-420 U/L (5-10-fold), and severe at levels >420 U/L (>10-fold), 165 U/L (<5-fold), and 330 U/L (>10-fold), respectively.

2.3 Data Analysis Strategies

All data were collected, computed, tabulated, and statistically analyzed using the mentioned tests. A Kolmogorov-Smirnov test verified the samples' normal distribution. Descriptive statistics were generated using Mean ± Standard Deviation (SD). A Chi-square test compared qualitative data between categories. Every two groups were compared using paired and independent sample t-tests regarding quantitative data. A P-value <0.05 indicated statistical significance. A correlation coefficient, using the Pearson test, was computed between age and enzymes. All statistical analyses were conducted using SPSS 26.0 (Statistical Package for Social Science, Armonk, NY: IBM Corp) at a significance level of 0.05 (P-value <0.05).

2.4 Ethics and Human Subjects Issues

The study received ethical approval from the Ethics Review Committee of Umm Al-Qura University (reference number KLAP170221, Appendix 2) and the Taif Research and Ethics Committee (approval number HAP-02-T-067, Appendix 1). The study was conducted in accordance with the guidelines of the research committee of KFMC, Taif, as it involved human subjects and access to confidential patient information.

3. Results

3.1 Demographic profile and General information

This study included 476 COVID-19 patients in KFMC, and all received Favipiravir. Table 1 shows the baseline characteristics of the population sample. The age range was from 18 to 65 years, with the mean age of the patients being 48.5 ± 11.2 years. Most patients were in the age range of 50 to 59 years, including 162 patients (34.03%), followed by 40-49 years (22.90%). There was a statistically significant difference between age categories using the Chi-square test (p <0.001). The majority of patients were males, with a total of 265 (55.67%), while females accounted for 211 patients (44.33%), indicating a nearly equal distribution between genders. In addition, regarding ethnicity, most of the patients were Saudi, with a total number of 310 (65.13%). Only 25 (5.25%) out of 476 patients discontinued their favipiravir due to elevated liver enzymes. For gender, ethnicity, and drug discontinuation, there was a statistically significant difference at p <0.05.

3.2 Comparison of liver enzymes and bilirubin levels in COVID-19 patients before and after favipiravir therapy

The liver enzymes AST, ALT, and bilirubin levels at the end of the study are shown in Table 2. For AST and ALT, the majority of patients had normal levels (78.2% and 45%) and mild elevation (20.2% and 48.7%) after favipiravir therapy, with a significant statistical difference (p = 0.007 and <0.001, respectively) using the Chi-square test. Regarding bilirubin, most patients had normal levels after favipiravir therapy (95.59%), while 4.41% showed elevated levels after therapy. However, there was no statistically significant difference between normal and high bilirubin levels before and after favipiravir treatment (p = 0.196).

3.3 Change in liver function values

The results in Table 3 showed a significant difference between before and after favipiravir therapy for AST, ALT, and bilirubin as the mean in all studied patients (P <0.001). AST, ALT, and bilirubin increased 19.24%, 98.04%, and 12.70%, respectively after administration of favipiravir.

3.4 Comparison of liver functions level in patients before and after favipiravir therapy according to age

The data presented in Table 4 illustrate the levels of liver enzymes across various age groups. These results showed no statistically significant difference for AST between age categories, except for the patients in the age group 50-59 years, who had an AST mean before the treatment (42.76 ±

Table 1: Demographic profile and general information about the patients

Age	N	%	Chi-test	P value
<20	2.0	0.42	101.94	<0.001**
20-29	25.0	5.25		
30-39	87.0	18.28		
40-49	109.0	22.90		
50-59	162.0	34.03		
>60	91.0	19.12		
Mean	**48.5**			
SD	**11.2**			
Min	**18.0**			
Max	**65.0**			
Gender				
Male	265.0	55.67	6.12	0.013**
Female	211.0	44.33		
Ethnicity				
Saudi	310.0	65.13	43.56	<0.001**
Non-Saudi	166.0	34.87		
Drug discontinue				
No	451.0	94.75	381.25	<0.001**
Yes	25.0	5.25		
****, means significant difference at P value<0.05**				

Table 2: Comparison of liver enzymes and bilirubin levels in COVID-19 patients before and after favipiravir therapy

	Before (total 476)	After (total 476)	Chi-test	P value
AST	**N (%)**	**N (%)**		
Normal	412(86.6%)	372(78.2%)	12.036	0.007**
Mild	64(13.4%)	96(20.2)		
Moderate	0(0.0)	4(0.8)		
severe	0(0.0)	4(0.8)		
ALT	**Before (total 476)**	**After (total 476)**		
Normal	399(83.8)	219(45.0)	152.09	<0.001**
Mild	73(15.3)	232(48.7)		
Moderate	4(0.8)	18(3.8)		
severe	0(0.0)	7(1.5)		
Bilirubin, total	**Before (total 476)**	**After (total 476)**		
Normal	476(100.0)	455(95.59)	1.67	0.196
high	0(0.0)	21(4.41)		
****, means significant difference at P value<0.05**				

3.72) and after the treatment (55.61 ± 4.69), with a significant statistical difference at (P = 0.012). Meanwhile, the mean of ALT and bilirubin after the treatment showed a statistically significant difference for all age categories, except for the patients less than 20 years, the group containing only two patients (P-value 0.520, 1.00, respectively).

Table 3: liver function values (Mean ±SD) for all studied cases before and after favipiravir therapy

	Before	After	%Change	t	P value
AST	43.324±38.69	53.006±55.17	19.24	3.253	<0.001**
ALT	36.870±36.32	74.059±70.71	98.04	11.031	<0.001**
Bilirubin	0.63±0.15	0.71±0.19	12.70	7.650	<0.001**
****, means significant difference at P value<0.05**					

Table 4: Comparison of level of liver enzymes and bilirubin in patients before and after favipiravir Therapy according to age

	AST			
	Before (mean±SD)	**After (mean±SD)**	**T test**	**P values**
<20	30.50±10.60	28.50±9.19	2.00	0.295
20-29	40.64±4.82	53.0±6.83	0.933	0.360
30-39	38.31±3.97	44.56±3.59	1.228	0.223
40-49	47.47±4.48	51.63±5.28	0.669	0.505
50-59	42.76±3.72	55.61±4.69	2.530	0.012**
>60	45.15±4.11	58.63±7.73	1.614	0.110
	ALT			
<20	22.50±1.70	68.0±7.88	0.938	0.520
20-29	34.72±5.06	74.56±7.02	2.508	0.019**
30-39	35.33±3.73	80.07±5.75	6.253	<0.001**
40-49	39.70±3.30	71.52±6.65	4.960	<0.001**
50-59	36.70±3.23	70.93±6.10	5.830	<0.001**
>60	36.14±4.66	76.90±7.74	4.625	<0.001**
	Bilirubin, total			
<20	0.45±0.00	0.45±0.00	0.00	1.00
20-29	0.56±0.12	0.61±0.11	2.19	0.038**
30-39	0.75±0.12	0.79±0.12	2.896	0.005**
40-49	0.59±0.15	0.64±0.18	2.380	0.019**
50-59	0.64±0.15	0.73±0.19	5.705	<0.001**
>60	0.60±0.14	0.68±0.23	3.795	<0.001**
****, means significant difference at P<0.05**				

3.5 Comparison of liver functions level in patients before and after favipiravir therapy according to gender

In the comparison between before and after therapy with favipiravir for males and females, there was a significant statistical difference in AST and ALT means before and after treatment in both genders, with p-values <0.001 and <0.001 for males and p-values 0.04 and <0.001 for females, as shown in Table 5. On the other hand, there was no significant statistical difference between male and female patients after favipiravir treatment for AST enzyme; p-value was 0.388. In addition, there was a significant statistical difference in the ALT mean after favipiravir treatment (p <0.001), where males had the highest values, as shown in Table 5. For bilirubin, statistical analysis showed a significant difference between before and after favipiravir therapy for both genders (p <0.001). Furthermore, in the comparison between males and females for bilirubin, males showed higher significant bilirubin levels than females after favipiravir therapy (p 0.01).

3.6 Pearson Correlations between age and liver functions

The result in Table 6 shows a non-significant correlation between age and AST, ALT, and

Table 5: Comparison of level of liver enzymes and bilirubin in patients before and after favipiravir Therapy according to gender

AST				
	Before (mean±SD)	**After (mean±SD)**	**T test**	**P values**
Male	43.72±2.34	54.95±3.57	2.67	**<0.001****
Female	42.81±7.15	50.55±3.52	1.86	**0.04****
Independent T test	**0.256**	**0.863**		
P values	**0.798**	**0.388**		
ALT				
Male	41.47±2.61	91.42±4.43	10.67	**<0.001****
Female	31.080±1.75	52.25±4.30	4.592	**<0.001****
Independent T test	**3.13**	**6.239**		
P values	**<0.001****	**<0.001****		
Bilirubin, total				
Male	0.632±0.09	0.729±0.014	6.822	**<0.001****
Female	0.636±0.12	0.683±0.01	3.686	**<0.001****
Independent T test	**0.314**	**2.60**		
P values	**0.754**	**0.01****		
****, means significant difference at P value<0.05**				

Table 6: Pearson Correlations between age and liver functions (AST, ALT and bilirubin)

	Age	**AST**	**ALT**	**Bilirubin**
Age	---	0.086	-0.018	-0.012
AST	0.086	---	0.488**	0.139**
ALT	-0.018	0.488**	---	0.278**
Bilirubin	-0.012	0.139**	0.278**	---
****. Correlation is significant at the 0.01 level (2-tailed).**				

bilirubin (0.086, -0.018, and -0.012), respectively. However, there was a significant positive moderate correlation between AST and ALT (0.488). In addition, there was a significant positive weak correlation between AST and bilirubin p (0.139), and between ALT and bilirubin (p 0.278).

4. Discussion

The SARS-CoV-2 pandemic began in China in late 2019, rapidly spreading worldwide, affecting human health and economies [28]. As of April 2022, there were over 500 million confirmed cases and 6 million deaths worldwide. Saudi Arabia had 761,079 confirmed cases and 9,123 deaths [1]. Research primarily focuses on the lungs, but some reports suggest liver involvement and other organs may also be affected. Various medications, including antivirals, antibacterials, antiparasitics, and immune modulators, have been tried for COVID-19 management. The disease has affected metabolism and excretion of medications, impacting the global economy [28]. Some of these drugs may cause COVID-19-related liver injury, and monitoring changes in liver profiles and the timing of administered drugs in COVID-19 patients during hospitalization could provide insight into the relationship between drugs and liver injury [28].

This retrospective study, conducted at KFMC in Taif, Saudi Arabia, aimed to investigate the relationship between loading and maintenance doses of favipiravir in 476 COVID-19 patients. The data were collected between January and October 2021, and the study was divided into normal and abnormal categories based on laboratory outcomes. The abnormalities or elevation of liver enzymes were subdivided into three grades: mild, moderate, and severe. The upper normal limit (UNL) of serum AST was 42 units/L, and ALT was 33 units/L.

Bilirubin levels were assessed as normal (0–1.1 mg/dL) and high levels (≥ 1.1 mg/dL). The study aimed to determine the probability of acute liver toxicity in these patients. The findings could help inform the development of effective treatment strategies for COVID-19 patients.

This study included randomly selected patients aged 18–65, males and females, diagnosed with COVID-19, admitted to the hospital with mild to moderate symptoms (fever, no requirement of oxygen, no pneumonia), and using favipiravir. The initial symptoms typically occurred within seven days. The study excluded patients with severe symptoms, existing liver diseases, previous allergic reactions to favipiravir or other antiviral medications, and pregnant or lactating women. Pregnant women were excluded due to the teratogenic effects of favipiravir. Shiraki et al. (2020) [28] found cases of reliable pregnancy or intended pregnancy, indicating that favipiravir must be contraindicated due to its teratogenic and embryotoxic effects. The study's exclusion criteria were based on the severity of symptoms and the use of other antiviral medications [29].

This study analyzed patients aged 18–65 years, with a mean age of 48.5 ± 11.2 years. The age group 50–59 years had significantly higher AST before and after treatment, while ALT and bilirubin levels were significantly different for all age groups except for those under 20 years. The study found that most acute liver injuries were caused by favipiravir therapy, with most cases occurring in patients over 50 years.

A case report study by Kumar P. et al. (2021) [29] reported three confirmed COVID-19 patients receiving favipiravir. The first was a 70-year-old female with abdominal pain and jaundice. The liver biopsy revealed moderate hepatic cholestasis with bilirubin stasis and mild inflammation. After proper management, the patient was diagnosed with favipiravir-induced acute cholestatic jaundice. The second patient, a 52-year-old female with essential hypertension, presented with jaundice and fatigue after receiving favipiravir for two weeks. The last patient, a 50-year-old male with hepatitis B-related cirrhosis, presented with abdominal distension and jaundice after receiving favipiravir for two weeks. The liver chemistry showed high elevations with a negative hepatitis B DNA titer, and cirrhosis with portal hypertension was discovered on a computed tomography (CT) scan [29]. The dosage of favipiravir used in the prior study was significantly higher and did not align with the dosing mentioned in the MoH protocol [20].

The study found that males (55.67%) had a higher risk factor for poor outcomes in COVID-19 compared to females (44.33%). According to Yeoman et al.'s (2020) study [30], males had a larger presence of the ACE2 receptor on the surface of their cholangiocytes, and elevated serum alkaline phosphatase and bilirubin. Yeoman et al.'s (2020) study found a 31% incidence of liver test abnormalities in 318 confirmed COVID-19 patients [30]. Furthermore, according to Channappanavar et al. (2017) [31], COVID-19 has a greater impact on males compared to females. Women have a lower vulnerability to viral infections due to the protective effects of the X chromosome and sex hormones, which play a crucial role in both innate and adaptive immunity [31].

The current study found a highly significant difference in AST, ALT, and total bilirubin levels before and after favipiravir therapy for males ($p<0.001$) and in ALT and total bilirubin levels before and after favipiravir therapy for females ($p<0.001$). In addition, males were more affected than females in ALT with mean±SD of 91.42±4.43 for males and 52.25±4.30 for females. The bilirubin level was 0.729±0.014 for males and 0.683±0.01 for females after favipiravir treatment, with significant statistical differences of $p<0.001$ and $p=0.01$, respectively.

The study followed the Saudi MoH protocol for managing mild to moderate COVID-19 cases, prescribing favipiravir therapy as the antiviral medication. The loading dose was 1800 mg twice daily for the first day, followed by the maintenance dose of 800 mg twice daily for 7–10 days [22].

The study found that favipiravir doses were similar to previous studies, with a median duration of 10 days. This aligns with a 2020 study by Udwadia et al., a randomized, open-label, parallel-arm, multicenter, phase 3 clinical trial, which randomized 150 COVID-19 patients aged 18–75 years to oral favipiravir, starting with 1800 mg twice a day for the first day and decreasing to 800 mg twice a day for 2–14 days, with standard supportive care versus supportive care alone [33].

A randomized clinical trial by Chen et al. (2020) [34] compared the efficacy and safety of favipiravir with different doses. The study found that the umifenovir group had a higher 7-day clinical recovery rate (54.86%), while the favipiravir group had a higher recovery rate (71.43%). The most common adverse events observed were gastrointestinal manifestations, high serum uric acid levels, and hepatic enzyme rises (2.5% in the umifenovir group vs. 13.79% in the favipiravir group), which is the same adverse event observed in the current study.

A recent randomized clinical trial by Chen et al. (2020) [34] studied different doses of favipiravir. The study compared the efficacy and safety of favipiravir with a dose of 1600 mg twice on the first day followed by 600 mg twice a day for ten days to umifenovir 200 mg three times a day in 240 COVID-19 hospitalized patients. Umifenovir had a 55.86% 7-day clinical recovery rate, while favipiravir had 71.43% (p=0.01) [34]. Adverse events, such as gastrointestinal symptoms, elevated serum uric acid levels, and hepatic enzyme increases, were more prevalent in the favipiravir group (13.79% vs. 2.5%, p<0.0001) [35], agreeing with the adverse events in the current study.

The Saudi MoH protocol recommends a loading dose of 1800 mg twice daily for the first day, followed by a maintenance dose of 800 mg twice daily for 7–10 days. The Saudi MoH protocol acknowledges appropriate doses as a key prognostic factor for clinical improvement, despite differences in treatment durations and the lack of therapeutic drug plasma concentrations in critically ill patients. Conversely, Irie et al. (2020) [35] documented favipiravir therapy for critically ill COVID-19 patients in the intensive care unit (ICU), with patients given 1600 mg twice daily on the first day and 600 mg twice daily from day 2 to day 5. Most samples in the Irie et al. (2020) [35] study had lower trough concentrations than the lower limit of quantification and half-maximal effective concentration against SARS-CoV-2 [36].

The current study found that patients with COVID-19 often had elevated liver enzymes, including ALT (13.4%) and AST (13.4%), on admission before taking favipiravir. This aligns with a study by Fu Y. et al. (2020) in Wuhan, China, where 29.5% of patients showed abnormal liver functions on admission, including a rise in ALT (67.6%), AST (69.0%), and total bilirubin (16.2%) [36]. Liver functions AST, ALT, and bilirubin were estimated at the end of the current study. AST and ALT enzymes in most patients showed normal and mild elevation after favipiravir therapy.

In agreement with the current study, a study in Turkey found that favipiravir treatment caused tolerable minor adverse events, such as a mild increase in hepatic enzymes ALT and AST, but no serious life-threatening complications. The study involved 40 confirmed COVID-19 patients, with two-thirds having at least one underlying disease, such as cardiovascular disease and diabetes mellitus. The protocol of management involved favipiravir tablets administered orally for a loading dose of 1600 mg twice a day, followed by 600 mg twice a day daily for 5 to 7 days. Thirteen percent of patients experienced side effects, including liver enzyme elevation, total bilirubin, uric acid, and gastrointestinal disorders, which were self-limited [22].

The study found that patients with mild elevation of ALT (48.7%) experienced more ALT elevation than AST (20.2%) after favipiravir treatment. In agreement, a randomized open-label clinical trial by Doi Y. et al. (2020) [37] involved 89 asymptomatic to mild COVID-19 patients who received 1800 mg twice daily for up to 19 doses over ten days. The regimen achieved a plasma concentration of approximately 60 μg/mL. Adverse events included hyperuricemia in 69 patients, serum triglyceride elevation in nine patients, and ALT elevation in seven patients [38].

Most patients had normal bilirubin levels after favipiravir therapy (95.59%), while bilirubin was elevated after favipiravir therapy in 4.41%, with no statistically significant difference between normal and high levels before and after favipiravir therapy (p=0.196). A study by Bosaeed et al. (2021) in Saudi Arabia found that a combination of favipiravir and hydroxychloroquine did not significantly improve clinical outcomes in patients with moderate-to-severe COVID-19. The study involved 254 patients who were assigned to standard care and 125 to treatment. The mean age was 52±13 years, and 41% were women. At randomization, six patients were on invasive mechanical ventilation, and 90.15% required supplemental oxygen. The most common adverse events were headache, mild to moderate elevation in ALT, and a prolonged QTc interval. However, favipiravir did not affect AST and bilirubin levels

[38]. The study's results contradict our research, which showed mild elevation of AST after favipiravir therapy.

Within this investigation, the use of favipiravir was discontinued in 25 patients (5.25%) due to significant increases in liver transaminase levels. However, in the study conducted by Dabbous et al. (2021), therapy was not terminated, and these elevations returned to normal levels within a span of two weeks [16].

The study had several limitations. First, the study was conducted in one hospital for coronavirus because it is the only one available in Taif city. There was an expectation to engage multiple hospitals for coronavirus, but unfortunately, there were no available facilities for this purpose. Second, the study only analyzed the hepatic profile as a target and lacked evaluation of the renal function profile, coagulation and bleeding tests, heart profile, and uric acid, but no data were available.

Despite these limitations, this study provides valuable insights into the management of liver-related adverse events caused by the use of favipiravir in COVID-19 treatment. It indicates that favipiravir is a secure medicine, as it does not pose any significant risks to liver functions.

5. Conclusion

Favipiravir is an emerging anti-viral drug that may be useful for managing mild to moderate COVID-19 cases. However, it has been reported to cause adverse events like hepatic function elevations, which are not serious and can be reversible after discontinuation. Further studies and clinical double blinded multicenter trials with larger sample sizes are needed to evaluate the safety and emerging adverse events of favipiravir in Saudi Arabia, ensuring a reliable data base for researchers.

Author Contributions: "All authors contributed to the study conception and design. Material preparation, data collection were performed by Doaa Johari. The first draft of the manuscript was written by Doaa Johari. Laboratory result interpretation and analysis by Tariq A. Alpakistany. Statistical analysis and over all data review by Abdullah R. Alzahrani. Manuscript formatting and proofreading and over all data review by Mohammad Melebari. All authors read and approved the final manuscript."

Conflicts of Interest: The authors declare no conflicts of interest.

Funding: This research received no external funding.

References:

1. World Health Organization. Coronavirus Disease (COVID-2019) Situation Reports (World Health Organization, 2022). https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
2. Wu Z, McGoogan JM. The outbreak in China: Summary of a Report of 72314 Cases from the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-1242. https://doi.org/10.1001/jama.2020.2648
3. World Health Organization: "Clinical management of COVID-19: interim guidance". https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-2
4. Zhang G, Zhang J, Wang B, Zhu X, Wang Q, Qiu S. Analysis of clinical characteristics and laboratory findings of 95 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A retrospective analysis. Respiratory Research.2020;21(74). https://doi.org/10.1186/s12931-020-01338-8
5. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell. 2020;181(2):271-280. https://doi.org/10.1016/j.cell.2020.02.052
6. Pacheco-Herrero M, Soto-Rojas LO, Harrington CR, Flores-Martinez YM, Villegas-Rojas MM, León-Aguilar AM, et al. Elucidating the Neuropathologic Mechanisms of SARS-CoV-2 Infection. Frontiers in Neurology. Frontiers Media S.A. 2021;12. https://doi.org/10.3389/fneur.2021.660087
7. Chen Y, Liu Q, Guo D. Emerging coronaviruses: Genome structure, replication, and pathogenesis. Journal of Medical Virology. John Wiley and Sons Inc. 2020;92:418–23. https://doi.org/10.1002/jmv.25681
8. Yu F, Du L, Ojcius DM, Pan C, Jiang S. Measures for diagnosing and treating infections by a novel coronavirus responsible for a pneumonia outbreak originating in Wuhan, China. Microbes and Infection. 2020;22(2):74–9. https://doi.org/10.1016/j.micinf.2020.01.003

9. Machado BAS, Hodel KVS, Barbosa-Júnior VG, Soares MBP, Badaró R. The main molecular and serological methods for diagnosing covid-19: An overview based on the literature. Viruses. 2021;13(1):40. https://doi.org/10.3390/v13010040
10. Yang Y, Yang M, Shen C, Wang F, Yuan J, Li J, et al. Evaluating the accuracy of different respiratory specimens in the laboratory diagnosis and monitoring the viral shedding of 2019-nCoV infections. medRxiv. 2020. https://doi.org/10.1101/2020.02.11.20021493
11. To KKW, Tsang OTY, Yip CCY, Chan KH, Wu TC, Chan JMC, et al. Consistent detection of 2019 novel coronavirus in saliva. Clinical Infectious Diseases. 2020;71(15):841–3. https://doi.org/10.1093/cid/ciaa149
12. Delang L, Abdelnabi R, Neyts J. Favipiravir as a potential countermeasure against neglected and emerging RNA viruses. Antiviral Res. 2018;153:85–94. https://doi.org/10.1016/j.antiviral.2018.03.003
13. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proceedings of the Japan Academy Series B: Physical and Biological Sciences. Japan Academy. 2017;93:449–63. https://doi.org/10.2183/pjab.93.027
14. Sood S, Kaur Bhatia G, Seth P, Kumar P, Kaur J, Gupta V, et al. Efficacy and Safety of New and Emerging Drugs for COVID-19: Favipiravir and Dexamethasone. Current Pharmacology Reports. 2021;7:49–54. https://doi.org/10.1007/s40495-021-00253-w
15. Baj J, Karakuła-Juchnowicz H, Teresiński G, Buszewicz G, Ciesielka M, Sitarz E, et al. COVID-19: Specific and non-specific clinical manifestations and symptoms: The current state of knowledge. Journal of Clinical Medicine. 2020;9(6):1753. https://doi.org/10.3390/jcm9061753
16. Dabbous, H. M., El-Sayed, M. H., El Assal, G., Elghazaly, H., Ebeid, F. F., Sherief, A. F. et al. Safety and efficacy of favipiravir versus hydroxychloroquine in management of COVID-19: A randomized controlled trial. Scientifc Reports. 2021;11:7282. https://doi.org/10.1038/s41598-021-85227-0
17. Sissoko D, Laouenan C, Folkesson E, M'Lebing AB, Beavogui AH, Baize S, et al. Experimental Treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial): A Historically Controlled, Single-Arm Proof-of-Concept Trial in Guinea. PLoS Medicine. 2016;13(3). https://doi.org/10.1371/journal.pmed.1001967
18. Bai C-Q, Mu J-S, Kargbo D, et al. Clinical and Virological Characteristics of Ebola Virus Disease Patients Treated with Favipiravir (T-705)-Sierra Leone, 2014. Clinical Infectious Diseases.2016;63:1288–94. https://doi.org/10.1093/cid/ciw571
19. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. New England Journal of Medicine. 2020;382(8):727–33. https://doi.org/10.1056/NEJMoa2001017
20. Saudi MoH Protocol for Patients Suspected of/Confirmed with COVID-19 Supportive care and antiviral treatment of suspected or confirmed COVID-19 infection [Internet]. https://covid19.cdc.gov.sa/pr
21. Erdem HA, Korkmaz PE, Çağlayan D, Işikgöz Taşbakan M, Yamazhan T, Taşbakan MS, et al. Treatment of sars-cov-2 pneumonia with favipiravir: Early results from the egeUniversity cohort, Turkey. Turkish Journal of Medical Sciences. 2021;51(3):912–20. https://doi.org/10.3906/sag-2008-33
22. Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J, et al. Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. Engineering. 2020;6(10):1192–98. https://doi.org/10.1016/j.eng.2020.03.007
23. Louchet M, Sibiude J, Peytavin G, Picone O, Tréluyer JM, Mandelbrot L. Placental transfer and safety in pregnancy of medications under investigation to treat coronavirus disease 2019. American Journal of Obstetrics and Gynecology MFM. 2020;2(3):100159. https://doi.org/10.1016/j.ajogmf.2020.100159
24. Marra F, Smolders EJ, El-Sherif O, Boyle A, Davidson K, Sommerville AJ, et al. Recommendations for Dosing of Repurposed COVID-19 Medications in Patients with Renal and Hepatic Impairment. Drugs in R&D. 2021;21:9–27. https://doi.org/10.1007/s40268-020-00333-0
25. Tejaswi P, Devashish K, Prasad RR. Pharmacological effects of favipiravir on coronavirus: An update. Biomedical and Pharmacology Journal. 2021;14(2):1087–95. https://link.gale.com/apps/doc/A670620246/HRCA?u=anon~c606c3e1&sid=googleScholar&xid=e33303df

26. Ghasemnejad-Berenji M, Pashapour S. Favipiravir and COVID-19: A Simplified Summary. Drug Research. 2021;71(3):166–170. https://doi.org/10.1055/a-1296-7935
27. National Guidelines for Clinical Management and Treatment of COVID-19 1 st June, 2020 Prepared and Reviewed by National Clinical Committee for COVID-19 Management Approved by Technical team for Pandemic Control National Guidelines for Clinical Management and Treatment of COVID-19). https://www.covidlawlab.org/wp-content/uploads/2021/06/United-Arab-Emirates_2020.06.01_Guidelines_National-Guidelines-for-Clinical-Management-and-Treatment-of-COVID-19_EN.pdf
28. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges. The Lancet Gastroenterology and Hepatology. 2020;5(5):428–30. https://doi.org/10.1016/S2468-253(20)30057-1
29. Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. Pharmacology and Therapeutics.2020;209:107512. https://doi.org/10.1016/j.pharmthera.2020.107512
30. Kumar P, Kulkarni A, Sharma M, Nagaraja Rao P, Nageshwar Reddy D. Favipiravir-induced liver injury in patients with coronavirus disease 2019. Journal of Clinical and Translational Hepatology. 2021; 9(2):276–278. https://doi.org/10.14218/JCTH.2021.00011
31. Yeoman A, Maggs DR, Gardezi SAA, Haboubi HN, Yahya MI, Yousuf F, et al. Incidence, pattern and severity of abnormal liver blood tests among hospitalised patients with SARS-COV2 (COVID-19) in South Wales. Frontline Gastroenterology. 2021;12(2):89–94. https://doi.org/10.1136/flgastro-2020-101532
32. Channappanavar R, Fett C, Mack M, ten Eyck PP, Meyerholz DK, Perlman S. Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection. The Journal of Immunology. 2017;198(10):4046–53. https://doi.org/10.4049/jimmunol.1601896
33. Udwadia ZF, Singh P, Barkate H, Patil S, Rangwala S, Pendse A, et al. Efficacy and safety of favipiravir, an oral RNA-dependent RNA polymerase inhibitor, in mild-to-moderate COVID-19: A randomized, comparative, open-label, multicenter, phase 3 clinical trial. International Journal of Infectious Diseases.2021;103:62–71. https://doi.org/10.1016/j.ijid.2020.11.142
34. Ivashchenko AA, Dmitriev KA, Vostokova N v, Azarova VN, Blinow AA, Egorova AN, et al. AVIFAVIR for Treatment of Patients with Moderate COVID-19: Interim Results of a Phase II/III Multicenter Randomized Clinical Trial. 2020. https://doi.org/10.1101/2020.07.26.20154724
35. Chen C, Zhang Y, Huang J, Yin P, Cheng Z, Wu J, et al. Favipiravir Versus Arbidol for Clinical Recovery Rate in Moderate and Severe Adult COVID-19 Patients: A Prospective, Multicenter, Open-Label, Randomized Controlled Clinical Trial. Frontiers in Pharmacology.2020;12. https://doi.org/10.3389/fphar.2021.683296
36. Irie K, Nakagawa A, Fujita H, Tamura R, Eto M, Ikesue H, et al. Pharmacokinetics of Favipiravir in Critically Ill Patients With COVID-19. Clinical and Translational Science. 2020;12(5):880–5. https://doi.org/10.1111/cts.12827
37. Fu Y, Zhu R, Bai T, Han P, He Q, Jing M, et al. Clinical Features of Patients Infected With Coronavirus Disease 2019 With Elevated Liver Biochemistries: A Multicenter, Retrospective Study. Hepatology. 2021;73(4):1509–20. https://doi.org/10.1002/hep.31446
38. Doi Y, Hibino M, Hase R, Yamamoto M, Kasamatsu Y, Hirose M, et al. A Prospective, Randomized, Open-Label Trial of Early versus Late Favipiravir Therapy in Hospitalized Patients with COVID-19. 2020;64(12). https://doi.org/10.1128/AAC
39. Bosaeed M, Mahmoud E, Alharbi A, Altayib H, Albayat H, Alharbi F, et al. Favipiravir and Hydroxychloroquine Combination Therapy in Patients with Moderate to Severe COVID-19 (FACCT Trial): An Open-Label, Multicenter, Randomized, Controlled Trial. Infectious Diseases and Therapy. 2021;10(4):2291–307. https://doi.org/10.1007/s40121-021-00496-6