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Effect Of Favipiravir And Standard COVID-19 Therapy On Amino Transferase İn A Sample Of Iraqi COVID-19 Patients

Alaa Abed Mikhwir , Dr. Raid J. M. Al-Timimi and Dr. Haider Abdulhameed Alqaraghuli

Al-Nahrain University /College of Medicine / Department of Chemistry and Biochemistry

Assistant. Prof. Al-Nahrain University /College of Medicine / Department of Chemistry and Biochemistry

Assistant. Prof**.** Al-Nahrain University /College of Medicine / Department of Medicine

Abstract

Background: COVID-19 is a condition that can proceed in a broad spectrum from asymptomatic moderate sickness to severe lung disease. Hepatic harm in COVID-19 may arise owing to the direct cytopathic action of the virus, uncontrolled immunological response, hypoxia related to pneumonia, and the medications used in therapy. In the literature, the rate of rise in blood transaminase levels of patients hospitalized with COVID-19 was determined to be 37.5%. Also, rise in serum transaminase levels in COVID-19 patients has been shown to be related with higher mortality in the literature. Favipiravir is a ribonucleic acid (RNA)-dependent RNA polymerase (RdRP) inhibitor antiviral drug used in the treatment of coronavirus disease-2019 (COVID-19)

Aims: In this study, we investigated the changes in serum transaminase levels of patients who were hospitalized with the diagnosis of COVID-19 and underwent favipiravir therapy.

Materials and methods: case-control research was done. It was done in a multi-hospital of Baghdad city over the period from November 1, 2020, to August 1, 2021. All patients in this study were hospitalized patients with polymerase chain reaction identified Coronavirus illness 2019 (severe cases) according to Iraqi criteria and supervision of a professional.

Results: case-control research was done. It was done in a multi-hospital of Baghdad city over the period from November 1, 2020, to August 1, 2021. All patients in this study were hospitalized patients with polymerase chain

reaction identified Coronavirus illness 2019 (severe cases) according to Iraqi criteria and supervision of a professional.

Introduction

Coronaviruses are a broad family of viruses which may cause sickness in animals or people. Seven coronaviruses can generate illness in persons around them. They frequently cause a respiratory infection ranging from the ordinary cold to more serious diseases such as Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS) and the most recently identified coronavirus (COVID-19) causes infectious disease. [World Health Organization ,2020] This zoonotic illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The WHO previously dubbed this infectious illness Novel Coronavirus-Infected Pneumonia (NCIP) and the virus had been named 2019 novel coronavirus (2019-nCoV). On 11th Feb 2020, the (WHO) formally termed the clinical illness COVID-19 (an abbreviation of Corona Virus Disease-19) (a shortening of Corona Virus Disease-19), An epidemic of COVID-19 caused by the 2019 new coronavirus (SARS-CoV-2) occurred in Wuhan, Hubei Province, China in December 2019, the present outbreak is declared a pandemic. [Murphy and Bell, 2020].Also there were a pandemic in Iraq and many researchwas done in Iraq like [Ali Y.Salem, et al., 2021][Hayder Y. Ali, et al., 2021].COVID-19 is a condition that can proceed in a broad spectrum from asymptomatic moderate sickness to serious lung disease. [Huang, Wang, Li, et al.,2020]. Hepatic damage in COVID-19 may arise owing to the direct cytopathic action of the virus, uncontrolled immunological response, hypoxia consequent to pneumonia, and the medications employed in therapy, [Zhang, Shi, Wang, 2020] In the literature, the incidence of rise in blood transaminase levels of patients hospitalized with COVID-19 was reported to be 37.5 percent. [Fan, Chen, Li, et al.,202]. Also, rise in blood transaminase levels in COVID-19 individuals has been discovered to be related with greater mortality in the literature. [Abdulla, Hussain, et al.,2020] The usual instrument of diagnosis is by reverse transcription polymerase chain reaction (rRT-PCR) from a throat swab or nasopharyngeal swab. The illness can potentially be detected from a combination of symptoms, risk factors and a chest CT scan revealing characteristics of pneumonia. [Velavan and Meyer, 2020]

Materials and Methods

case-control research was done. It was done in a multi-hospital of Baghdad city over the period from November 1, 2020, to August 1, 2021. All patients in this study were hospitalized patients with polymerase chain reaction identified Coronavirus illness 2019 (severe cases) according to Iraqi criteria and supervision of a professional. The study was authorized by the scientific body “Institutional Review Board” (IRB) of Al-Nahrain University, College of Medicine. The targeted population contains 60 samples

of both genders (male & female) aged (36 - 72 years) samples were sorted into three groups, 20 patients who got favipiravir and 20 patients who did not get favipiravir were analyzed. Serum transaminase levels of the patients were compared with 20 healthy people who not infected, before and after 10 days of therapy

Inclusion criteria:

- All patients who have COVID-19 (PCR positive)
- age of patients above 18 years

Exclusion criteria:

- Individuals who were not hospitalized
- Pregnancy
- History of chronic liver disease
- Any history chronic hepatotoxic medication

Results:

SerumALT (alanine aminotransferase)

Table (3-1) shows the levels of serum ALT as (mean±SD) U/L in COVID-19 patients with pretreatment of favipiravir, post treatment of favipiravir, pretreatment of other drugs, posttreatment of other drugs and control group.

Table (3-1):Serum ALT levels in COVID-19 patients with pre& post treatmentsgroup compared with control group

Group	No.	Mean ± SD	P-Value
Control Pre 1	20	16.85 ± 4.89	0.495
	20	17.90 ± 4.72	
Pre1 Post 1	20	17.90 ± 4.72	0.031
	20	19.80 ± 5.18	
Control Pre 2	20	16.85 ± 4.89	
	20	18.30 ± 5.04	

			0.416
Pre 2	20	18.30 ± 5.04	
Post 2	20	18.40 ± 5.74	0.9

Pre1: patients with covid19 pretreatment of favipiravir

Post1: patients with covid19 post treatment of favipiravir

Pre2: patients with covid19 pretreatment of other drugs

Post2: patients with covid19 post treatment of other drugs

P> 0.05: non-significant, P< 0.05: significant

The results have shown that there were non-significant increase in the serum levels of ALT in COVID-19 patients with pretreatment of favipiravir compared to control group (p>0.05). There were significant increase in the levels of ALT in COVID-19 patients with post treatment of favipiravir compared to COVID-19 patients with pretreatment of favipiravir(p<0.05). Also, the results have shown that there were non-significant increase in the serum levels of ALT in COVID-19 patients with pretreatment of other drugs compared to control group (p>0.05). There were non-significant increase in the levels of ALT in COVID-19 patients with posttreatment of other drugs compared to COVID-19 patients with pretreatment of other drugs (p>0.05).

In addition, there were non-significant increase in the serum levels of ALT in COVID-19 patientsaged from 36 to 53 yearspretreatment of favipiravir compared to control group (p>0.05), and non-significant decrease in the levels of ALT in COVID-19 patients aged from 36 to 53 years with posttreatment of favipiravir compared to COVID-19 patients with pretreatment of favipiravir(p>0.05), as shown in table (3-2).

Table (3-2): Levels serum of ALT for COVID-19 patients aged from 36 to 53 years with pre& post treatment compared with the control group

Group	NO	Mean ± SD	P-Value
Control	8	16.25±4.23	0.952

Pre 1	8	16.37±5.31	
Pre1	8	16.37±5.31	0.876
Post 1	8	16.12±4.05	

Pre1: patients with covid19 pretreatment of favipiravir

Post1: patients with covid19 post treatment of favipiravir

P> 0.05: non-significant

In covid-19 patients whose ages were ranged54 and 72 years, the results were non-significant increase in the serum levels of ALT in COVID-19 patientspretreatment of favipiravir compared to control group (p>0.05), and significant increase in the levels of ALT in COVID-19 patientswith posttreatment of favipiravir compared to COVID-19 patients with pretreatment of favipiravir(p<0.05), as shown in table (3-3)

Table (3-3): Levels serum of ALT for COVID-19 patients aged from 54 to 72 years with pre& post treatment compared with the control group

Group	No.	Mean ± SD	P-Value
Control Pre	12	17.25±5.42	
1	12	18.91±4.20	0.489
Pre 1	12	18.91±4.20	0.016
Post 1	12	22.25±4.43	

Pre1: patients with covid19 pretreatment of favipiravir

Post1: patients with covid19 post treatment of favipiravir

P< 0.05: significant, P> 0.05: non-significant

In this study, showing the highest percentage for elevated level ALT in patients withCOVID-19 were between 54-72years as 54% (mean±SD=18.91±4.2), as shown in figure (3-1)

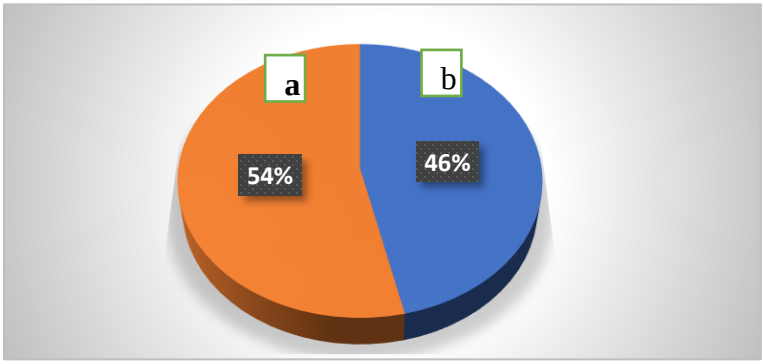

Figure 3-1percentage for elevated level ALT in patients withCOVID-19 with ages(a) 54-72 years (b) 36-53 years

3.2-Serum AST (Aspartate aminotransferase)

Table (3-6) shows the levels of serum AST as (mean±SD) U/L in COVID-19 patients with pretreatment of favipiravir, post treatment of favipiravir, pretreatment of other drugs, posttreatment of other drugs and control group.

Group	No.	Mean ± SD	P-Value
ControlPre 1	20	18.45 ± 4.86	0.161
	20	20.30 ± 3.88	
Pre1 Post 1	20	20.30 ± 3.88	0.210
	20	22.25 ± 7.15	
Control Pre 2	20	18.45 ± 4.86	0.160
	20	20.45 ± 4.35	
Pre 2Post 2	20	20.45 ± 4.35	0.789
	20	20.15 ± 3.82	

Table (3-6): Serum AST levels in COVID-19 patients with pre& posttreatments group compared with control group

Pre1: patients with covid19 pretreatment of favipiravir

Post1: patients with covid19 post treatment of favipiravir

Pre2: patients with covid19 pretreatment of other drugs

Post2: patients with covid19 post treatment of other drugs

P> 0.05: non-significant

The results have shown that there were non-significant increase in the serum levels of AST in COVID-19 patients with pretreatment of favipiravir compared to control group (p>0.05), and non-significant increase in the levels of AST in COVID-19 patients with post treatment of favipiravir compared to COVID-19 patients with pretreatment of favipiravir (p>0.05).There were non-significant increase in the serum levels of AST in COVID-19 patients with pretreatment of other drugs compared to control group (p>0.05), and non-significant decrease in the levels of AST in COVID-19 patients with post treatment of other drugs compared to COVID-19 patients with pretreatment of other drugs (p>0.05).

In addition, there were non-significant increase in the serum levels of AST in COVID-19 patientsaged from 36 to 53 years pretreatment of favipiravir compared to control group (p>0.05), and non-significant decrease in the levels of AST in COVID-19 patients aged from 36 to 53 years with post treatment of favipiravir compared to COVID-19 patients with pretreatment of favipiravir(p>0.05), as shown in table(3-7).

Table (3-7): Levels serum of AST for COVID-19 patients aged from 36 to 53 years with pre& post treatment compared with the control group

Group	No.	Mean ± SD	P-Value
Control Pre 1	8	17.87±4.73	0.51
	8	19.62±3.62	
Pre1 Post 1	8	19.62±3.62	0.5
	8	22.00±9.16	

Pre1: patients with covid19 pretreatment of favipiravir

Post1: patients with covid19 post treatment of favipiravir

P> 0.05 : non-significant

In covid-19 patients whose ages were ranged 54 and 72 years, the results were non-significant increase in the serum levels of AST in COVID-19 patientspretreatment of favipiravir compared to control group (p>0.05), and non-significant increase in the levels of AST in COVID-19 patients with post treatment of favipiravir compared to COVID-19 patients with pretreatment of favipiravir(p>0.05), as shown in table(3-8).

Table (3-8): Levels serum of AST for COVID-19 patients aged from 54 to 72 years with pre& post teatment compared with the control group

Group	No.	Mean ± SD	P-Value
Control Pre 1	12	18.83±5.11	0.238
	12	20.75±4.13	
Pre 1Post 1	12	20.75±4.13	0.232
	12	22.41±5.90	

Pre1: patients with covid19 pretreatment of favipiravir

Post1: patients with covid19 post treatment of favipiravir

P> 0.05: non-significant

In this study, showing the highest percentage for elevated level AST in patients withCOVID-19 were between 54-72 years as 51% (mean±SD= 20.75±4.13), as

shown in figure (3-2).

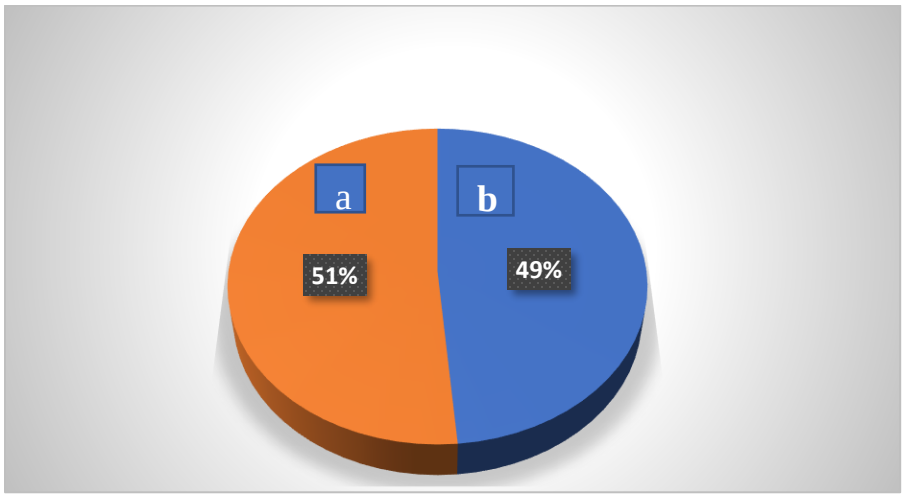

Figure 3-2:percentage for elevated level AST in patients with COVID-19 with ages (a) 54-72 years (b) 36- 53 years

Discussion:

Qingxian , Cai, Deliang Huang, Hong Yu revealed that more than 10 percent of those patients suffered higher levels of liver enzymes during hospitalization, which might be attributable to the employed drugs .[Cai , Huang , et al. 2020] . In a meta-analysis done by Kulkarni et al. which covered 20 874 COVID-19 patients, the pooled incidence of drug-induced liver damage was 25.4 percent. [Kulkarni, Kumar, et al. 2020] . Currently recommended drugs for COVID-19 (e.g. oseltamivir, lopinavir/ritonavir, and chloroquines) are all metabolized in the liver .[Rismanbaf and Zarei .2020] . For this reason, anytime any liver test abnormality arises in COVID-19 patients, the drug-induced liver damage should first be confirmed or ruled out [Li and Fan. 2020] It was noted that many individuals suffering from COVID19 had a history of antipyretic usage, notably paracetamol, overdose of which is a well-established etiology for liver damage.[Boeckmans, Rodrigue, et al. 2020].

As for the alanine aminotransferase (ALT) that the present outcome of our investigation coincides with Chen, Zhao, et al. that noticed the patients who resevingfavipiravir are considerable increase in liver enzyme with subjects aged between 45 and 64 years, Evidence demonstrates that the increase in viral load of SARS-CoV-2 has a tight connection with increased IL-6 levels. Raised IL-6 levels with cytokine storm can decrease prognosis and have a bad result with greater mortality. [Chen, Zhao, et al.,2020] Favipiravir, being a powerful inhibitor of viral growth, potentially causes reduced cytokine production, thus protecting the lung from inflammatory damage. [Takahashi, Watanabe, et al.,2020], as well as Erdem, Ekren, et al. that studied the effects of severe COVID-19 pneumonia patients who underwent at least 5 days of favipiravir treatment. The laboratory parameters of the patients were tested before and

after favipiravir therapy. At the completion of favipiravir treatment, a statistically significant rise in ALT. [Erdem, Ekren, Çağlayan, et al. 2021], Favipiravir is metabolized in the liver predominantly by the enzyme called aldehyde oxidase, and the xanthine oxidase metabolizes a tiny fraction , There is evidence that the elevation in liver enzymes is observed in ≥1 percent of the patients , which leads towards the possible liver impairment by the medication. [Madelain, Nguyen, Olivo, et al.,2016],also according to the resent study that was done here in Iraq our result disagrees with Ali Yahia Salem Resch that observed there were non-significant increase in the serum levels of ALT in COVID-19[Ali Y. Salem, et al.,2021]

And for the Aspartate aminotransferase (AST) we disagree Zydecka, Kotfis, et al. that gave the following results; increased AST, which may imply limited direct virus-related liver damage due to the overexpression pattern of Angiotensin-converting enzyme 2 (ACE2). [Kotfis, et al.2020]And for the Aspartate aminotransferase (AST) we disagree Zydecka, Kotfis, et al. that gave the following results; increased AST, which may imply limited direct virus-related liver damage due to the overexpression pattern of Angiotensin-converting enzyme 2 (ACE2).[Kotfis, et al.2020]

Conclusion :

There was statistically significant rise in the overall transaminase levels related to favipiravir treatment in patients hospitalized with COVID-19

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