ORIGINAL RESEARCH

A potential drug interaction between Favipiravir and Warfarin in patients with COVID-19: A real-world observational study

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Abstract

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Favipiravir is one of the mostly used antiviral agents for the treatment of COVID-19 infection in many countries, including Thailand. This study aimed to investigate the effect of favipiravir-warfarin interaction in terms of changing in INR of patients. Medication charts of all inpatients in a hospital in Thailand between April 2021 and March 2022 were reviewed. Patients who received either warfarin with standard care or warfarin with favipiravir were included. The INR levels of patients were monitored at baseline and the earliest date post-treatment, as well as other laboratory parameters. There were 43 and 53 patients in the warfarin-favipiravir and the warfarin only groups. Baseline characteristics, such as sex, age, BMI, and warfarin dose, were not significant different between the two groups. The results showed that the mean INR of patients using favipiravir and warfarin was increased from 2.14 to 3.88 (p-value <0.001), while the patients using warfarin alone had no increase in the mean INR (1.93 vs. 1.91, p-value 0.906). Other parameters were not significantly changed, including WBC, RBC, hemoglobin, hematocrit, and liver function. However, an increase in platelet count was observed in the favipiravir-warfarin group, but not in the control group. This real-world study highlighted a significant increase in the INR levels of patients who used favipiravir together with warfarin, compared to patients who used only warfarin. However, the interaction did not affect other laboratory parameters, except an increase in platelet count.

Keywords: warfarin, favipiravir, drug interaction, COVID-19

Introduction

Coronavirus disease (COVID-19) is a pandemic infectious disease caused by the SARS-CoV-2 virus[1]. Although there are many vaccines developed to prevent the infection nowadays, antiviral agents are still important in treatment of the disease. The recently approved antiviral treatment of COVID-19 include favipiravir, remdesivir, molnupiravir, and paxlovid[2-5]. Favipiravir is an antiviral agent that has been approved for medical use in Japan in 2014 for the treatment of pandemic influenza virus infections[6]. This drug is widely used for the treatment of COVID-19 infection in many countries and currently is the first-line treatment in Thailand.

Favipiravir is a prodrug of purine base analog. It is converted by intracellular phosphoribosylation to be favipiravir ribofuranosyl-5B-triphosphate (favipiravir-RTP) that is the active form. The mechanism of action of this drug is a selective and potent inhibitor of RNA-dependent RNA polymerase (RdRp) of RNA viruses, resulting in the inhibition of RNA synthesis of SARS-CoV-2 in the infected cells, and therefore the infected cells cannot duplicate[7]. As favipiravir was developed and approved for other diseases, the information of this drug is not fully studied especially pharmacokinetic profile. According to the data from manufacturer, favipiravir is mainly metabolized in liver, and mainly by aldehyde oxidase enzyme[8]. In addition, this drug is shown to

inhibit CYP2C8, so co-administration of favipiravir with any drugs that are metabolized by CYP2C8 should be closely monitored[8-9].

There are several drugs that are known to be metabolized via CYP2C8, such as pioglitazone, rosiglitazone, loperamide, including warfarin[10]. Warfarin is an anticoagulant drug that has many indication, e.g. atrial fibrillation, venous thromboembolism, and pulmonary embolism[11]. Warfarin that is available in the market consists of a racemic mixture of two optical isomers (S-warfarin and R-warfarin, 1:1). R-isomer is mainly metabolized by CYP1A2 and CYP3A4, while S-isomer is mainly metabolized by CYP2C9[12]. Moreover, both R- and S-isomers are metabolized by CYP2C8[13], Consequently, warfarin is one of the drugs that have numerous reports on drug interaction.

Since favipiravir can inhibit CYP2C8 and warfarin is metabolized by the same enzyme, theoretically, these two drugs can have drug interaction. However, there have never been the reports that described favipiravir-warfarin interaction, except a case report in Japan[14]. Therefore, this study aimed to investigate the interaction between favipiravir and warfarin in patients with indications of both drugs.

Methods

Ethical approval

This study was approved by the Human Research Ethics Committee of Songkhla Hospital (Registration number: SKH IRB 2022-Pharm-IN3-1016). The requirement of patient informed consent was waived because it was a retrospective study that did not directly involve with any patient.

Study design

This was a retrospective observational study. All patients who were admitted at a hospital in Thailand between April 2021 and March 2022 were screened. The inclusion criteria of this study were patients who were equal or older than 18 years and were prescribed warfarin for the treatment of underlying diseases while admission. Patients who were prescribed favipiravir for the treatment of COVID-19 were collected as an intervention group.

Due to the regulation of the Ministry of Public Health, Thailand, all patients with cardiovascular diseases who were infected with SARS-CoV-2 virus had to receive favipiravir regardless of their symptoms [15], thus it was impossible to find patients with COVID-19 who did not use favipiravir to be a control group. The control group in this study therefore was the patients who were admitted in the hospital due to any causes, and received warfarin but not favipiravir. These patients might receive any standard care of treatment for COVID-19 infection. Patients were excluded if they had incomplete data listed for analysis.

Electronic medication records of all recruited patients were reviewed. The relevant variables were collected, including age, sex, weight, height, comorbid diseases, concurrent medication, and laboratory results, i.e. international normalized ratio (INR), white blood cell (WBC), red blood cell (RBC), platelets, hemoglobin, and hematocrit levels. Serum creatinine, aspartate transaminase (AST), alanine transferase (ALT), and serum albumin were also collected.

The characteristics of patients were recorded on the first date of admission. Other parameters including concurrent medication and laboratory results were collected twice throughout the admission: the first date of prescription of warfarin and/or favipiravir, and the first date that had laboratory data after the treatment. Incomplete data was defined as there was no INR level at pre-treatment of warfarin and favipiravir, there was no INR level at post-treatment, or there were no any other relevant parameters. The primary outcome of this study was the mean change in INR after treatment of favipiravir compared with no favipiravir. The secondary outcomes were the mean changes in hematologic parameters, including Hb, Hct, Plt, RBC, and WBC levels.

Statistical analysis

Baseline characteristics of all patients were analyzed using descriptive statistics and reported as numbers, means, and percentages. Wilcoxon Signed-Rank test was used to compare INR levels pre- and post-treatment within the groups, as well as other continuous variables. Chi-square was used for the analysis of all categorical variables. Mann-Whitney U test was used to compare the differences in INR levels between patients who were treated and were not treated with favipiravir. All statistical analyses were performed using IBM SPSS Statistics software version 28.0.0.0 (190), and statistical significance was set at $p < 0.05$.

Results

Baseline characteristics

Between April 2021 and March 2022, there were 108 patients who were screened in the study setting. Of them, only 96 patients had the complete clinical data and were recruited for the analysis (Figure 1). Forty-three patients were assigned to the intervention group (warfarin and favipiravir) and 53 patients were assigned to the control group (warfarin and standard care).

The baseline characteristics of both groups are described in Table 1. There was no statistically significant difference between the intervention and control groups in almost all baseline variables, except WBC. The patients in both groups contained similar number of men and women with the average age of ≥60 years. The mean body mass index (BMI) of both groups were lower than 23.00 kg/m^2. The mean warfarin dose was 19.84 mg/week in the intervention group and 16.54 mg/week in the control group. Additionally, no statistically significant difference in RBC, hemoglobin,

hematocrit, platelet, serum creatinine, AST, ALT, and serum albumin level was observed in this study. The mean WBC count of the intervention group was 6.85 x 10^3 cell/mm^3 (95%CI 5.90-7.79) which was different from 7.58 x 10^3 cell/mm^3 (95%CI 6.04-9.13) of the control group (p-value 0.036).

Regarding the concurrent medication, Table 2 shows the medication that each patient received in the hospital admission as a standard care. Markedly, the patients in both groups were similarly prescribed medicine (i.e. enoxaparin, piperacillin/tazobactam, clopidogrel, and sertraline). In addition, the patients in both groups had other medication, such as simvastatin, amiodarone, allopurinol, levofloxacin, and ceftazidime. Medication was no statistically significant difference between the intervention and control groups. However, only the intervention group received azithromycin, cotrimoxazole, and rosuvastatin. Metronidazole, dicloxacillin, and apixaban were specially received in control group.

The effects on patient INR

Figure 2 describes the changes in INR levels of all 96 patients, divided to 43 patients in the intervention group (Figure 2A) and 53 patients in the control group (Figure 2B). At baseline, the average INR levels of patients in the intervention and the control groups were 2.14 (95%CI 1.84-2.45) and 1.93 (95%CI 1.72-2.14), respectively (Figure 3). The pre-treatment INR levels of both groups were not significantly different (p-value 0.446). For the post-treatment, the average INR of patients in the intervention group significantly increased to 3.88 (95%CI 3.22-4.55) (p-value <0.001). However, the mean post-treatment INR of the control group did not significantly different from the baseline (mean 1.91, 95%CI 1.73-2.09) (p-value 0.906). Furthermore, the increases in post-treatment INR of both groups were significant different at p-value <0.001.

The effects on other parameters

The comparison of all laboratory parameters showed no statistically significant difference between pre- and post-treatment in both intervention and control groups, except platelet count in patients who received favipiravir (Table 3). In the intervention group, the mean changes in WBC, RBC, hemoglobin, hematocrit, and serum creatinine levels between post- and pre-treatment were 7.30x10^3 cell/mm^3, -0.22x10^6 cell/mm^3, -0.40 g/dL, -1.38%, and 0.05 mg/dL, respectively. AST, ALT, and serum albumin levels were not assessed in this group because of too low sample size. For platelet count, the results showed a significant increase in mean platelet count from 214.41 to 256.91 x 10^3 cell/mm^3 (p-value 0.018).

Likewise, in the control group, the mean differences of all laboratory parameters were not significant, including WBC, RBC, hemoglobin, hematocrit, platelet, serum creatinine, AST, ALT, and serum albumin levels. For instance, WBC count were changed from 7.58 to 7.54 x 10^3 cell/mm^3 (p-value 0.310). Hemoglobin increased from 11.35 to 11.54 g/dL (p-value 0.600), while platelet count decreased from 193.13 to 181.13 x 10^3 cell/mm^3 (p-value 0.237).

Discussion

The results of this study indicated significant INR elevation in patients who were prescribed favipiravir together with warfarin compared to patients with warfarin only. This interaction did not affect other parameters including white blood cells, red blood cells, hemoglobin, hematocrit, serum creatinine, aspartate transaminase, alanine transferase, and serum albumin. However, platelets seemed to be increased in patients who received favipiravir and warfarin, but this did not impact on the patient INR levels.

Favipiravir is a novel antiviral agent that is currently used for the treatment of COVID-19 infection in many countries, including Thailand[2,16]. Therefore, this drug has to be used in various population of patients. In patients who are receiving warfarin and have COVID-19 positive, concurrent use of favipiravir and warfarin is feasible, resulting in a potential drug interaction.

According to the previous studies, favipiravir was shown to inhibit CYP2C8[8-9], which was the enzyme that partly involved in warfarin metabolism[13]. The inhibition of this enzyme could increase the level of warfarin, and therefore potentially increase the INR level in patients. The data sheet suggested that favipiravir could inhibit CYP2C8 with an IC_{50} value of 74.9 μg/mL[8]. The pharmacokinetic profile indicated that administration of 1800 mg favipiravir – the starting dose of favipiravir in Thai patients – provided maximal concentration of 74.7-85.5 μg/mL[17], which is likely to inhibit CYP2C8 and results in an increase in warfarin level. Nonetheless, the exact mechanism of this interaction is still unknown and needs more studies, as well as the actual effects of favipiravir on patient INR.

Although this study was a retrospective study with several possible confounding factors, many factors were compared between the intervention and control groups and showed no significant difference. The results from a previous study demonstrated that hematocrit was an important determinant of the viscosity of blood and might affect the INR level[18], but this parameter was similar in both groups. The baseline platelet count which affects a blood clot[19] was not significantly different between the two groups. In addition, the liver function tests showed normal results in mean AST and ALT levels at baseline and post-treatment of all groups. Hepatic impairment is known to be a cause of the altered response to warfarin due to the impaired synthesis of clotting factors and the decrease in metabolism of warfarin. The unchanged AST and ALT levels after treatment therefore suggested that the increased INR levels might not result from the impaired liver function.

Concurrent drugs were the other most critical factors that could affect patient INR. However, the patients in both groups were not able to receive the same medication as standard of care due to the retrospective methods of this study together with different underlying diseases of the patients. For instance, some patients were administered aspirin, or clopidogrel, which can augment the effect of warfarin, resulting in an increase in INR[11,20-21]. On the other hand, some drugs such as dicloxacillin and spironolactone could decrease the warfarin level and INR[11,22-23]. Thus, the statistical analysis was

performed in order to ensure that the patients in both groups received the same drugs, particularly the drugs that were known to have a robust interaction with warfarin. Nevertheless, it should be noted that some patients with favipiravir treatment had different concurrent medication from the others and might result in the decreases in INR (Figure 2A), while most patients had the increased INR.

Apart from the INR levels, the results in this study showed no other effect of favipiravir-warfarin interaction. However, interestingly, this study found that the platelet count was significantly increased in patients treated with favipiravir. This phenomenon may guide in the follow-up of Favipiravir treatment and in determining the prognosis. It is known that low number of platelets is related to longer duration of blood clot, and vice versa[24-25]. Therefore, patients in this study who had higher mean platelet count should theoretically have lower INR, but the mean INR of such patients was significantly higher after using favipiravir. In spite of that, the INR of patients was significantly increased.

Several limitations should be noted for the results of this study. Firstly, there are numerous factors that are known to affect warfarin and/or INR levels, so it was impossible for the retrospective methods to control all potential confounding factors. Although this study best tried to compare as many factors as possible, it was truly believed that there might be some other underlying factors that might affect the INR, such as food. However, as all patients were admitted in the same hospital, almost all food that patients received was from the hospital kitchen and should be very similar. Moreover, some patients were prescribed the medicines that can have clinical interaction with warfarin, such as amiodarone, allopurinol, metronidazole, and statins. These concomitant medications could alter the INR levels. Secondly, the INR levels of all patients were not collected at the same period of time; meaning is the effects of warfarin in this study were not from the same levels of warfarin. As there is no official guideline to monitor the INR in the setting, blood samples of the patients were only collected following doctors' orders. Thus some patients had the first post-treatment INR at the 10th day of admission. Thirdly, there were no other blood clotting parameters collected in this study, such as prothrombin time, partial thromboplastin time, blood clotting duration, as well as coagulation factors. Furthermore, this study did not observe any pharmacokinetic parameters, such as peak and through concentrations, time-to-peak concentration, and area under the curve, of the patients.

Future research should emphasize on the mechanism of interaction of favipiravir and warfarin, as well as other drugs that are metabolized via CYP2C8. The expression of the relevant proteins should be measured together with the concentration of favipiravir in the body in order to confirm the interaction. However, according to the previous case report of interaction[14] and the results of this study, co-administration of favipiravir and drugs that are metabolized by the CYP2C8 system should be done with care until the mechanism is better revealed[26].

Conclusion

This study suggested that patients who received favipiravir with warfarin had significantly higher INR, compared with those who received only warfarin. Other parameters were not affected by this interaction, including WBC, RBC, hemoglobin, hematocrit, serum creatinine, AST, ALT, and albumin. The mechanism of interaction is recently unknown, but there is a high possibility that it involves CYP2C8 inhibitory effect of favipiravir. Further studies are needed to indicate the actual mechanism; in the meantime, patients who received favipiravir for the treatment of COVID-19 together with warfarin should be closely monitored their INR and signs of bleeding.

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Author contributions

S.U. designed the research, analyzed data, and wrote the manuscript. K.W. and N.L. collected and analyzed data. P.K. wrote the manuscript.

Conflict of interest

All authors report no conflicts of interest in this work.

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Data sharing statement

All patient data that were used in this study can be requested from the corresponding author with appropriate reason of use.

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Table 1 Baseline characteristics of patients who were admitted to the clinical setting and received warfarin prior to receive either favipiravir or standard care (N=96)

Variable	Normal range	Warfarin and favipiravir (n=43)	Warfarin and standard care (n=53)	P-value
Male, n (%)	-	20 (46.5)	27 (50.9)	0.666
Age (year), median (Range)	-	69 (38-87)	73 (45-87)	0.979
Body mass index (kg/m^2), mean (95%CI)	-	22.77 (21.44-24.12)	22.37 (19.95-24.79)	0.614
Warfarin dose (mg/week), mean (95%CI)	-	19.84 (16.40-23.29)	16.54 (13.64-19.45)	0.293
White blood cell count (x10^3 cell/mm^3), mean (95%CI)	4.5-10.0	6.85 (5.90-7.79)	7.58 (6.04-9.13)	0.036
Red blood cell count (x10^6 cell/mm^3), mean (95%CI)	4.2-5.5	4.34 (4.06-4.61)	4.13 (3.89-4.37)	0.396
Hemoglobin (g/dL), mean (95%CI)	12-16	11.74 (10.92-12.57)	11.35 (10.38-12.33)	0.692
Hematocrit (%), mean (95%CI)	36-48	36.13 (33.51-38.74)	35.04 (32.33-37.76)	0.685
Platelet count (x10^3 cell/mm^3), mean (95%CI)	140-400	214.41 (182.18-246.63)	193.13 (160.93-225.33)	0.713
Serum creatinine (mg/dL), mean	0.55-1.02	1.60 (0.95-2.45)	1.30 (0.90-1.70)	0.613

(95%CI)				
Aspartate transaminase (IU), mean (95%CI)	<35	42.78 (30.37-55.19)	34.52 (23.37-45.67)	0.103
Alanine transferase (IU), mean (95%CI)	<35	21.28 (13.71-28.85)	20.52 (13.28-27.76)	0.729
Serum albumin (mg/dL), mean (95%CI)	3.5-5.2	3.60 (3.43-3.77)	3.55 (3.34-3.75)	0.990

Note: The difference in sex was calculated using Chi-square, while other differences were calculated using Mann-Whitney U test.

Table 2 Medication of standard treatment that patients in both groups received while admission in the hospital

Medication	**Warfarin and favipiravir, n (%) (n=43)**	**Warfarin and standard care, n (%) (n=53)**	**P-value**
Simvastatin	24 (55.8)	29 (54.7)	0.692
Enoxaparin	5 (11.6)	5 (9.4)	0.951
Aspirin	6 (13.9)	12 (22.6)	0.176
Amiodarone	4 (9.3)	6 (11.3)	0.468
Allopurinol	2 (4.7)	3 (5.7)	0.617
Azithromycin	1 (2.3)	0	0.324
Levofloxacin	2 (4.7)	1 (1.9)	0.580
Ceftazidime	1 (2.3)	2 (3.8)	0.536
Cotrimoxazole	1 (2.3)	0	0.324

Rosuvastatin	1 (2.3)	0	0.324
Piperacillin / Tazobactam	4 (9.3)	4 (7.6)	0.957
Clopidogrel	7 (16.3)	7 (13.2)	0.941
Sertraline	1 (2.3)	1 (1.9)	0.979
Metronidazole	0	1 (1.9)	0.306
Dicloxacillin	0	1 (1.9)	0.306
Apixaban	0	1 (1.9)	0.306

Note: Each patient could receive more than one medicine.

Table 3 The differences in laboratory parameters between pre- and post-treatment with warfarin with favipiravir and warfarin with standard care (N=96)

Variable	**Mean difference (p-value)**	
	Warfarin and favipiravir (n=43)	**Warfarin and standard care (n=53)**
White blood cell count (x10^3 cell/mm^3) (4.5-10.0 x 10^3 cell/mm^3)	7.30 (0.050)	-0.04 (0.310)
Red blood cell count (x10^6 cell/mm^3) (4.2-5.5 x 10^6 cell/mm^3)	-0.22 (0.484)	0.05 (0.612)
Hemoglobin (g/dL) (12.0-16.0 g/dL)	-0.40 (0.483)	0.19 (0.600)
Hematocrit (%) (36% - 48%)	-1.38 (0.397)	0.71 (0.599)
Platelet count (x10^3 cell/mm^3) (140-400 x 10^3	42.50 (0.018)	-12.00 (0.237)

cell/mm^3)		
Serum creatinine (mg/dL) (0.55-1.02 mg/dL)	0.05 (0.465)	-0.02 (0.711)
Aspartate transaminase (IU) (<35 IU)	N/A	7.50 (0.180)
Alanine transferase (IU) (<35 IU)	N/A	9.50 (0.180)
Serum albumin (mg/dL) (3.5-5.2 mg/dL)	N/A	-0.35 (0.317)

Note: N/A, not applicable because some variables could not calculate the differences due to very low sample sizes. Normal ranges are provided in the brackets after the tests.

Figure 1 Flow diagram of the patient recruitment process

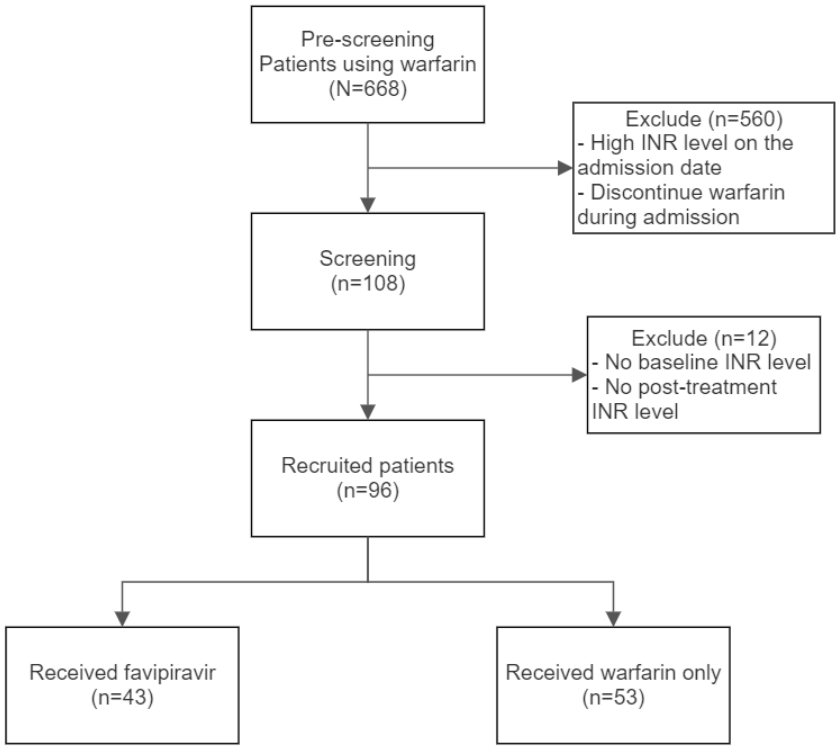
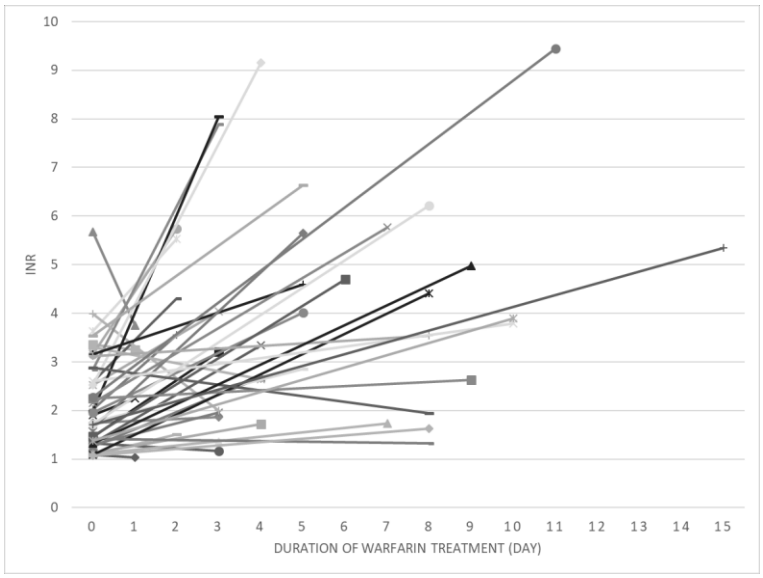


Figure 2 The changes in INR of individual patients who were treated with warfarin and favipiravir (A) (n=43) and warfarin without favipiravir (B) (n=53)

(A)



(B)

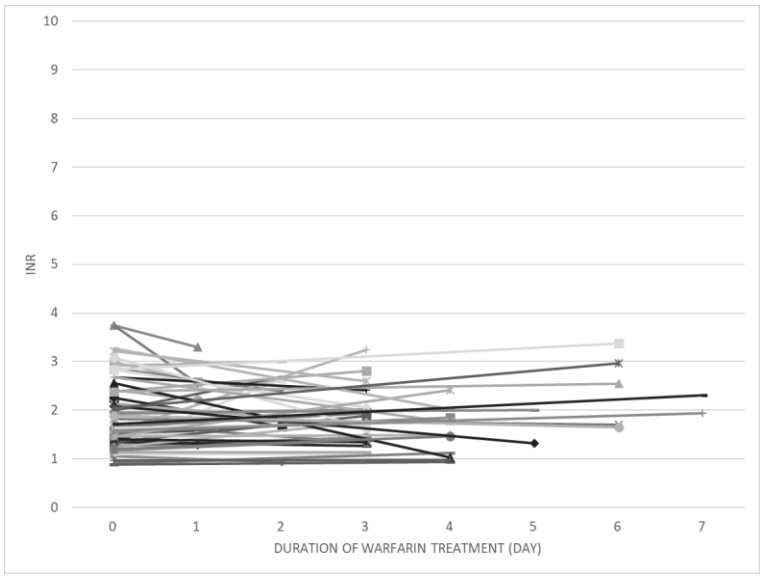


Figure 3 Comparison of the average INR between pre- and post-treatment of patients who received warfarin with and without favipiravir (n=53)