Meta-Analysis on the Potency of Favipiravir against SARS-CoV-2 and its Effect on Uric Acid Levels

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Abstract: - An outbreak of a novel virus, SARS-CoV-2, reported in Wuhan, China in December 2019, caused COVID-19 which led the WHO to declare a state of pandemic due to its high morbidity rates. More than 300 clinical trials have emerged in determining potential sources of treatment. One of the most studied drugs is Favipiravir, an antiviral agent known for treating influenza, which is said to exhibit effects in targeting SARS-CoV-2. Uric acid elevation is one of the adverse effects that may be of clinical importance upon administration to patients with hyperuricemia, impaired kidneys, undertaking medications and with history of gout due to redevelopment of disease. This study aimed to provide a valid estimate of Favipiravir's potency by determining the proportion of patients who were tested negative for COVID-19 after 10 days and to review the occurrence of uric acid elevation. A search method with inclusion and exclusion criteria was utilized for browsing online databases, namely PubMed, Science Direct, and Embase. Two data mining processes were done and analyses for each objective were made using Mantel-Haenszel Fixed Effects Odd Ratio and Forest Plot. Incidence of viral negativity after 10 days with OR 1.76[0.90, 3.43] and overall effect Z of 1.67 (P = 0.10) showed no statistical significance while occurrence of uric acid elevation with OR 30.69 [1.78, 528.82] and overall effect Z of 2.36 (P = 0.02) showed statistical significance. In conclusion, administration of Favipiravir has no effect on the clearance of SARS-CoV-2 after 10 days and can cause an increase in uric acid levels.

Key Words: — ***COVID-19, Favipiravir, Uric Acid.***

I. INTRODUCTION

SARS-CoV-2 is a virus responsible for this recent and ongoing worldwide COVID-19 pandemic. It started last December 2019 as an initial outbreak at the Seafood market in Wuhan City China. Due to the growing concerns regarding social, economic and health impacts, scientists and health practitioners all over the world are in search of treatments in combating this disease. With this, more than 300 clinical trials have emerged and certain agents are being studied based on in vitro or observational studies [1].

A widely known antiviral agent in treating strains of Influenza called Favipiravir is being studied due to its promising effects in combatting COVID-19 shown in several clinical trials. Favipiravir, developed by Toyama Chemical Fujifilm, acts as a matching substrate to RdRp (RNA dependent RNA polymerase) causing inhibition to the replication process of RNAs [2]. Clinical outcomes of several conducted clinical trials have shown Favipiravir to exhibit increased potency than Lopinavir and Ritonavir [3], decreased the symptoms of pneumonia [4], and decreased the incidence of fever and cough and possess a higher clinical recovery rate by 7 days [5]. Favipiravir combined with other drugs such as with the addition of Tocilizumab improved pulmonary inflammation [5] and a reduction in mortality rate and inhibition of hypercoagulopathy is seen with the addition of Nafamostat mesylate [6]. As promising as it may seem, the appearance of some adverse effects that can cause clinical significance are inevitable. Some of the reported clinical adverse effects of Favipiravir are as follows; diarrhea and liver injury [7], prolongation of QT intervals and TdP (Torsade de Pointes) [8], teratogenicity, increased analytes such as ALT, AST, GGT, blood triglycerides

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and uric acid, and decreased neutrophil and WBC count [9]. Studies made by Agrawal, Raju, and Udwadia (2020) [9], and Pilkington, Pepperrell, and Hill's (2020) [10] have found that administration of FVP monotherapy or polytherapy can cause uric acid elevation that can be of clinical value for establishing treatments. With this, uric acid elevation is given importance due to its frequent occurrence and the possibility of a redevelopment of hyperuricemia and acute gouty arthritis [11]. In the Philippines, PGH and Sta. Ana Hospitals are two from several hospitals participating in FVP trials. As of January 2021, 37 COVID-19 patients with non-severe pneumonia have enrolled in these clinical trials which are still going on [12].

This study aims to provide a comprehensive synthesis regarding the usage of Favipiravir as a monotherapy in terms of potency and the capability to cause uric acid elevation. The study utilizes trials using a Favipiravir monotherapy and a specific dose of 1800 mg twice on the 1st day followed by 800 mg on subsequent days in providing a valid estimate of Favipiravir's potency by the proportion of patients who were tested negative after the treatment with Favipiravir after 10 days and reviewing the occurrence of uric acid elevation in a specific dosage for Favipiravir-treated patients.

II. METHODS

A. Introduction

This study is a meta-analysis on the potency of Favipiravir, as a treatment modality to SARS-CoV-2 intended for the patients infected with COVID-19 and its effect on uric acid levels. This study utilized a quantitative research design, which derived data from published peer-reviewed journal articles to synthesize new data via meta-analysis.

A search engine was utilized, and a search engine is defined as an information retrieval system designed for use on collections with massive amounts of text [13]. The data came from peer-reviewed journal articles from the following databases: PubMed, Science Direct, Cochrane Library, PsycInfo, Embase, and Web of Science. The articles were screened based on the inclusion and exclusion criteria as seen in Table 1. A step-by-step guide regarding the conduct of a systematic review and meta-analysis by the University of Edinburgh's Centre for Cognitive Ageing and Cognitive Epidemiology (2013) was followed [14].

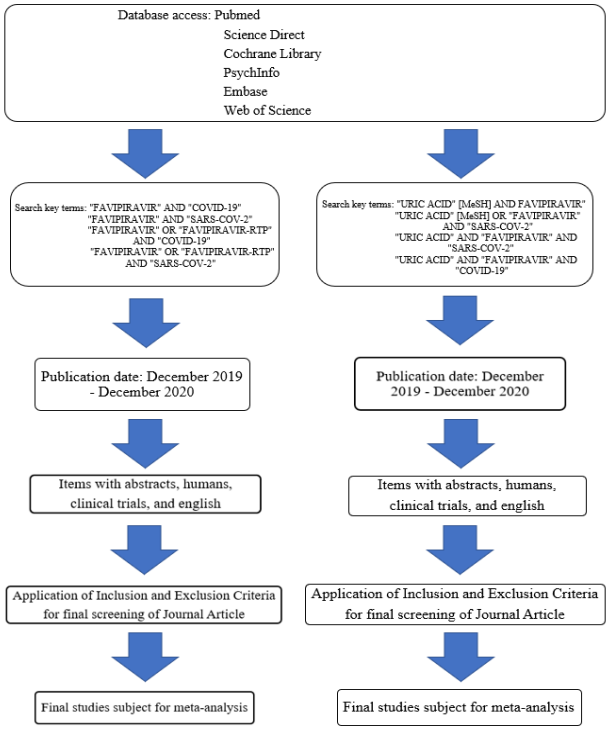

Fig.1. A Flowchart summarizing the Data Mining Method.

B. The Selection Criteria

All the results were manually screened based on the inclusion and exclusion criteria, and the studies which passed the inclusion criteria were collected. The studies were sorted according to their relevance in answering the research problems and information was extracted based on the values needed for the planned statistical analysis.

The journal articles that were utilized in this study had a research design of either descriptive, comparative, correlational, or quasi-experimental. Each set of studies with the same research design had different functions in answering specific objectives. Studies with a descriptive research design were used in finding out the estimated Favipiravir's potency in curing COVID-19 and its adverse effects. Articles with a comparative research design of Favipiravir with other antiviral drugs were used to gather data for the proportion of patients who were tested negative after the treatment with Favipiravir, and how many patients exhibited uric acid elevations upon the treatment with Favipiravir. Studies with a correlational research design were also used in assessing the relationship between the concentration of Favipiravir and hyperuricemia. They were also

used in assessing the concentration of Favipiravir in relation to exhibiting better clinical outcomes. Lastly, studies with a quasi-experimental research design that utilized clinical trials of Favipiravir treatments alone and/or in combination therapy with other antiviral drugs were used to determine and evaluate the uric acid elevation and clinical outcomes of Favipiravir treatment. The target population or subjects are patients infected with the COVID-19 disease.

Since the study is a systematic review, the inclusion and exclusion criteria were aimed in the studies included in the review. Among the inclusion criteria are the qualities of articles being published by more than 3 authors and with a publication date from December 2019 to December 2020, containing clinical data on the direct application of Favipiravir as the mode of treatment for SARS-CoV-2. The studies' subjects would be patients with mild including asymptomatic to severe symptoms of COVID-19 infection, aged 18-85 years old, and critically ill patients with COVID-19 infection, aged 18-85 years old. The included outcomes that were assessed in the studies are the number of patients who were tested negative after the treatment with Favipiravir and uric acid elevation occurrence.

Table.1. Summary of the Inclusion and Exclusion Criteria.

Categories	Inclusion Criteria	Exclusion Criteria
Intervention	Clinical studies utilizing Favipiravir as a mode of treatment for COVID-19	Clinical studies which reported placebo responses but did not employ any interventions
Outcomes	Potency Uric Acid Elevation Patients who tested negative after treatment with Favipiravir	Treatment for diseases other than COVID-19 Pharmaceutical costs
Clinical study samples	Patients with mild (including asymptomatic) to life-threatening symptoms (18-85 years old) Critically ill patients (18-85 years old) COVID-19 infected patients with comorbidities prior to contacting COVID-19	Immunocompromised patients
Languages	English	Publications whose languages are not in English
Publication status	Scientific Journal Articles and Research Articles with publication dates ranging from December 2019 to December 2020, published by verified sources and 3 authors or more	Scientific Journal Articles and Research Articles with a publication date of November 2019 and older, published by unverified sources and 2 authors or less
Information sources	The following search engines were included in the data collection process: PubMed, Science Direct, Cochrane Library, PsycInfo, Embase, and Web of Science.	Articles from the following are not included in the data collection process: Wikipedia, Quora, blog posts, and unofficial websites.

Among the exclusion criteria would be studies which were published by less than 3 authors or the date of publication was until June 2015, studies with immunocompromised patients, and studies which have reported the presence of a placebo response that may have contaminated their results with bias. Furthermore, the patients' expectation is a major mediator of the placebo response [15]. Aside from the mentioned qualities, studies from the following search engines were not included: Wikipedia, Quora, blog posts, and unofficial websites.

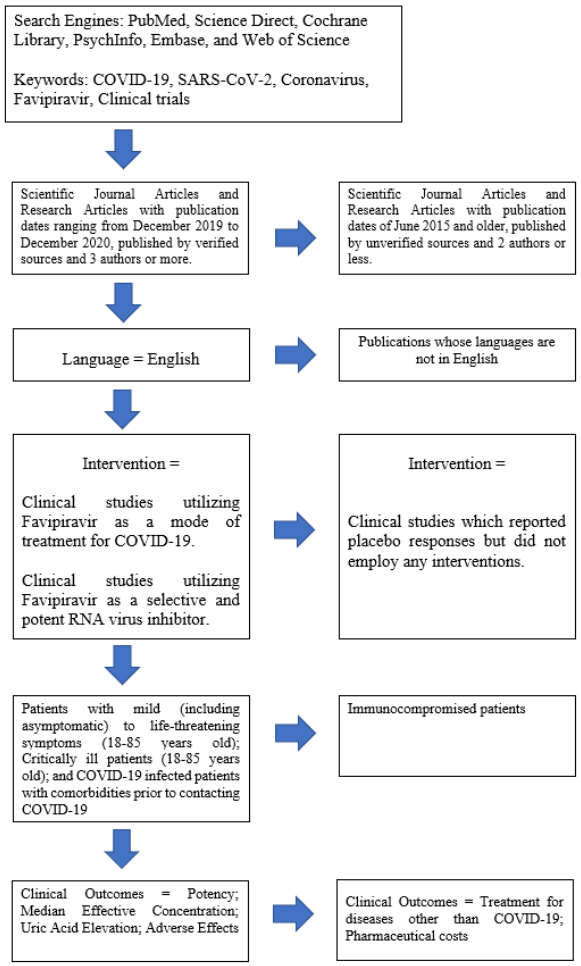

Fig.2. Schematic Diagram of the Data Mining Process using the Search Engines based on the Inclusion and Exclusion Criteria

C. Data extraction

The review authors used a data extraction form constructed using Microsoft Excel 2019. The data extraction of all included studies was independently performed by two review authors (M.I.A.S., A.M.V.S.). The following study characteristics were collected: study information (author, year, study design, country), target population (age group, number, symptom severity, COVID-19 status), and relevant parameters (number of patients who tested negative for COVID-19 after treatment with Favipiravir for 10 days, number of patients whose uric acid

levels were elevated upon the administration of Favipiravir). Disagreements between the two review authors concerning the inclusions, data extraction, and quality assessment were resolved by a third reviewer (L.J.D.R.).

D. Quality Assessment

Two review authors (I.M.B.S., M.N.L.S.) independently evaluated the methodological quality using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) for all included RCT studies. RoB 2 includes a framework for determining the risk of bias in the results and findings of any type of a randomized clinical trial [16]. This assessment is distinctly utilized for a single trial result which corresponds to an estimate of the relative effect of two interventions, namely the experimental intervention and comparator intervention or intervention strategies on a particular outcome. RoB 2 follows a five-domain structure through which bias might be introduced into the result. The JBI Critical Appraisal Checklist was also used for case reports, since it is more appropriate than RoB 2 for assessing the quality and extent of bias in the design, conduct and analysis of case reports [17]. Disagreements between the two review authors were resolved by a third reviewer (R.J.P.T.).

E. Statistical Analysis

The quality of the data collected from the clinical trials were assessed through the Revised Cochrane risk-of-bias tool for randomized trials which measured the risk of bias from the data gathered. The data was compared and represented through the Forest Plot and Mantel-Haenszel Fixed-Effects Odds Ratio to visualize significant differences within the gathered data.

Forest plot. The data analysis used to elaborate the data provided by the following three clinical trials namely Doi et al. (2020), Ivashchenko et al. (2020), and Udwadia et al. (2020) were represented graphically and were shown and illustrated for the relationship between the variables [18, 19, 20]. Presented were two zones wherein the left zone is a descriptive area of each study where it contains the list of randomized controlled trials along with the event rates that are listed within the criteria of the meta-analysis. The right zone, on the other hand, is presented graphically wherein the graph represents the measure of effect or the odds ratio for the studies by integrating confidence intervals represented by graphical horizontal lines. Furthermore, a vertical line is also present which represents the "line of null-effect" wherein it is placed at a value where there is no association between an outcome and exposure or no difference between the two interventions. If the confidence intervals for the trials cross the vertical line, it means that the null present within the 95% confidence interval implies that the study result is indeed the null value, therefore, the study did not observe a statistically significant difference between the control and the treatment groups for the individual study.

Mantel-Haenszel Fixed-Effects Odds Ratio. The Mantel-Haenszel Fixed-Effects Odds Ratio evaluated the association between the recorded outcome and its exposure that were shown statistically in this study that measured the effectiveness of the clinical trials of Doi et al. (2020), Ivashchenko et al. (2020), and Udwadia et al. (2020), which were also included further in the forest plot presentation [18, 19, 20]. The odds ratio was utilized to determine whether a particular exposure is a risk factor for a particular outcome and compared the magnitude of various risk factors for that outcome. Accordingly, if the odds ratio is equal to 1, then the exposure does not affect the odds of the outcome. If the odds ratio is less than 1, then the exposure is associated with lower odds of the outcome. If the odds ratio is greater than 1, then the exposure is associated with higher odds of the outcome.

Table.2. Mantel-Haenszel Fixed-Effects Odds Ratio Sample Table

RCT - 1	**Events**	**Non-events**
With Favipiravir	a	b
Control	c	d

$$Odds\ Ratio = \frac{a/b}{c/d}$$

When data is scarce, in times when the event risks are too low or the study size is limited in number, the estimates of certain standard errors used in the inverse-variance methods may have a poor result [21]. The Mantel-Haenszel method is preferred generally to the inverse variance method in fixed-effect meta-analyses. Mantel-Haenszel methods are fixed-effect meta-analysis methods using a different weighting scheme that depends on which effect measure is being used.

The Mantel-Haenszel summary log odds ratio is given by

$$In(OR_{MH}) = \left(\frac{\sum W_{MH,}OR_i}{\sum W_{MH,}}\right)$$

And the Mantel-Haenszel summary odds ratio by

$$OR_{MH} = \frac{\sum W_{MH,}OR_i}{\sum W_{MH,}},$$

The larger the weight given to the specific study, the more it would contribute to the weighted average, wherein each given study's odd ratio is given weight by

$$W_{MH,}i = \frac{b_i c_i}{N_i}$$

The summary log odds ratio has standard error given by

$$SE\{In(OR_{MH})\} = \sqrt{\frac{1}{2}\left(\frac{E}{R^2} + \frac{F+G}{RS} + \frac{H}{S^2}\right)},$$

Where:

$$R = \sum \frac{a_i d_i}{N_i};\ S = \sum \frac{b_i c_i}{N_i};$$
$$E = \sum \frac{(a_i + d_i) a_i d_i}{N_i^2};\ F = \sum \frac{(a_i + d_i) b_i c_i}{N_i^2};$$
$$G = \sum \frac{(b_i + c_i) a_i d_i}{N_i^2};\ H = \sum \frac{(b_i + c_i) b_i c_i}{N_i^2};$$

III. RESULTS AND DISCUSSION

A. Data Mining Results of Viral Clearance

Out of initially 1,384 studies, only 3 studies qualified based on the selection criteria and were further assessed based on the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) as seen in Figure 3.

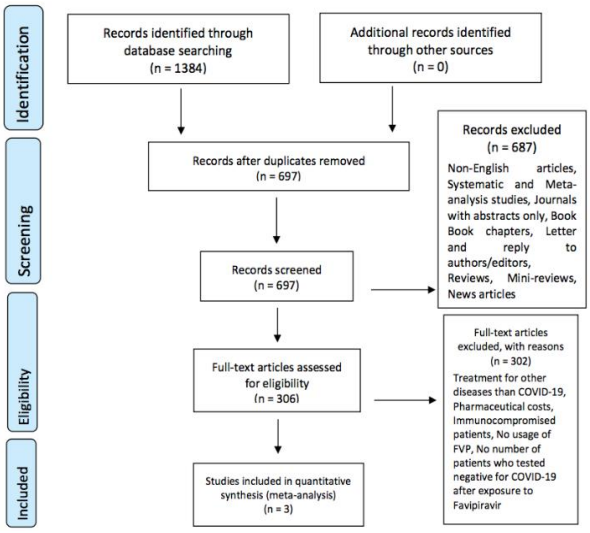

Fig.3. The PRISMA 2009 Flow Diagram of collected studies for estimating Favipiravir's potency by the proportion of patients who were tested negative after treatment with Favipiravir after 10 days.

B. Quality Assessment of Viral Clearance

The included studies were subjected to the quality assessment tool, specifically the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) as seen in Table 3.

Table.3. Quality Assessment of the Studies qualified for estimating Favipiravir's potency by the proportion of patients who tested negative after the treatment with Favipiravir after 10 days (RoB 2).

Unique ID	Authors, Date, and Location	Outcome	Weight	D1	D2	D3	D4	D5	Overall
RCT-1	Udwadia et al. (2020) – India	Number of negative patients after (n) days & Uric acid levels	1	+	+	+	-	+	-
RCT-2	Doi et al. (2020) – Japan	Number of negative patients after (n) days & Uric Acid Level	1	+	!	+	+	+	!
RCT-3	Ivashchenko et al. (2020) – Russia	Number of negative patients after (n) days	1	!	!	+	+	!	!

D1 Randomization process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

+ - Low risk
! - Some concerns
- - High risk

All the included studies were randomized and open-label trials. The final judgements for the risk of bias are RCT-1 is high risk, RCT-2 has some concerns, and RCT-3 has some concerns. The quality assessments were done by 2 independent authors, namely I.M.B.S., and M.N.L.S., and any conflicts were resolved by a 3rd author, namely R.J.P.T. To resolve a conflict, the 3rd author made an independent review, based on the full guide for using the RoB 2 tool. The RoB 2 tool has five domains, and in RCT-2 in Table 3, the two initial review authors disagreed on the first and fourth domains. This was resolved by R.J.P.T. for finalization. The study by Udwadia et al. (2020) and Doi et al. (2020) were both used in estimating Favipiravir's potency by the proportion of patients who were tested negative after the treatment with Favipiravir after 10 days and reviewing the occurrence of uric acid elevation in COVID-19 patients treated with Favipiravir [18, 20].

C. Data Mining Results of Uric Acid

Out of initially 1,389 studies, only 4 studies qualified based on the selection criteria and were further assessed based on RoB 2 and JBI Critical Appraisal Checklist for Case Reports, and only 2 studies were qualified for the meta-analysis, since the other 2 studies were case reports as seen in Figure 4.

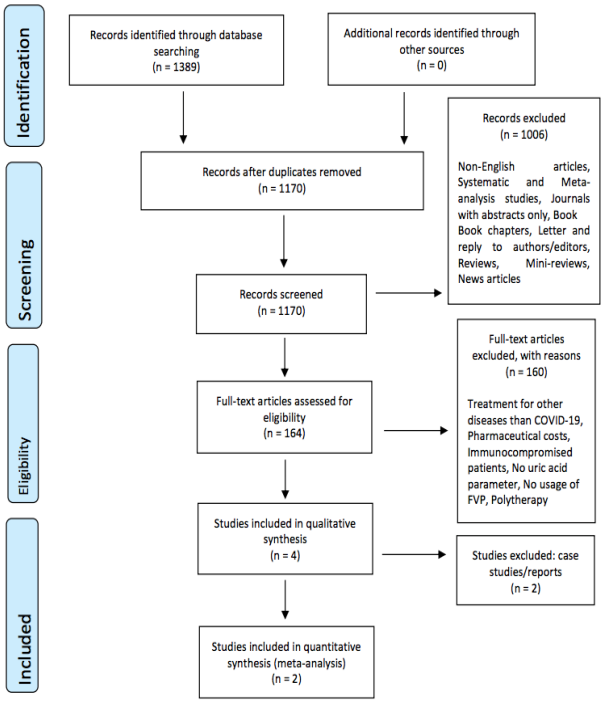

Fig.4. The PRISMA 2009 Flow Diagram of collected studies for reviewing the occurrence of uric acid elevation in COVID-19 patients who were treated with Favipiravir.

D. Quality Assessment of Uric Acid

The included studies were subjected to the quality assessment tools such as the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) for randomized clinical trials and JBI Critical Appraisal Checklist for Case Reports as seen in Table 4.

Table. 4. Summary of the Quality Assessment of the Studies qualified for reviewing the Occurrence of Uric Acid Elevation in COVID-19 patients treated with Favipiravir, based on RoB 2

Unique ID	Authors, Date, and Location	Outcome	Weight	D1	D2	D3	D4	D5	Overall
RCT-1	Udwadia et al. (2020) – India	Number of negative patients after (n) days & Uric acid levels	1	+	+	+	-	+	-
RCT-2	Doi et al. (2020) – Japan	Number of negative patients after (n) days & Uric Acid Level	1	+	!	+	+	+	!

D1 Randomization process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

\+ - Low risk
! - Some concerns
\- High risk

The two included studies were randomized and open-label trials. The final judgements for the risk of bias are RCT-1 is high risk and RCT-2 has some concerns. The quality assessments were also done by 2 independent authors, namely I.M.B.S., and M.N.L.S., and any conflicts were resolved by a 3rd author, namely R.J.P.T. To resolve a conflict, the 3rd author, R.J.P.T. made an independent review, based on the full guide for using the RoB 2 tool.

Table.5. Summary of the Quality Assessment of the Studies qualified for reviewing the Occurrence of Uric Acid Elevation in COVID-19 patients treated with Favipiravir, based on the JBI Critical Appraisal Checklist for Case Reports.

Authors, Date, and Location	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Included
Hase et al. (2020) – Japan	Y	Y	Y	Y	Y	Y	Y	Y	Y	✓
Takoi et al. (2020) – Japan	Y	N	Y	Y	Y	Y	Y	Y	Y	✓

Y, Yes; N, No; U, Unclear; NA, Not Applicable; Q1, Were patient's demographic characteristics clearly described?; Q2, Was the patient's history clearly described and presented as a timeline?; Q3, Was the current clinical condition of the patient in the presentation clearly described?; Q4, Were diagnostic tests or assessment methods and the results clearly described?; Q5, Was the intervention(s) or treatment procedure(s) clearly described?; Q6, Was the post-intervention clinical condition clearly described?; Q7, Were adverse events (harms) or unanticipated events identified and described?; and Q8, Does the case report provide takeaway lessons?

A separate quality assessment tool was used for evaluating case report studies, since the RoB 2 tool was not appropriate for evaluating case reports and it is most appropriately used for randomized clinical trials. For evaluating the case reports, the JBI Critical Appraisal Checklist for Case Reports was utilized, and the overall appraisal was to include both case reports collected. There were no discrepancies between the review authors. Both case reports were then used in reviewing the occurrence of uric acid elevation in COVID-19 patients treated with Favipiravir as seen in Table 5.

E. Results

Upon the implementation of the data mining process described in Figure 1, the following data were collected for estimating Favipiravir's potency by the proportion of patients who were tested negative after the treatment with Favipiravir after 10 days:

Table.6. Summary of the Data collected from the studies qualified for estimating Favipiravir's potency by the proportion of patients who were tested negative after the treatment with Favipiravir after 10 days

Authors, Date, and Location	Title	Study Design	Favipiravir Dose	Number of COVID-19 infected patients who tested negative after 10 days
Udwadia et al. (2020) – India	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	Randomized Open-Label Trial	Oral (day 1: 1800 mg BID and days 2−14: 800 mg BID)	53/72 patients
Doi et al. (2020) – Japan	A Prospective, Randomized, Open-Label Trial of Early versus Late Favipiravir Therapy in Hospitalized Patients with COVID-19	Randomized Open-Label Trial	Oral (Day 1: 1800 mg twice at least 4 hours apart and followed by 800 mg twice a day for 10 days)	31/36 patients
Ivashchenko et al. (2020) – Russia	AVIFAVIR for Treatment of Patients with Moderate COVID-19: Interim Results of a Phase II/III Multicenter Randomized Clinical Trial	Randomized Open-Label Trial	Oral (1800 mg BID on Day 1 followed by 800 mg BID on Days 2-14)	19/20 patients

All the included studies reported similar doses of Favipiravir, which is 1,800 mg twice on the first day, followed by 800 mg twice on the subsequent days until the 14th day. A meta-analysis via forest plot was conducted to interpret the data as seen in Table 6.

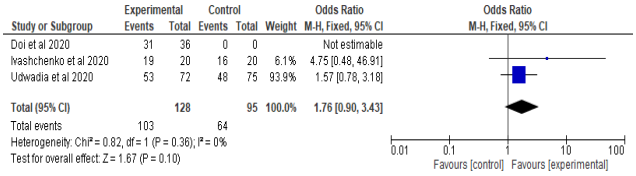

Fig.5. Forest Plot of Incidence of Viral Negativity after 10 days of taking Favipiravir.

Figure 5 above presents the forest plot of the odds ratio of viral negativity when taking Favipiravir in treating for COVID-19. Doi et al. (2020) noted that 31 out of 36 patients who have taken Favipiravir are cleared from COVID-19 after 10 days of treatment. The study did not have a control group, thus, Doi et al. (2020) did not report the corresponding odds ratio for viral clearance [18]. Meanwhile, in the study of Ivashchenko (2020), 19 out of 20 patients or 95% under the treatment group were cleared from COVID-19 after 10 days of treatment compared to only 16 out of 20 patients or 80% in the control group. The Mantel Haenszel fixed-effects odds ratio is estimated to be 4.75 (95% CI: [0.48, 46.91]) for the study of Ivashchenko (2020) [19]. This indicates that the odds of being viral negative after 10 days of treatment with Favipiravir is 375% higher compared to the odds of being viral negative if only standard care treatment was done to the patient. In addition, Udwadia et al (2020) reported that 53 out of 72 patients or 73.6% treated with Favipiravir were cleared from COVID-19 after 10 days of treatment while 48 out of 75 patients or 64% in the control group were cleared from COVID-19 after 10 days [20]. The estimated odds ratio is 1.57 (95% CI: [0.78, 3.18]) which means that the odds of being viral negative after 10 days is 57% higher for those treated with Favipiravir compared to those who are left untreated.

The pooled odds ratio is 1.76 with a 95% confidence interval of 0.90 to 3.43. This means that there is a 75% increase in the odds of being viral negative after 10 days if the patient is treated with Favipiravir compared to those who are not treated with Favipiravir. However, since the confidence interval contains the value of 1.0, the estimated odds ratio is not statistically significant at a 95% confidence level. This means that there is no sufficient evidence from the included studies to conclude that Favipiravir helps in the treatment of COVID-19 patients.

On the other hand, to review the occurrence of uric acid elevation in COVID-19 patients treated with Favipiravir, another data mining process was conducted, and the following data were collected from the included studies.

Table.7. Summary of the Data Collected from the Studies qualified for reviewing the Occurrence of Uric Acid Elevation in COVID-19 patients who were treated with Favipiravir

Authors Date, and Location	Title	Study Design	Favipiravir Dose	Number of Patients with Hyperuricemia
Doi et al. (2020) – Japan	A Prospective, Randomized, Open-Label Trial of Early versus Late Favipiravir Therapy in Hospitalized Patients with COVID-19	Randomized Open-Label Trial	Oral (Day 1: 1,800 mg twice at least 4 hours apart and followed by 800 mg twice a day for 10 days)	69/82 patients
Udwadia et al. (2020) – India	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	Randomized Open-Label Trial	Oral (day 1: 1800 mg BID and days 2−14: 800 mg BID)	12/73 patients
Hase et al. (2020) – Japan	Acute Gouty Arthritis During Favipiravir Treatment for Coronavirus Disease 2019	Case Report	Oral (day 1: 1,800 mg twice a day and day 2-14: 800 mg twice a day)	1/2 patients
Takoi et al. (2020) – Japan	Favipiravir-induced fever in coronavirus disease 2019: A report of two cases	Case Report	Two doses of 1800 mg on Day 1 and 800 mg twice daily thereafter	1/1 patient

All the included studies reported similar doses of Favipiravir, which is 1,800 mg twice on the first day, followed by 800 mg twice on the subsequent days as seen in Table 7.

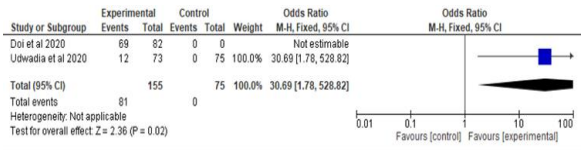

Fig.6. Forest Plot of Incidence of Prevalence of Uric Acid Elevation Associated with Favipiravir.

Figure 6 presents the forest plot of the prevalence of uric acid elevation on COVID-19 patients treated with Favipiravir. Doi et al. (2020) reported a total of 69 out of 82 patients (84.1%) have experienced an increase in uric acid concentrations after taking Favipiravir [18]. Odds ratios are not reported for Doi et al. (2020) since their study did not have a control group. For Udwadia et al. (2020), only 12 out of 73 patients or 16.4% have experienced an increase in uric acid levels while none of the patients in the control group have experienced an increase in uric acid levels [20]. The risk estimate with 95% CI is at 30.69 [1.78, 528.82]. For the overall meta-analysis, the total risk estimate with 95% CI is at 30.69 [1.78, 528.82]. Heterogeneity is not applicable since only one study is eligible for estimation. The test for overall effect is at Z = 2.36 (P = 0.02). Also, the confidence interval does not contain the value of 1.0, the estimated odds ratio is statistically significant at a 95% confidence level. With this, it shows that there is a significant correlation between the occurrence of uric acid and its administration with FVP. Furthermore, 2 case studies/reports were reported that observed uric acid elevation. These case studies were excluded in the meta-analysis as it is not considered as a representative sample. A case study by Hase et al. (2020) has reported a 42-year-old man with positive COVID-19 disease that experienced uric acid elevation upon his 13th day of administration of FVP at a dose of 1800 mg and then later developed into acute gouty arthritis on day 15th of administration of FVP [11]. Another case study by Takoi et al. (2020) also reported a uric acid elevation in a 42-year-old man with positive COVID-19 infection upon administration of Favipiravir with a dose of 1800 mg [22].

F. Discussion

The findings of the meta-analysis for estimating Favipiravir's potency by the proportion of patients who were tested negative after the treatment with Favipiravir after 10 days were not statistically significant since the confidence interval contains a value of 1. This is supported by the forest plot wherein the overall odds ratio of the studies is 1.76 (95% CI 0.90-3.43), which indicates that there is an increase in the viral negativity after 10 days of taking Favipiravir. However, with a confidence interval of 1, this indicates that the difference in the viral negativity of the experiment and control group is insignificant at a 95% confidence level and therefore, both treatments have high probability of viral negativity after 10 days. With that, the statistical results suggest that it may not only be Favipiravir which is the prime cause of viral negativity and that there is no sufficient evidence that it helps with treatment of COVID-19 patients. Favipiravir's capability to induce viral negativity in COVID-19 infected patients was not proven in this study due to the lack of statistical significance, despite its mechanism of action, which is inhibiting the RNA-dependent RNA polymerase (RdRp) of RNA viruses, one of which is SARS-CoV-2. Favipiravir possesses a strong binding affinity to the RdRp complex of SARS-CoV-2 [23], and this is important because RdRp plays an important role in the replication or transcription of SARS-CoV-2 [24]. The lack of statistical significance may be attributed to the closeness of the number of patients who tested negative for COVID-19 between the treatment groups and the control groups, which indicates the independence of the viral clearance from the usage of Favipiravir. This is further supported by Lou et al. (2020) which reported that Favipiravir's antiviral activity was not as effective as the previously reported in vitro half maximal effective concentration by Wang et al. (2020) of 61.88 μM, since Favipiravir was only able to inhibit less than 50% of SARS-CoV-2 in patients, even in concentrations up to 100 μM [25, 26]. In the study by Lou et al. (2020), the median time that Favipiravir can cause a clinical improvement was 14 days, while their control group achieved clinical improvement in 15 days [25], which may further indicate the independence of viral clearance from Favipiravir, since the difference is small.

On the other hand, the findings of the meta-analysis on the prevalence of uric acid elevation in association to the administration of FVP were statistically significant although a best estimate cannot be provided since only one study was able to be quantified due to the lack of control in the study conducted by Doi et al. (2020) [18]. Both participants in this study reported no history of gout and hyperuricemia. Udwadia et al. (2020) have observed that uric acid elevation is rather dose dependent since no incremental increase in serum uric acid was observed after Day 5 to 10 wherein the dosage was reduced to 800 mg from the initial dose of 1800 mg [20]. The significant correlation of the prevalence of uric acid elevation with FVP was further portrayed in the forest plot where the horizontal line that signifies the confidence interval of the study lies beyond the value of 1.0, which indicates the statistically significance of the estimated odds ratio at a 95% confidence level. Since there is only one qualified study, heterogeneity was not recorded. This is supported by the total odds ratio of 30.69 [1.78, 528.82] which means the probability of uric acid elevation with administration of FVP is statistically significant. To further support the occurrence of uric acid elevation in relation to FVP

administration, a case report by Hase et al. (2020) reported a 42-year-old man with a medical history of hyperuricemia, gout attack, type 2 diabetes, and hyperlipidemia [11]. The patient was administered with FVP twice daily with a dosage of 1800 mg on the 3rd day upon admission and was later reduced to 800 mg taken twice a day. It was reported that the patient experienced increased levels of uric acid after administration of FVP and the development of acute gouty arthritis due to the longer duration of FVP administration. With this, it was treated with non-steroidal anti-inflammatory drugs that later on improved the patient's condition which made him recover. Another case study by Takoi et al. (2020) reported 1 out of 2 patients developed an increased uric acid level [22]. The patient was reported to be taking febuxostat for hyperuricemia but upon FVP administration with a dosage of 1800 mg taken twice daily on the 1st day upon admission, the uric acid level of the patient was elevated. Thus, the elevated uric acid level of the patient was upon FVP administration. To conclude, patients with or without symptoms of hyperuricemia and gout still developed an increase in serum uric acid levels upon FVP administration.

As mentioned, one of the known adverse effects caused by Favipiravir is the increase of uric acid due to the mechanism of FVP in inhibiting the OAT1 and OAT3 which are transporter anions important for the tubular secretion of uric acid. In line with this, FVP hydroxide promotes the reuptake of uric acid. Thus, impaired excretion of uric acid in the urine causes the serum uric acid levels to accumulate in the blood [11, 27]. With this, it supports the findings of this research that FVP can increase blood uric acid upon its administration and can lead to the reappearance of the previous clinically significant medical illnesses such as acute gouty arthritis and hyperuricemia. Upon observation, the reappearance of these medical illnesses did not result in any deaths in the reported case studies. In addition to this, since it has been reported that Favipiravir does not cause any severe illness and severe side effects, Favipiravir can still be used in treating patients with COVID-19. However, proper usage in dosing regimens and awareness of its reported side effects must be observed. Overall, with the use of the forest plot, the predominating results of the studies show that Favipiravir's viral negativity induction is insignificant while its capability for uric acid elevation is significant. In the analyzed studies, both the control and experimental (Favipiravir) group present a high probability of inducing viral negativity in COVID-19 patients after 10 days of treatment. In assessing the effect of FVP on uric acid levels, the analyzed studies showed that the incorporation of this drug in COVID19 treatment can increase serum uric acid levels without causing severe illness and death to any of the patients.

G. Limitations

Interpretation of the results of these meta-analyses has its limitations. The limitations of our study include: (1) There is limited data on the treatment of Favipiravir and its effects on COVID-19 patients, thus, the study is not of a comprehensive evaluation of data and analysis; (2) The overall effect of the efficacy and safety of Favipiravir in combination with other antiviral drugs is not included in the analysis; (3) The severity of uric acid elevation in the administration of oral vs intravenous FVP is not measured; and (4) Only a single dosing regimen was used to measure the outcomes.

IV. CONCLUSION

In conclusion, Favipiravir's potency as regards to the proportion of negatively tested patients after administration of the drug, for a duration of 10 days, showed no statistical significance. Favipiravir's lack of capacity to induce viral negativity in patients infected with COVID-19 did not exhibit consistency with its inhibitory effect on the RNA-dependent RNA polymerase (RdRp) of SARS-CoV-2 [23]. FVP can also induce an increase in the blood uric acid levels upon administration and may lead to the re-emergence of diseases associated with uric acid levels, specifically acute gouty arthritis and hyperuricemia. The reappearance of diseases had no reports of death and severe side effects of FVP in the included studies. The 4 studies that show uric acid elevation gives us evidence about the occurrence of the adverse effect. However, these findings are inconclusive in terms of frequency of occurrence due to the scarcity of evidence. Although there was an observed statistical significance between the occurrence of uric acid elevation with respect to different dosages of Favipiravir, this study was not able to stipulate an estimate of the relationship between the uric acid elevation and the administration of FVP due to insufficient studies that qualified this meta-analysis' criteria.

This study may impart an extensive knowledge on students, researchers, as well as doctors, about the potency of Favipiravir in connection to the number of negatively tested patients after a duration of 10 days and its correlation to blood uric acid levels. With this, physicians, most especially the *frontliners* in

this time of pandemic, can widen their knowledge about the drug and expand their options on the possible treatments for COVID-19 patients. More information about Favipiravir can also help patients in exercising their right to choose what treatment they want by being critical of Favipiravir's safety and efficacy on the basis of this study's findings. Teaching personnel may incorporate this study and other studies concerning antivirals for SARS-CoV-2 in their course plans. This research may also serve as a reference material not only to students but for future researchers as a source of evidence that can support their studies. Information on the proper assessment done in clinical trials like this research, specifically finding the right parameters for the potency of the drug while taking into consideration the capacity of the body to tolerate the drug's action. And lastly, may this study be of high relevance in the current situation and for our future society.

Ethical Considerations

There was no human subject participation involved in the study since it only includes the systematic assessment and synthesis of data from published studies. No ethical approval was required for the completion of study analysis.

Conflict of Interest

The authors of the study declared no competing interests in the conducted research.

REFERENCES

[1]. Yavuz, S. S., & Unal, S. (2020). Antiviral treatment of COVID-19. Turkish Journal of Medical Sciences, 50(SI-1), 611-619.

[2]. Furuta, Y., Komeno, T., & Nakamura, T. (2017). Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proceedings of the Japan Academy, Series B, 93(7), 449-463.

[3]. Dong, L., Hu, S., & Gao, J. (2020). Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discoveries & Therapeutics, 14(1), 58-60.

[4]. Watanabe, S., Chan, M., & Suzuki, W. (2020). China says Japan-developed drug Avigan works against coronavirus. Positive reception by Chinese government contrasts with reservations in Japan.

[5]. Chen, C., Huang, J., Cheng, Z., Wu, J., Chen, S., Zhang, Y., Wang, X. (2020). Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial.

[6]. Doi, K., Ikeda, M., Hayase, N., Moriya, K., & Morimura, N., (2020). Nafamostat mesylate treatment in combination with favipiravir for patients critically ill with Covid-19: a case series. Critical Care, 24(1), 392.

[7]. Bishara, D., Kalafatis, C., & Taylor, D. (2020). Emerging and experimental treatments for COVID-19 and drug interactions with psychotropic agents. Therapeutic Advances in Psychopharmacology, 10, 1-15.

[8]. Naksuk, N., Lazar, S., & Peeraphatdit, T. (2020). Cardiac safety of off-label COVID-19 drug therapy: A review and proposed monitoring protocol. European Heart Journal: Acute Cardiovascular Care, 9(3), 215-221.

[9]. Agrawal, U., Raju, R., & Udwadia, Z. F. (2020). Favipiravir: A new and emerging antiviral option in COVID-19. Medical Journal Armed Forces India, 1–7.

[10]. Pilkington, V., Pepperrell, T. & Hill, A. (2020). A review of the safety of favipiravir – a potential treatment in the COVID-19 pandemic? Journal of Virus Eradication 2020, 6, 45–51.

[11]. Hase, R., Ishida, K., Kurata, R., Kurita, T., Mito, H., & Muranaka, E. (2020). Acute gouty arthritis during Favipiravir treatment for coronavirus disease 2019. Internal Medicine, 59(18), 2327-2329.

[12]. Sabillo, K. (2020). Avigan clinical trials in PH eyed to start this week after delays. Retrieved June 22, 2021, from ABS-CBN News.

[13]. Croft, W. B., Metzler, D., & Strohman, T. (2015). Search Engines: Information Retrieval in Practice. Pearson Education, Inc.

[14]. Centre for Cognitive Ageing and Cognitive Epidemiology. (2013). Systematic reviews and meta-analyses: a step-by-step guide.

[15]. Frisaldi, E., Shaibani, A., & Benedetti, F. (2017). Why we should Assess Patients' Expectations in Clinical Trials. Pain and Therapy, 6, 107-110.

[16]. Higgins, J. P., Savović, J., Page, M. J., & Sterne, J. A. (2019). Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [Scholarly project]. In Riskofbias.info. Retrieved February 6, 2021.

[17]. Joanna Briggs Institute. (2017). The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews: Checklist for Case Reports.

[18]. Doi, Y., Hibino, M., Hase, R., Yamamoto, M., Kasamatsu, Y., Hirose, M., Kondo, M. (2020). A prospective, randomized, open-label trial of early versus late favipiravir therapy in hospitalized patients with COVID-19. Antimicrobial Agents and Chemotherapy, 64(12), e01897-20.

[19]. Ivashchenko, A. A., Dmitriev, K. A., Vostokova, N. V., Azarova, V. N., Blinow, A. A., Egorova, A. N., … Ivachtchenko, A. V. (2020). AVIFAVIR for Treatment of Patients with Moderate COVID-19: Interim Results of a Phase

II/III Multicenter Randomized Clinical Trial. Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America.

[20]. Udwadia, Z. F., Singh, P., Barkate, H., Patil, S., Rangwala, S., Pendse, A., Tandon, M. (2020). 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, 103, 62-71.

[21]. Higgins, C., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M., & Welch, V. (2021). Cochrane Handbook for Systematic Reviews of Interventions.

[22]. Takoi H., Togashi Y., Fujimori, D., Kaizuka, H., Otsuki, S., Wada, T., Takeuchi, Y., & Abe, S. (2020). Favipiravir-induced fever in coronavirus disease 2019: A report of two cases. International Journal of Infectious Diseases (2020).

[23]. Joshi, S. Parkar, J., Ansari, A., Vora, A., Talwar, D., Tiwaskar, M., Patil, S., & Barkate, H. (2020). Role of favipiravir in the treatment of COVID-19. International Journal of Infectious Diseases, 102(2021), 501-508.

[24]. Pachetti, M., Marini, B., Benedetti, F., Giudici, F., Mauro, E., Storici, P., & Ippodrino, R. Emerging SARS-CoV-2 mutation hot spots include a novel RNA-dependent-RNA polymerase variant. Journal of Translational Medicine, 18(1).

[25]. Lou, Y., Liu, L., Yao, H., Hu, X., Su, J., Xu, & Qiu, Y. (2020). Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in COVID-19 Patients: An Exploratory Randomized, Controlled Trial. European Journal of Pharmaceutical Sciences, 157 (2021).

[26]. Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., & Xiao, G. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Research, 30, 269–271.

[27]. Mishima, E., Anzai, N., Miyazaki, M., & Abe, T. (2020). Uric Acid Elevation by Favipiravir, an Antiviral Drug. The Tohoku Journal of Experimental Medicine, 251(2), 87–90.