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Safety of Covid-19 Medication in Special Populations

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ABSTRACT

COVID-19 has no particular therapy yet, although researchers are looking for an appropriate medication. Diabetes mellitus patients had greater Covid-19 morbidity and mortality because of comorbidities and acquired immunodeficiency. This was a review study to detect Safety of Covid-19 medication in a special population. We conducted our search of the following database: PubMed using a broad term and keywords Safety of Covid 19 medication in special population up to December 2021. There were two studies in Saudi Arabia out of eight total. The participants in the 8 trials varied in age from 36 to 65. In the studies, for example, favipiravir was shown to be safe and well-tolerated. There were no new indications or adverse events that required drug discontinuation or dose changes; nevertheless, one patient died as a consequence of a serious adverse event, acute respiratory distress syndrome. Favipiravir may be crucial for ensuring successful therapy, minimizing mortality, and enabling early discharge when it comes to Covid-19 medicine. However, more clinical trials are urgently needed to determine the efficacy and safety of this antiviral nucleoside for COVID-19 treatment.

1. INTRODUCTION

The COVID-19 pandemic is placing an enormous burden on global healthcare systems [1]. According to current research, COVID-19 individuals become infected 2-3 days before symptoms appear. After 5-7 days, infectivity diminishes [2]. The signs and clinical manifestations of COVID-19 (high temperature, high blood pressure, dehydration, breathing trouble, thromboembolic events, etc.) are poorly tolerated by elderly individuals with various underlying conditions [3]. Many individuals acquire additional diseases during COVID-19 infection, such as high blood pressure, diabetes, and hyperlipidemia, which must be monitored even after COVID-19 infection [4]. For detection of viral RNA from a clinical sample of SARS-CoV-2 infection using reverse transcription-polymerase chain reaction (RT-PCR), the commercially available COVID-19 test currently dominates. A chest CT scan and isothermal nucleic acid amplification tests are also promising for diagnosing COVID-19 [5].

COVID-19 has no particular therapy yet, although researchers are looking for an appropriate medication. The compounds under study include immunoglobulins, interferon, thalidomide, and glucocorticoids, as well as viruses such as oseltamivir, and darunavir, which were created in Russia to treat influenza [6]. Immunosuppressive therapy users are more vulnerable to Covid-19-related morbidity and death. Vaccinating these people should be a top priority for healthcare practitioners and governments, but it isn't [7]. Immunosuppressive medications may decrease vaccination-induced humoral and cellular immunological responses, making it difficult to assess vaccine efficacy [8].

Cancer patients receiving glucocorticoids, chemotherapy, radiation, hormonal treatment, immunotherapy, or surgery are not contraindicated from receiving the Covid-19 vaccination [9].

Transplant recipients should also be immunized since they are at higher risk of infection and severe Covid-19 [10]. Cirrhosis, hepatobiliary cancers, and transplant candidates (or recipients) are susceptible groups at risk of severe Covid-19 and greater mortality [11]. Vaccination should be prioritized for these individuals. Compensated cirrhosis and viral hepatitis appear safe for vaccination [11].

Patients with ESRD are more susceptible to Covid-19 infection because of frequent or occasional dialysis treatments in a highly-populated area with a high risk of SARS-CoV-2 transmission [12].

Diabetes mellitus patients had greater Covid-19 morbidity and mortality because of comorbidities and acquired immunodeficiency. Comorbidity related to poor results in Covid-19 patients is diabetes [13].

With increasing body fat, the probability of serious sickness and prolonged hospitalization in an intensive care unit (ICU) increased [14].

Vaccination protects high-risk groups against severe COVID-19 infections and death [15]. Vaccination should be emphasized for those without contraindications, after weighing the advantages and dangers. Changing existing drugs and therapies may be warranted in certain cases, according to recommendations and new findings [16].

More study on COVID-19 immunization in particular groups is needed in the future to fully understand the consequences. Globally, public education is essential to address patient misconceptions [17].

2. Material and methods

This was a systematic study to see if the medicine Covid 19 was safe in a specific group. Preferred Reporting Items for Systematic Reviews were used to conduct this study.

2.1 Search strategy

We used the following database to perform our research: Up to December 2021, PubMed used a wide term and keywords to search for the safety of Covid 19 medicine in a specific group. Initial search records were loaded into an excel sheet. After removing duplicates, the authors reviewed all included papers by title and abstract for our inclusion criteria.

2.2 Eligibility criteria

Studies published in international peer-reviewed journals that investigated the dependability of the Safety of Covid 19 drug, Favipiravir in particular groups, without regard to language or age, were considered. Animal studies, reviews, case reports, and letters, on the other hand, were excluded.

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2.3 Data extraction

Authors independently extracted data about baseline characteristics from the included studies; first author name, year of publication, study design, country, sample size, characteristics of participants (sex and age), symptoms and signs, the aim, and the result. We also assessed "Favipiravir" medication's different side effects and improvement period after infection. When the results of a study were published more than once, we included only the most complete data.

3. Results

Application of inclusion and exclusion criteria to study abstracts yielded 8 articles. A total of 280 studies were identified from the database search. After review, a total of 8 studies consisting of 1954 patients with confirmed COVID-19 were selected. Among 8 studies, there were 2 of them in Saudi Arabia. The age ranged from 36 years to 65 years among the 8 studies. The follow-up duration ranged from 14 to 30 days. There were 40-82.5% males while there were 17.5-57.5% females among our studies shown in Table (1).

Table (1): Summary of the 8 studies regarding country, age, follow-up, and gender

First author	Country	Age (years),%	Follow up (days)	Gender	
				Male (n,%)	Female (n,%)
[19]	Egypt	36.3 (12.5)	30	50	50
[20]	Oman	55 (14)	5-21	52	37
[21]	Saudi Arabia	52 (13)	28	151 (59%)	103 (41%)
[22]	India	43.3 (11.7)	14	108 (73.5%)	39 (26.5%)
[23]	Saudi Arabia	51.00 (14.96)	14	306 (60.2%)	202 (39.8%)
[24]	Japan	43.8 (12.5)	NM	28 (57.1%)	21 (42.9%)
[25]	Saudi Arabia	51.4 (12.5)	NM	377 (82.5)	80 (17.5)
[26]	China	41 (34.17)	NM	59 (50.86)	57 (49.14)

NM: not measurable

The 8 studies had participants with confirmed COVID 19 infection, some of the mild to moderate symptoms and others with moderate to severe symptoms. Comorbidities as diabetes, hypertension, dyslipidemia, obesity, heart diseases, and respiratory diseases were found among the participants (Table 2).

Table (2): Study population and comorbidities among the 8 studies

First author	Year of publication	Study population	Comorbidities
[19]	2021	mild to moderate symptoms according to the national protocol classification	12% among favipiravir group 18% among Hydroxychloroquine and oseltamivir group In form of DM, HTN, Ischemic heart
[20]	2020	adult patients hospitalized with moderate to severe COVID-19 pneumonia	DM 40 (45 %) HTN 48 (54 %) Heart disease 13 (15 %)

[21]	2021	adults with moderate-to-severe COVID-19	DM 52 (41.6%) HTN 47 (37.6%) Asthma 15 (12%)
[22]	2020	Adult patients with mild-to-moderate symptoms of COVID-19	DM, HTN, Obesity 38 (25.9%)
[23]	2021	patients with COVID-19	DM, HTN, CVD, Asthma 282 (55.5%)
[24]	2021	COVID-19 patients with moderate pneumonia (SpO2 C 94%) within 10 days of onset of fever (temperature C 37.5 C)	Placebo= 35 (71.4%) Favipiravir= 83 (77.6%)
[25]	2021	Adult patients with confirmed SARS-CoV-2 diagnosed by real-time polymerase chain reaction (RT-PCR) from nasopharyngeal swab	DM= 217 (47.5) HTN= 183(40.0) Dyslipidemia= 34 (7.4)
[26]	2020	adult patients with COVID-19	HTN= 36 (31.03), 30 (25.00) DM= 14 (12.07) 13 (10.83)

(RT-PCR): real-time polymerase chain reaction; DM: diabetes mellitus; HTP: hypertension; CVD: cardiovascular disease

The serum ferritin and D dimer data were available in two studies only. The main symptoms were fever, cough, shortness of breath, dyspnea, GIT symptoms, tachypnea, low oxygen saturation, and fatigue (Table 3).

Table (3): The summary of the 8 studies regarding serum ferritin, D dimer, and main symptoms

First author	S. Ferritin	D dimer	Main symptoms
[19]	Favipiravir 201.5 (197.3) HCQ 280.7 (296.0)	Favipiravir 785.7 (1103.1) HCQ 390.0 (359.3)	Fever 36% Cough 38%
[20]	1367 (1851)	5.2 (17)	Fever 82%, shortness of breath 79%, Sore throat 39%
[21]	NM	NM	Fever, dry cough, shortness of breath, fatigue, and gastrointestinal symptoms
[22]	NM	NM	Cough and fever 102 (69.4%)
[23]	NM	NM	Cough 425 (83.7%) Fever 355 (69.9%) Low O2 saturation 336 (66.1%)
[24]	NM	NM	Fever Low oxygen saturation
[25]	NM	NM	Fever Tachypnea Dyspnea
[26]	NM	NM	Fever 64 (55.17) 61 (50.83) Fatigue 40 (34.48) 27 (22.50) Cough 70 (60.34) 64 (53.33)

NM: not measurable

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Among the 8 studies, participants were ranging from 7 to 26 patients needed respiratory support. In a study by Udwadia, 7 patients needed mechanical ventilation in each group but by Alamer the control group had 27 patients who needed mechanical ventilation in comparison to 4 in favipiravir as a treatment. Regarding outcome, about 5.2% to 26.4% transferred to ICU, about 32% to 67.4% discharged and death occurred among 1.3% to 12.4% of the participant's Figure (1). The MINORS scores the 8 included studies ranging from 9 to 15 out of 16 (Table 4).

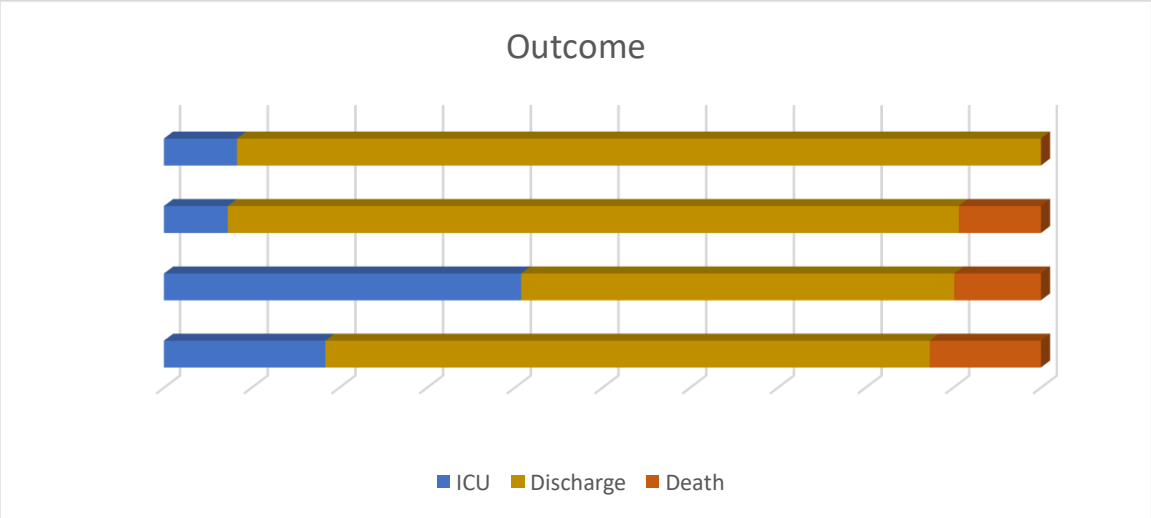

Figure (1): Comparison between 4 studies regarding the outcome

Table (4): Literature appraisal using MINORS assessment tool.

First author	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Appropriate endpoints	Unbiased assessment of study endpoint	Appropriate follow-up period	Loss to follow-up less than 5%	Prospective calculation of study size	Total
[19]	2	2	2	2	1	1	1	0	11
[20]	2	2	2	1	1	1	2	1	12
[21]	2	2	2	2	1	1	2	0	12
[22]	2	2	2	1	1	1	1	1	11
[23]	2	2	0	2	2	0	1	0	10
[24]	2	2	2	2	2	1	2	2	15
[25]	2	2	0	2	2	0	1	0	9
[26]	2	2	2	2	1	1	1	1	12

4. Discussion

Since late 2019, the novel coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread over the world, causing an unparalleled pandemic. COVID-19 has infected at least 28 million individuals and killed over 900,000 people [27]. While the majority of SARS-CoV-2 infections result in mild, self-limiting illness, with some patients staying completely asymptomatic throughout the course, some individuals proceed to severe pneumonia, multiorgan failure, and death [28]. In mid-December 2019, an epidemic of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was discovered in Wuhan, China, and the WHO declared a pandemic on March 11, 2020. The novel coronavirus 2019, dubbed COVID-19 by WHO, causes a variety of symptoms such as fever, coughing, and shortness of breath [29]. There are no medications that have been developed specifically for the treatment of COVID-19. Favipiravir is being tested in clinical trials with various medications to prevent SARS-CoV-2 infection, including azithromycin, hydroxychloroquine, chloroquine, LPV/RTV, ribavirin, remdesivir, and tocilizumab [30].

As the illness advances and has the potential to affect global health, it is critical to identify effective treatment alternatives. In addition to other medicines used to treat this condition, such as lopinavir, ritonavir, ribavirin, and chloroquine phosphate, favipiravir is being tested in several clinical studies [31]. Favipiravir has in vitro activity against SARS-CoV-2, and a nonrandomized study conducted in China found that patients with mild to moderate COVID-19 who were treated with favipiravir and interferon-alpha had a significantly shorter time to viral clearance than those treated with lopinavir-ritonavir and interferon-alpha [32]. Interim findings of a pilot multicenter, randomized study performed in Russia also revealed a considerably greater rate of viral clearance on the fifth day among hospitalized COVID-19 patients randomized to favipiravir resynthesized in Russia, compared to standard of care [27].

A total of 1954 COVID-19 individuals were chosen for the present investigation. The eight studies span the years 2020 to 2021. Only two of the eight investigations were retrospective, with the other six being prospective randomized control trials. Favipiravir was used to treat 999 of the patients. And the other subjects were given HCQ or Arbidol, or merely supportive care. Our systematic review focused on Favipiravir's major outcomes: the impact of Favipiravir on mortality and mechanical ventilation. Our data suggest that Favipiravir has no advantage over the standard of treatment or other antivirals previously found to be ineffective for COVID-19, such as hydroxychloroquine or Arbidol, for up to 30 days. Participants in our systematic review's eight trials varied from 7 to 26 patients who required breathing assistance. In research by [33], 7 patients required mechanical breathing in each group, whereas in a study by [34], the control group saw 27 patients need mechanical ventilation compared to 4 in the favipiravir treatment group.

[35] conducted a recent prospective randomized control study among adolescents and adults hospitalized with COVID-19 who were asymptomatic or slightly unwell. They claimed that no patients in either favipiravir therapy group had illness progression or death throughout their 28-day participation. Even though there is minimal clinical experience with favipiravir for COVID19 management, [36] revealed that major side effects were not found. Furthermore, because of the potential of teratogenicity and embryotoxicity, Japan's Ministry of Health, Labor, and Welfare has only given conditional marketing permission for its manufacture and clinical usage for influenza virus infection. Our findings are consistent with those of [37], who found favipiravir to be safe and well-tolerated in their investigation, despite the potential bias for overreporting of TEAEs in open-label studies. There were no new safety signals, and no adverse events that necessitated medication cessation or a modification in dosage regimen; a single patient in the control group died as a result of a significant adverse event, acute respiratory distress syndrome. Following our findings, [38] researched to evaluate the effectiveness and safety of favipiravir for the treatment of mild to moderate coronavirus illness (COVID-19). They revealed that favipiravir was well tolerated, with the majority of adverse events (AE) being minor. Asymptomatic hyperuricemia, transitory elevations of ALT and AST, and gastrointestinal disturbances were the most prevalent adverse events (diarrhea, nausea, abdominal pain).

There were two of them in Saudi Arabia, according to our systematic study. The age range of the participants in the eight trials varied from 36 to 65 years. The length of the follow-up varied from 14 to 30 days. In our investigations, men made up 40-82.5 percent of the population, while females made up 17.5-57.5 percent of the population. According to a systematic review and meta-analysis of the efficiency and safety of favipiravir in the treatment of individuals infected with a new coronavirus (COVID-19). Which included four studies (n= 405), three of which (n= 325) assessed the requirement for mechanical ventilation. When compared to the SOC/control, the OR of 0.80 (95 percent CI, 0.43, 1.47) indicated low probabilities and the necessity for mechanical ventilation in the patients [39]. [40] conducted a meta-analysis to evaluate the therapeutic result and side effects of FVP treatment. They discovered that patients in the FVP groups improved significantly on the 7th and 14th days of therapy (Day 7: RR 1.25, 95 percent CI 1.01 to 1.53; Day 14: RR 1.29, 95 percent

CI 1.08 to 1.54). Clinical deterioration is less common in FVP treatment groups than in other antiviral medications (OR 0.59, 95 percent CI 0.30 to 1.14) after treatments, albeit this is not statistically significant.

In addition to our findings, [36] conducted a systematic review that comprised 11 eligible papers. The majority of patients had mild-to-moderate COVID-19, and favipiravir medication may have contributed to lung healing within 14 days of treatment beginning. A comparison of early and late favipiravir introduction in patients with asymptomatic or moderate COVID-19 found a significant difference in hospitalization length.

5. Conclusion

Favipiravir may be crucial for ensuring successful therapy, minimizing mortality, and enabling early discharge when it comes to Covid-19 medicine. However, more clinical trials are urgently needed to determine the efficacy and safety of this antiviral nucleoside for COVID-19 treatment.

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