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Srinivasa Jayachandra, Sadhana Sonti, Vijaya Vathsa, C.M.A. Beliappa, Praneetha Achanta РЕТРОСПЕКТИВНЫЙ АНАЛИЗ ПЕРЕПРОФИЛИРОВАННЫХ ТЕРАПЕВТИЧЕСКИХ СРЕДСТВ, ИСПОЛЬЗОВАННЫХ ВО ВРЕМЯ ИНДУЦИРОВАННОГО ДЕЛЬТА-ВАРИАНТОМ COVID-19 КРИЗИСА В ИНДИИ, 2021 ГОД //Медицина в Кузбассе. 2023. №4. С. 38-47.

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РЕТРОСПЕКТИВНЫЙ АНАЛИЗ ПЕРЕПРОФИЛИРОВАННЫХ ТЕРАПЕВТИЧЕСКИХ СРЕДСТВ, ИСПОЛЬЗОВАННЫХ ВО ВРЕМЯ ИНДУЦИРОВАННОГО ДЕЛЬТА-ВАРИАНТОМ COVID-19 КРИЗИСА В ИНДИИ, 2021 ГОД

COVID-19 привел к серьезному мировому кризису в области здравоохранения и экономики, в результате которого более 27 миллионов человек заразились этим заболеванием и более 800 000 умерли.
Цель: изучить влияние перепрофилированных терапевтических средств, таких как ивермектин/фавипиравир, со стероидами или без них, на клинические исходы заболевания COVID-19 легкой и среднетяжелой степени тяжести в Индии.
Методы. В исследование были включены 99 негоспитализированных пациентов с симптомами COVID-19 легкой и умеренной степени тяжести, которые получали повторно назначенные препараты, такие как ивермектин или фавипиравир, или оба вместе со стероидами или без них. Было сформировано 3 группы пациентов. Были проанализированы такие клинические исходы, как насыщение кислородом, госпитализация, время восстановления, смертность, побочные эффекты или осложнения в течение 2 недель после лечения. Ретроспективный анализ данных выполнен с помощью соответствующих статистических тестов с использованием статистического пакета SPSS версии 23.
Результаты. Ивермектин или фавипиравир, независимо друг от друга, не оказывали влияния на клинический исход (18/99, 25/99 пациентов соответственно), тогда как ивермектин плюс фавипиравир в комбинации положительно влияли на время выздоровления, составив менее или равно 4 дням (56/99 пациентов). Также ивермектин плюс фавипиравир плюс стероиды (51/99 пациентов) показали положительный эффект с точки зрения времени восстановления. Пациенты выздоравливали через 4 дня или меньше.
Заключение. Это исследование продемонстрировало относительную безопасность и эффективность ивермектина и фавипиравира, включая стероиды, при надлежащем мониторинге/адаптации при ведении пациентов с COVID-19 легкой и среднетяжелой степени тяжести.
Ключевые слова: COVID-19; стероиды; ивермектин; фавипиравир

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A RETROSPECTIVE ANALYSIS OF REPURPOSED THERAPEUTICS USED DURING THE DELTA VARIANT INDUCED COVID-19 CRISIS OF INDIA, 2021

COVID-19 has led to a major worldwide health and economic crisis, with more than 27 million people having contracted the disease and more than 800 000 deaths.
Objectives – to study the effects of repurposed therapeutics such as ivermectin/favipiravir with or without steroids in clinical outcomes of mild to moderately severe COVID-19 disease in India.
Methods. 99 nonhospitalized patients with mild to moderate symptomatic COVID-19 who received repurposed drugs like ivermectin or favipiravir or both with or without steroids were included 3 groups of patients were formed. The clinical outcome like oxygen saturation, hospitalization, recovery time, mortality, side effects or complications within 2 weeks after treatment were analyzed. Retrospective data analysis done by appropriate statistical tests using SPSS statistical package version 23.
Results. Ivermectin or favipiravir, independently had no effect on clinical outcome (18/99, 25/99 patients respectively), whereas ivermectin plus favipiravir in combination positively affected recovery time to less than or equal to 4 days (56/99 patients). However ivermectin plus favipiravir plus steroids (51/99 patients) showed a positive effect in terms of recovery time. Patients recovered in 4 days or less.
Conclusion. This study demonstrated the relative safety and efficacy of ivermectin and favipiravir including steroids when appropriately monitored/tailored in managing mild to moderate COVID-19 patients.
Key words: COVID-19; Steriods; Ivermectin; Favipiravir

Coronavirus disease 2019 (COVID-19), the highly contagious viral illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has had a terrible effect on the world resulting in more than 3.8 million deaths worldwide, emerging as the most significant global health crisis since the influenza pandemic of 1918. After the first cases of this mainly respiratory viral illness were first reported in Wuhan, Hubei Province, China, in late December 2019, SARS-CoV-2 rapidly spread across the world in a short span of time, convincing the World Health Organization (WHO) to declare it as a global pandemic on March 11, 2020 [1, 2]. Since being declared a global pandemic, COVID-19 has ravaged many countries globally and has overwhelmed many healthcare systems. The pandemic has also resulted in the loss of livelihoods due to prolonged shutdowns, which have had a rippling outcome on the global economy. Even though considerable progress in clinical research has led to a better understanding of SARS-CoV-2 and the management of COVID-19, limiting the continuing increase of this virus and its variants has become an issue of increasing concern, as SARS-CoV-2 continues to wreak havoc across the world, with many countries experiencing a second or third wave of outbreaks of this viral illness attributed mainly due to the emergence of mutant variants of the virus.

It was disaster time during April and May 2021 in India. Healthcare workers were not only dealing with a fear of hospitals, but also an acute shortage of vital medical resources. Entire families were sick. Physicians were trying to keep patients out of the hospitals as much as possible. Only the sickest were referred for hospitalization. People across the country suffered severe bed shortages and a critical shortage of medical oxygen supplies. Physicians and other volunteers from around the world helped India during this crisis.

There was no widespread availability of Remdesevir or monoclonal antibodies at that particular time. The combination of ivermectin and doxycycline was used for mild to moderate cases due to their combined antiviral and antiinflammatory properties.

The Drug Controller General of India, granted fast track permission to manufacture and market the antiviral drug Favipiravir, for moderate to severe cases of COVID-19. Favipiravir is an oral, broad-spectrum inhibitor of viral RNA-dependent RNA polymerase which also elicits viral mutagenesis [3]. Its mechanism of action is selective inhibition of viral RNA polymerase in vivo by its triphosphorylated derivative (T-705RTP), which translates to broad-spectrum inhibition of RNA viruses [4]. Favipiravir has in vitro activity against SARS-CoV-2, and a nonrandomized study conducted in China has shown significantly shorter time to viral clearance among patients with mild to moderate COVID-19 who were treated with favipiravir and interferon alpha than in those treated with lopinavir-ritonavir and interferon alpha 9 [5].

Ivermectin is a widely used antiparasitic drug with known partial efficacy against several single-strain RNA viruses [6-8]. Caly et al. reported in vitro inhibition of SARS-CoV-2 replication using micromolar concentrations of ivermectin [9].

Aim – this retrospective study was undertaken to assess the efficacy of off label and repurposed drugs like ivermectin and favipiravir, independently or in combination,and with or without steroids,used during the second COVID-19 wave in India,caused by the delta variant of SARS-COV2 virus .

METHODS

Study design. This is a retrospective analysis of patients seen during April-June 2021 of COVID-19 outbreak. The patients were predominantly from in and around Bengaluru but also from different states of India and were treated via teleconsultation. All data was extracted from clinical records of patients who were referred from Non-Governmental Organisations volunteering in rural areas. A team of doctors got organized as a Karnataka Covid Volunteer Team to provide teleconsultation and some of us volunteered with this group. Other patients were managed by doctors at the Telerad RXDX Multispecialty clinic in Bangalore, Karnataka.

All procedures were conducted in compliance with the latest revision of the Helsinki Declaration and Good Clinical Practice. All patients provided verbal informed consent for their data to be used for this study. They filled out a questionnaire sent out by us.

The protocol was approved by the Ethics Committee of Telerad RXDX Health Centre, a Multispecialty Hospital at Bangalore.

We used Karnataka government guidelines for covid therapy as well as the AIIMS (All India Institute of Medical Sciences) guidelines at that time.

Inclusion criteria: Mild to moderately symptomatic patients who had a positive result on reverse-transcriptase–polymerase-chain-reaction or antigen SARS-CoV-2 testing.

A total of 99 patients with RT -PCR proven covid were selected retrospectively for this analysis (picture 1). Age of patients varied between 24 years to 76 years. There were 51 males and 48 females. Social demographics varied from home makers to retired and actively working individuals.

Mild COVID-19 was defined as patients with uncomplicated upper respiratory infection or fever without evidence of breathlessness or Hypoxia (normal saturation > 94 %).

Moderate illness was defined as patients with pneumonia not severe form and having clinical features of dyspnea and or hypoxia, fever, cough, including SpO_2 less than 94 % (90-94 %) on room air, respiratory rate more or equal to 24 per minute.

Severe illness was defined as patient with severe pneumonia plus one of the following: respiratory rate > 30 breaths/min, severe respiratory distress, SpO_2 less than 90 %.

Most but not all patients underwent various types of Laboratory investigations including complete blood count, D-dimer, CRP, IL6, LDH, LFT, Ferritin and a Chest CT scan to assess the severity of inflammation and extent of lung involvement. All patients were managed from home through teleconsultation and those requiring hospitalization were admitted to a nearby facility. They were triaged into mild, moderate and severe cases based on their symptomatology, CT Chest Corads Score wherever CT could be done, and oxygen saturation levels at initial evaluation.

Patients were divided into 3 groups according to the medications administered – Ivermectin, Favipiravir or both. Other medications (Steroids, blood thinners, anti-inflammatory and antibiotics) were also prescribed for the patients, as needed.

Ivermectin group had received a dose 12 mg/day for a period of 3 to 5 days.

Favipiravir, had been administered at a loa.ding dose of 3600 mg on day one, followed by 1600 mg for a period of 7 to 14 days.

The Ivermectin and favipiravir, combination had been administered to 33 patients. The therapeutic cocktail was augmented with blood thinners as per current local guidelines.

Steroids used were either decadron 4-8 mg daily for around 3-10 days or methylprednisolone at equivalent doses, for as long as it was required, typically around 10-14 days. Steroids were typically started during the second week, if required for worsening hypoxia or worsening inflammatory markers, ongoing fever etc.

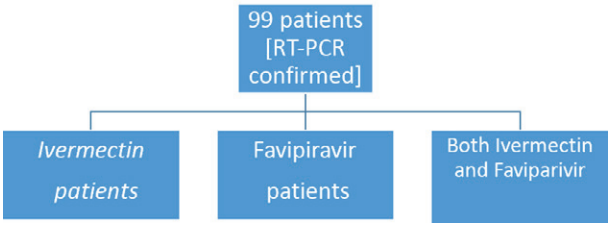
Hydroxychloroquine was not typically used although the Karnataka guideline allowed for it. This was owing to the popular concern about side effects.

65 patients had received blood thinners varying from ecosprin 75 mg, apixaban 2.5 to 5 mg and enoxaparin depending upon the case and availability of these medicines. These drugs were given for a duration of 2 to 3 weeks. We had also used antibiotics like amoxycillin clavulanate, cephalosporins and doxycycline as required Supportive care like bed rest, isolation, proning, steam inhalation, incentive spirometry had been appropriately prescribed.

All patients were explained the Red Flag signs including low oxygen saturation below 94 %, pulse consistently above 120 beats per minute, chest pain, breathlessness, high fever ,extreme exhaustion, blue tongue, blue lips and which warranted immediate care escalation and hospitalization.

51 patients had received steroids. Steroids were given to patients with moderate to severe COVID-19 who had persistent clinical deterioration in the form of high grade fevers and hypoxia. The recovery was remarkable with noticeably quick turnaround after initiation of steroids. Once afebrile period was reached, steroids were quickly tapered off. Of the 51 who took steroids, 11 had to be hospitalized. 40 were managed at home. Out of a total of 8 cases with severe COVID-19 at initial diagnosis, 5 could be managed at home itself. Steroids were given in the second week

Рисунок 1
Распределение пациентов
Figure 1
Distribution of patients



of infection typically, as indicated for worsening hypoxia.

All patients who went on steroids were asked to monitor their blood sugars. Some of them needed temporary management for glucose intolerance with oral medications or insulin as required.. The sugar levels invariably improved with tapering of steroids.

The principal outcomes of the study were the hospitalization, recovery time, side effects/complications and oxygen saturation and mortality rate.

Statistical analysis. Continuous variables were expressed as the mean, SD and median, while the categorical variables were expressed as numbers and percentages. The chi-square test (χ^2) and Fisher's exact test was used for categorical variables. A P-value less than 0.05 was considered statistically significant. The analysis was done with SPSS Statistical Package version 23.

RESULTS

A total of 99 laboratory-confirmed SARS-CoV-2 infection were selected, 51 were males and 48 were females.

Table 1 showing the baseline details (mean ± Standard deviation) of age , blood parameters – hemoglobin, WBCs, platelets, CRP, ferritin, D Dimer, LDH and AST and ALT in confirmed COVID-19 patients. Neutrophil to Lymphocyte ratio was calculated, 42 of them had a normal ratio of upto 3.5 and 32 had a high ratio with more than 3.5. Chest CT Scan was done to assess the score . The CT score was zero in 5 patients, mild (score, 1-8) in 49 patients, moderate (score, 9 to 15) in 19 patients and severe (score more than 16) in 6 patients. D Dimer was checked in 82 patients, the value was low (upto 500 ng/ml) in 65 patients, moderate (501 to 1000 ng/ml) in 12 patients and high (1000 ng/ml or more) in 5 patients. LDH levels were checked in 47 patients, it was normal (upto 250 U/L) in 23 patients and was elevated (more than 250 U/L) in 24 patients. Ferritin levels were available in 32 patients, was found to be elevated (more than 150 ng/ml) in 18 patients.

39 patients had varied comorbidities ranging from hypertension, diabetes, coronary artery disease, sarcoidosis, leukemia, asthma and COPD. One first trimester pregnant lady and one patient who had

delivered a baby were also a part of the study. All patients were RT-PCR positive. 8 patients had received one vaccine and 9 patients had received both COVID-19 vaccines. Clinical features varied from fever to cough, breathlessness, body pain and loss of smell to mention a few common symptoms.

Majority were mildly ill (48 patients), 19 were moderately ill and severely ill were 15. The rest had moderate to severe illness but did not require hospitalization. 15 severely ill patients needed hospitalization. All of them recovered between 3 to 6 weeks with no sequelae of infection. 82 patients received antibiotics like Doxycycline, azithromycin or amoxycillin clavulanate for secondary bacterial infections (table 2, pictures 2 and 3). There was no significant association between Ivermectin and clinical outcomes, parameters in patients (table 3).

Table 4 shows that, there was no significant association between Favipiravir and its clinical outcome parameters in patients without steroids ($p > 0.05$). However there was significant association between Side effects /complications and Favipiravir given (i.e., $p < 0.05$). Bradycardia and hyperuricemia was seen in 2 patients secondary to use of Favipiravir. The medicine was discontinued in these individuals with correction of the abnormalities.

Above table 5 demonstrates that there was significant association between Recovery time (days) with both Ivermectin plus Favipiravir (i.e., $p < 0.05$), though, there was no statistically significant association with other clinical parameters.

51 COVID-19 patients received steroids. Hospitalisation, recovery time (days/weeks), O_2 saturation and Liver Function Tests were improved by the steroids ($p < 0.05$) (table 6) in the treated groups. Side effects like nausea, headache, diarrhea, and neutrophil (N) to Lymphocyte (L) Ratio (NLR) were not significantly associated with the steroids ($p > 0.05$).

Side effects varied from nausea and vomiting in 7 patients, loose motions in 3 patients, bleeding from

Таблица 1. Исходные клинико-лабораторные характеристики исследуемой группы
Table 1. Baseline clinical and laboratory characteristics of the studied group

Variables	Mean ± SD
Age (years)	45.27 ± 16.27
Haemoglobin (g/dL)	13.01 ± 1.90
Total leukocyte count($\times10^9$/L)	5.60 ± 2.61
Neutrophils count ($\times10^9$/L)	66.01 ± 13.21
Lymphocytes count ($\times10^9$/L)	23.77 ± 11.72
Platelets count ($\times10^9$/L)	261.64 ± 107.77
Serum ferritin (µg/L)	229.63 ± 187.29
D-dimer (ng/mL)	432.16 ± 935.14
Lactate dehydrogenase (IU/L)	189.60 ± 127.61
C-Reactive Protein (CRP) (mg/L)	17.91 ± 24.79
ALT(IU/L)	29.10 ± 19.96
AST(IU/L)	26.68 ± 8.15

Таблица 2. Демографические и клинические характеристики различных переменных
Table 2. Demographic and clinical Characteristics of various variables

		No. of patients (n = 99)	%
Male		51	51.52
Female		48	48.48
Oxygen Saturation level	normal	67	67.68
	low	32	32.32
Comorbidities	yes	39	39.01
	no	60	60.99
Vaccination status	fully	10	10.10
	partially	9	9.09
	unvaccinated	80	80.81
Relevant CT chest scores	low	5	5.05
	intermediate	49	49.49
	moderate	19	19.19
	high	6	6.06
Neutrophil-to-lymphocyte ratio (mean ±SD)		3.86 ± 2.71	

Рисунок 2. Симптомы COVID-19 у пациентов (%)
Figure 2. Symptoms of COVID-19 in patients (percentage %)

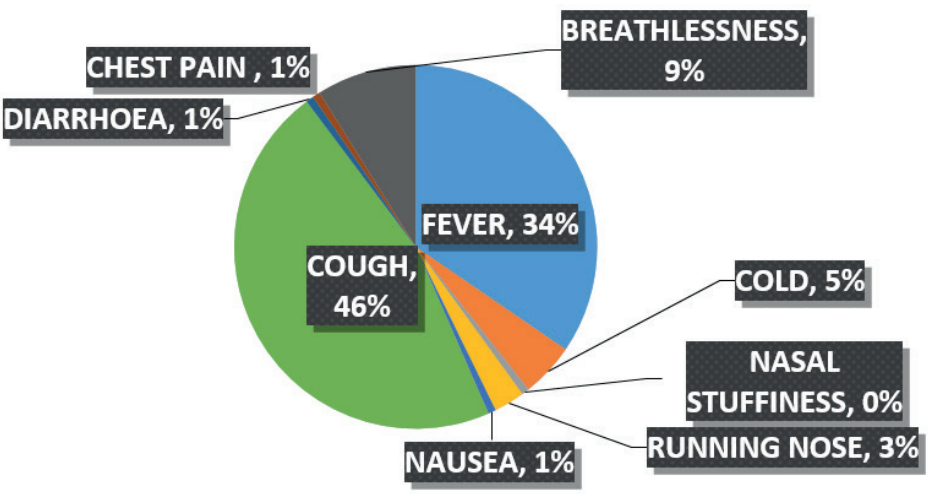


Рисунок 3. Лекарства, назначаемые пациентам с COVID-19
Figure 3. Medication administered to COVID-19 patients

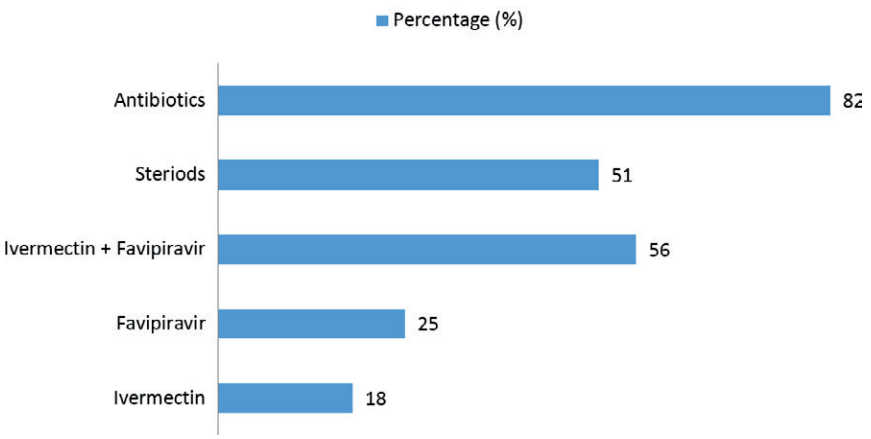


Таблица 3.
Связь между ивермектином и клиническим исходом
Table 3.
Association between Ivermectin with clinical outcome

Parameter		Ivermectin Given group		P-value
		yes	no	
Hospitalisation	hospitalized	1	0	-
	homecare	10	37	
Recovery time (days/weeks)	≤ 4days	4	23	0.130
	≥ 5 days	7	14	
O_2 saturation	normal (≥ 95%)	10	28	0.275
	low (≤ 94%)	1	9	
Side effects /complications	yes	2	8	0.805
	no	9	29	
Nausea	yes	11	37	-
	no	0	0	
Headache	yes	0	1	-
	no	11	36	
Diarrhea	yes	1	0	-
	no	10	37	
Liver Function Test Taken	yes	4	20	0.303
	no	7	17	
Neutrophil (N) to Lymphocyte (L) Ratio (NLR)	normal (up to 3.5)	6	26	0.785
	high (above 3.5)	5	18	

nose 1 patient, gastritis 3 patients and mouth ulcers 1 person. Clinical response and oxygen were evaluated at the end of the treatment. Effectiveness and safety of the drugs were analyzed. However we could not differentiate if clinical effects such as nausea or bradycardia or hyperuricemia were related to the disease process or were side effects attributable to a particular drug or the therapeutic cocktail of medicines used.

DISCUSSION

Following reports of patients with severe pneumonia caused by a β coronavirus in China, the World Health Organization (WHO) named the causative agent severe acute respiratory syndrome (SARS) coronavirus (SARS-CoV)-2 and named the disease as the 2019 novel coronavirus disease (COVID-19). The clinical manifestations of COVID-19 include asymptomatic carriers, presymptomatic carriers, and symptomatic patients with acute respiratory distress syndrome (ARDS) or pneumonia. Though the incubation period for COVID-19 varies between 4 and 14 days, one study reported that over 97 % of infected individuals who were presymptomatic developed clinical symptoms within 11-12 days. The prevalence of asymptomatic cases is over 80 %, and cases are defined as individuals with positive viral tests but without any COVID-19 symptoms. Among symptomatic patients, the severity of illness ranges from mild to moderate pneumonia symptoms (fever, fatigue, and cough) (81 %), severe pneumonia symptoms (dyspnea, tachypnea with respiratory rates ≥ 30/min, and hypoxia) and lung

Таблица 4. Связь между Фавипиравиром и его клиническим исходом
Table 4. Association between Favipiravir and its clinical outcome

Parameter		Favipiravir Given		P-value
		yes	no	
Hospitalisation	hospitalized	0	1	-
	homecare	10	37	
Recovery time (days/weeks)	≤ 4days	8	19	0.089
	≥5 days	2	19	
O_2 saturation	normal (≥ 95%)	9	29	0.343
	low (≤ 94%)	1	9	
Side effects /complications	yes	6	4	0.001
	no	4	34	
Nausea	yes	10	38	-
	no	0	0	
Headache	yes	0	1	-
	no	10	37	
Diarrhea	yes	0	1	-
	no	10	37	
Liver Function Test Available	yes	7	17	0.155
	no	3	21	
Neutrophil (N) to Lymphocyte (L) Ratio (NLR)	normal (up to 3.5)	7	11	0.136
	high (above 3.5)	1	8	

Таблица 5.
Связь между ивермектином и фавипиравиром и клиническими исходами
Table 5.
Association between both Ivermectin plus Favipiravir and clinical outcomes

Parameter		Both		P-value
		yes	no	
Hospitalisation	hospitalized	0	1	0.496
	homecare	15	32	
Recovery time (days/weeks)	≤ 4days	15	12	0.0001
	≥5 days	0	21	
O_2 saturation	normal (≥ 95%)	15	23	0.344
	low (≤ 94%)	0	3	
Side effects /complications	yes	1	9	0.103
	no	14	14	
Nausea	yes	0	0	-
	no	15	33	
Headache	yes	0	1	0.496
	no	15	32	
Diarrhea	yes	0	1	0.496
	no	15	32	
Liver Function Test Available	yes	11	13	0.029
	no	4	20	
Neutrophil (N) to Lymphocyte (L) Ratio (NLR)	normal (up to 3.5)	8	15	0.613
	high (above 3.5)	7	18	

infiltrates (14 %), and critical condition associated with respiratory failure or multiorgan system dysfunction (5 %). The most serious complications of COVID-19 are sepsis-like inflammation, coagulopathy, and respiratory or cardiovascular complications. In response to injury or infection, the innate immune system mounts immediate inflammatory responses to limit the infection and to help the adaptive immune system develop long-lasting, host-protective Antibody and T-cell responses against the virus within 7-10 days postinfection. However, when inflammation is not modulated or resolved after serving its purpose, it turns into hyperinflammation or becomes chronic and results in the inhibition of adaptive immune responses, tissue damage, or organ failure. Such dysregulated inflammation results in a «cytokine storm» that is evident in sepsis as well as in patients with severe respiratory diseases caused by coronaviruses such as SARS, MERS, and COVID-19. A cytokine storm is manifested by uncontrolled production of inflammatory

Таблица 6.
Клинический результат лечения стероидами в дополнение к ивермектину, фавипиравиру или обоим препаратам
Table 6.
Clinical outcome of treatment with steroids in addition to ivermectin, favipiravir or both

Parameter		Steroids Given		P-value
		yes	no	
Hospitalisation	hospitalized	11	1	0.003
	homecare	40	47	
Recovery time (days/weeks)	≤ 4 days	45	27	0.000
	≥5 days	6	21	
O_2 saturation	normal (≥ 95%)	31	38	0.000
	low (≤ 94%)	20	3	
Side effects /complications	yes	10	10	0.879
	no	41	38	
Nausea	yes	1	0	0.330
	no	50	48	
Headache	yes	2	1	0.594
	no	49	47	
Diarrhea	yes	0	1	0.300
	no	51	47	
Liver Function Test	yes	36	24	0.036
	no	15	24	
Neutrophil (N) to Lymphocyte (L) Ratio (NLR)	normal (up to 3.5)	24	18	0.098
	high (above 3.5)	23	34	

cytokines such as IL-6, G-CSF, IP-10, MCP-1, MIP-1α, TNF-α, IL-10, IL-7, and IL-2, which are significantly higher in intensive care unit (ICU) patients than non-ICU patients hospitalized with COVID-19 [10-14]. A cytokine storm causes lymphopenia and prevents the adaptive immune system to produce antiviral Abs. Emerging evidence suggest that complications of COVID-19 are associated with a gender or age disparity in inflammatory immune responses to SARS-CoV-2 infection as well as underlying health issue. Its mortality is reported to be between 2 and 4 %. However, in early 2021 there were no proven treatments for patients with COVID-19 disease except repurposed medicines with antiviral, anti-inflammatory and immunomodulatory properties [15-18]. Advanced age (> 65), hypertension, presence of coronary heart disease, diabetes mellitus and male gender are risk factors that have been shown to be associated with severe prognosis [19, 20].This retrospective study highlights the potential use of Favipiravir, Ivermectin and Steroids in COVID-19 until more COVID-19 specific treatments become available in future. Our study found that drugs such as ivermectin or favipiravir independently appeared to have had no significant impact on the clinical outcome of COVID-19 disease. However Ivermectin and favipiravir, in combination appear to lead to a faster recovery from COVID-19 symptoms. This association was found to be statistically significant.

There was a statistically significant association between steroid administration and hospitalization status. Clinical deterioration and hospitalization was clearly avoided due to steroid administration. The study clearly shows that steroids are a game changer drug due to their anti-inflammatory properties. Steroid administration prevented patients from going into severe hypoxia in moderate to severe COVID-19, thereby reducing mortality from COVID-19 pneumonia.

It appears that favipiravir independently as an agent may have potential benefits when used early on, in viral clearance, mortality reduction as well as in terms of cost and risk benefit ratios etc [21]. Although our analysis did not show a potential benefit for favipiravir that was statistically significant, the fact that there was no real harm and that steroids helped these moderately ill patients improve, suggests an indirect potential benefit. Large prospective trials may be appropriate to independently assess the benefit of favipiravir, given that other smaller studies also suggest a potential benefit, although statistically unproven.

As far as ivermectin is concerned, we found that at the doses used by us, it was well tolerated with minimal side effects. Whether stability of the unvaccinated patient against delta variant of the SARS-COV2 virus, on ivermectin alone was a random chance event vs an actual benefit attributable to ivermectin, we could not prove conclusively. We conclude that it probably was a combination of factors due to which patients improved while on ivermectin alone, such as their inherent immunity due to microexposures related to population density, young age, limited comorbidity profile apart from a possible positive ivermectin effect on disease trajectory.

To support our conclusion, we refer to a recent metaanalysis of 15 studies (mostly from the developing nations) in which the authors have concluded that Moderate-certainty evidence finds that large reductions in COVID-19 deaths are possible using ivermectin. Using ivermectin early in the clinical course may reduce numbers progressing to severe disease. The apparent safety and low cost suggest that ivermectin is likely to have a significant impact on the SARS-CoV-2 pandemic globally [22].

The combination of ivermectin with favipiravir however does appear to have a statistically significant effect on the recovery time of moderately ill patients. This is clinically significant in areas such as India, where hospital resources continue to remain stretched at all times. This combination of drugs may be safely used to treat this disease effectively in the outpatient setting, prevent disease progression, hospital use. Early use of favipiravir in combination with ivermectin may be important in changing disease trajectory overall.

The combination of ivermectin, favipiravir and steroids also was found to be statistically significant in reducing recovery time, as discussed above. Clinical deterioration and hospitalization was clearly avoided by the addition of steroids.

An issue often faced with steroids is that they are known to lead to immune suppression, which could potentially complicate the recovery process of those who have been infected with the virus. Indiscriminate and early use of steroids can aggravate COVID-19 as well as lead to lead to dangerous fungal infections like mucormycosis and aspergillosis. Because of this challenge, physicians need to be extremely cautious with steroid usage.

Steroids are easily available and priced lower than all the other drugs approved for emergency use in COVID-19. In a study of patients hospitalized with COVID-19, dexamethasone reduced 28-day mortality among those receiving invasive mechanical ventilation or oxygen at randomization, but not among patients not receiving respiratory support [23]. In an another study, it showed that use of steroids as a potential life-saving drug in COVID-19 based on the RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial which demonstrated its benefits in oxygen requiring patients [24, 25]. During the pandemic, hospital beds and ICU care was not easily available and inpatient resources had become sparse. Hence we felt that timely administration of steroids at the correct dose kept people out of the hospital., Patients need to be vigilant and monitor their blood sugars while on steroids. In the present study, we augmented the therapeutic cocktail with blood thinners given the fact that COVID induces a coagulopathy. We also used antibiotics like amoxicillin clavulanate, advanced cephalosporins and doxycycline as required based on the individual situation, for persistent fever, elevated white cell counts, greenish expectoration and multiple areas of lung involvement.

Limitations of the study

This study had several limitations, including the small sample size in each group and limited data regarding the complications and lab data. Given the limitations, further randomized controlled trials are required with larger sample sizes and later follow-ups to evaluate the beneficial effect of antivirals and steroids in patients with COVID-19 pneumonia. We were unable to obtain follow up for symptoms of long COVID syndrome. We were also unable to get repeated laboratory parameters post discharge to see if abnormal variables returned to normal. Given that it was a retrospective study, there was no control group. The treatment was restricted to mild to moderate COVID cases. Patients with severe disease were straight away excluded and advised immediate hospitalisation.

Patients treated for mild and moderate COVID in our retrospective study did well with usage of repurposed therapeutics such as Favipiravir and Ivermectin even though there was no statistically significant advantage to using either of these medications independently. However for moderately ill patients the combination of ivermectin and favipiravir improved recovery time and potentially altered the disease trajectory positively. The addition of steroids in moderate to severe disease turned out to be a game changer. This study has shown that moderate to severe cases of COVID can be safely managed at home with the use of combined therapy with ivermectin and favipiravir along with oral steroids. In view of the nature of the pandemic such drastic steps needed to be taken on account of paucity of hospital infrastructure. We do not suggest routine management of severe illness at home without appropriate monitoring, due to the adverse risks involved.

Though our study shows a potential for home care of moderate to severe COVID disease, by optimizing drug management with the use of ivermectin, favipiravir and steroids. Timely administration of steroids in moderate to severe COVID-19, led to rapid recovery, improved clinical status and averted the need for hospitalization, overall reducing morbidity and mortality. This study also demonstrates the relative safety and efficacy of the all the 3 therapeutics including steroids when appropriately monitored / tailored and the repurposed drugs ivermectin and favipiravir. Mild hyperuricemia and bradycardia were noted with favipiravir in 2 patients, but it was uncertain if it was entirely attributable to favipiravir. However discontinuation of same resulted in improvement of bradycardia.

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Информация о финансировании и конфликте интересов
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Dr Srinivasa Jayachandra, corresponding author, have submitted for consideration for possible publication in the Journal of) a manuscript entitled A retrospective analysis of repuiposecl therapeutics used dining the Delta variant Induced COVID-19 Crisis of India, 2021.

I hereby certify on be ha If of authors that, to the best of my knowledge, (1) the work which is reported on in said manuscript has not received financial support from any pharmaceutical company or other commercial source except as described below, and (2) neither I nor other authors have any first degree relative has any special financial interest in the subject matter discussed in said manuscript.

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