Open Access

Journal of Clinical Immunology and Microbiology

Research Article

Outcome of Different Therapeutic Interventions in Mild COVID-19 Infection

Sayak Roy^{1*}, Shambo Samrat Samajdar², Santanu K Tripathi³, Shatavisa Mukherjee⁴, Kingshuk Bhattacharjee⁵

¹Consultant Physician, Department of Internal Medicine, Medica Super Speciality Hospital, Kolkata, India

²Senior Resident, Department of Clinical and Experimental Pharmacology, School of Tropical Medicine, Kolkata, India

³Dean (Academics) and Head, Department of Pharmacology, Netaji Subhash Medical College and Hospital, Bihta, Patna, India

⁴PhD Research Scholar, Department of Clinical and Experimental Pharmacology, School of Tropical Medicine, Kolkata, India

⁵Independent Biostatistician, Kolkata, India

*Corresponding Author: Sayak Roy, Consultant Physician, Department of Internal Medicine, Medical Super Speciality Hospital, Kolkata, India; Email: sayak.roy.123@gmail.com

Received Date: 13-07-2021; Accepted Date: 06-08-2021; Published Date: 13-08-2021

Copyright© 2021 by Roy S, et al. All rights reserved. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution and reproduction in any medium, provided the original author and source are credited.

Abstract

Background: Coronavirus disease 2019 (COVID-19) case and the death toll has reached milestones of over 12,28,22,505 and 27,09,041 respectively worldwide as of 22nd March 2021. Treatment regimens are cropping up daily and adding up to the dilemma of the treating physicians.

Aims: This present study aimed to see the Clinical Response of Well-Being (CRWB) reporting time in mild COVID-19 infected patients after their treatment initiation in four different treatment arms.

Methods: A total of 56 patients meeting the case definition of mild COVID-19 infection were included after the retrospective screening of the investigators' electronic database. Patients

Roy S | Volume 2; Issue 2 (2021) | JCIM-2(2)-028 | Research Article

Citation: Roy S, et al. Outcome of Different Therapeutic Interventions in Mild COVID-19 Infection. J Clin Immunol Microbiol. 2021;2(2):1-10.

DOI: <http://dx.doi.org/10.46889/JCIM.2021.2203>

were divided into four groups - Hydroxychloroquine (HCQ) taking group, patients on the combination of Doxycycline (DOX) + Ivermectin (IVR), Azithromycin (AZ) taking group and symptomatic treatment receiving group.

Results: There was no difference in CRWB between the four groups (p-value 0.846). The group on symptomatic management arm showed significant correlation between CRP (p-value 0.01), LDH (p-value 0.001), and age (p-value 0.035) with CRWB. Significant correlation was also seen between blood levels of CRP (p-value 0.03), LDH (p-value 0.001) and D-dimer (p-value 0.04) with CRWB in the IVR+DOX group.

Conclusion: No specific drug treatment is required to treat mild COVID-19 infection other than symptomatic management in patients with a low risk of progression.

Keywords

SARS-COV-2; COVID 19; Therapeutic Interventions; Symptomatic Management

Abbreviations

COVID-19: Coronavirus Disease 2019; SARS-COV-2: Severe Acute Respiratory Syndrome Coronavirus-2; RT-PCR: Reverse Transcription Polymerase Chain Reaction; CRWB: Clinical Response of Well-Being; NLR: Neutrophil to Lymphocyte Ratio; CRP: C-Reactive Protein; LDH: Lactate Dehydrogenase; Htn: Hypertension; NAFLD: Non-Alcoholic Fatty Liver Disease; WHO: World Health Organization; NIH: National Institutes of Health; EDB: Electronic Database; SD: Standard Deviation; n: Number of Patients; T2DM: Type 2 Diabetes Mellitus; COPD: Chronic Obstructive Pulmonary Disease; BMI: Body Mass Index; IVR + DOX: Ivermectin + Doxycycline; AZR: Azithromycin; HCQ: Hydroxychloroquine

Introduction

As of 22nd March 2021, a worldwide record hit of 12,28,22,505 cases and 27,09,041 deaths due to the COVID-19 [1]. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) belongs to the betacoronavirus family with 79% genomic similarity with SARS-CoV and 50% with MERS-CoV [2]. The clinical spectrum of the disease varies widely from asymptomatic cases to mild, moderate, severe or, critical illness. At one end, in mild cases, patients have symptoms of COVID-19 without hypoxia or pneumonia and at the end of the spectrum, in patients with critical illness, there is multi-organ failure with high case fatality rates [3].

Treatment guidelines also vary as per the clinical severity of the disease, from symptomatic management to the use of dexamethasone or tocilizumab or a combination of both in selected candidates [4]. Guidelines have been quite variable when it comes to treating mild COVID-19 infections, from only symptomatic treatments as per the National Institutes of Health (NIH) [5] to IVR+DOX or HCQ in others [6]. The various recommendations are creating confusion amongst treating physicians.

This study will show a direction in treating mild COVID-19 infections after comparing all four treatment regimens.

Objective

Since there is no universally adopted single guideline for the treatment of mild COVID-19 infection, this study will try to look back into the available data of the patients who received the four different types of treatments and look for Clinical Response of Well-Being (CRWB) reporting time difference after treatment initiation between the four different treatment groups.

Materials and methods

Study Design and Setting

This is a single-center, retrospective study comprising of patients having received four different treatment strategies for mild COVID-19 infection. SARS-CoV-2 RT-PCR positive patients having mild symptoms with a duration of fewer than three days were considered for inclusion after retrieving their medical data from the Electronic Database (EDB) of the investigator. These patients visited the outpatient clinic of the investigator from 5th April 2020 to 11th January 2021. Informed consent forms were distributed and collected from participants who fell under the case definition of mild COVID-19 infection after an initial screening of the EDB of mild COVID-19 patient category from the investigator's database. The study was approved by the concerned institutional ethics committee and was performed following all applicable ethical guidelines. All the patients were under telephonic supervision for 14 days, like any other COVID-19 mild symptomatic patient, as per home isolation guidelines of the government from the first initial check-up in the clinic [7]. All patients were routinely screened for any existing comorbidities by asking screening questions and looking into their past medical data. All mild COVID-19 patients received vitamin C and D and oral zinc supplements throughout his/her 14 days home isolation period.

Patient Population

COVID-19 patients having reverse transcription-polymerase chain reaction (RT-PCR) positive report and meeting the case definition of mild infection as per WHO [8], as defined by the presence of symptoms without evidence of viral pneumonia or hypoxia, and willing to give written consent were included in the study. Those requiring oxygenation or admission or not willing to provide data and consent were excluded from the study. There were four groups:

1. Patients on HCQ 200 mg twice daily (on Day 1, the dose was 400 mg)
2. Patients on IVR+DOX combination (once-daily IVR of 12 mg and DOX as 100 mg twice daily)
3. Those on AZR 500 mg once daily in empty stomach
4. The last group of patients who resorted to only symptomatic management with antipyretics and oral rehydration solution

Variables Analysed

Clinical response of well-being is defined as an absence of fever and a sense of well-being as reported by the patient. All the patients had to have both these variables for the definition of the outcome.

Exposure parameters that could have affected the outcome between each group were divided into quantitative parameters like age, BMI and blood for

1. D-dimer
2. Neutrophil to Lymphocyte Ratio (NLR)
3. C-Reactive Protein (CRP)
4. Lactate Dehydrogenase (LDH) and qualitative parameters namely, Sex ratio (Male: Female), Diabetes (T2DM), Hypertension (Htn), dyslipidemia, Non-Alcoholic Fatty Liver Disease (NAFLD) and Chronic Obstructive Pulmonary Disease (COPD).

Blood tests were done within the second day of treatment initiation. The tests were done from a laboratory having National Accreditation Board for Testing and Calibration Laboratories (NABL) accreditation. To check for the IgG SARS-CoV-2 level after 21 days, the blood test was done by LIAISON®SARS-CoV-2 S1/S2 IgG test kit.

Sample Size Calculation

Since there is a lack of evidence on this type of study, we took a minimum of 30 samples as a rule of thumb [9].

Statistical Analysis

All data were captured by the treating physician during treatment and recorded electronically. EDB of the investigator was used to retrieve data for the study retrospectively. Completed Data were analyzed using SPSS Version 21.0 for Windows. One-way Analysis of variance (ANOVA) was performed to see any statistical significance between various treatment regimens and CRWB reporting time. Spearman's Correlation test was performed to assess the correlation between various parameters with CRWB in different arms. Pooled Chi-Square Test was conducted to look for a difference between baseline qualitative parameters, namely, Sex ratio (Male: Female), T2DM, Hypertension, Dyslipidemia, NAFLD and COPD which could have affected the outcome.

Result

A total of 56 patients out of an initially screened 73 patients with mild COVID-19 met the definition of CRWB, baseline inclusion criteria, and gave consent to be a part of the study. Out of those 17 patients who were excluded, six refused giving consent for publication, ten were admitted to the hospital for new-onset breathlessness, and one patient in the symptomatic arm with dyslipidemia suffered an acute pain abdomen on the 2nd day of follow-up and was admitted. The flowchart of the study is summarized in Fig. 1.

Figure 1: Study flowchart. (RT-PCR: Reverse transcription polymerase chain reaction; COVID-19: Coronavirus disease 2019; CRWB: Clinical response of well-being).

The baseline demographics with pooled Chi-square test of qualitative parameters are given in Table 1.

	IVR+DOX	AZR	HCQ	Symptomatic Rx only	P-value
Total (N)	14	13	14	15	
Sex ratio (Male: Female)	9:05	7:07	7:07	6:09	0.626
Mean age (years) ± SD	54.92 ±4.52	53.92 ±4.47	54.07 ±4.48	55.93 ±4.01	
BMI (Kg/m²) ± SD	23.70 ±0.89	23.2 ±1.13	23.62 ±1.07	24.10 ±1.03	
Comorbidities					
T2DM (%)	57.14	53.84	57.14	66.66	0.909
Hypertension (%)	71.42	69.23	78.57	53.33	0.516
Dyslipidaemia (%)	50	69.23	78.57	60	0.432
COPD (%)	28.57	53.84	35.71	46.66	0.544
NAFLD (%)	50	61.53	42.85	60	0.729
SD: Standard Deviation; n: Number of Patients; T2DM: Type 2 Diabetes Mellitus; COPD: Chronic Obstructive Pulmonary Disease; NAFLD: Non-Alcoholic Fatty Liver Disease; BMI: Body Mass Index; IVR + DOX: Ivermectin + Doxycycline; AZR: Azithromycin; HCQ: Hydroxychloroquine					

Table 1: Baseline demographics with p-value of qualitative parameters.

ANOVA did not show any difference amongst all the treatment arms in terms of (CRWB). Pooled Chi-square test, done to see any difference in the baseline qualitative parameters that could have affected the outcome of CRWB, showed no statistical significance between each group. Spearman's correlation test was done to look for any correlation between CRWB with various parameters of each group and it showed a significant correlation between CRP (p-value 0.01), LDH (p-value 0.001), and age (p-value 0.035) in the arm receiving symptomatic management and between levels of CRP (p-value 0.03), LDH (p-value 0.001) and D-dimer (p-value 0.04) in the IVR+DOX group with CRWB. There was no difference amongst the quantitative baseline parameters that could have affected our individual group's outcome or treatment protocols as measured by ANOVA. They have been summarised in Table 2.

ANOVA Analysis of Various Parameters					
Parameters (Mean, SD)	IVR + DOX N = 14	AZR N = 13	HCQ N = 14	Symptomatic Rx N = 15	P-value
Age	54.93 ± 8.96	53.92 ± 8.57	54.07 ± 8.87	55.93 ± 8.20	0.92
BMI	23.71 ± 1.77	23.2 ± 2.16	23.62 ± 2.13	24.10 ± 2.1	0.71
LDH	230.43 ± 41.49	215.61 ± 33.58	226.71 ± 53.86	232.73 ± 52.22	0.78
CRP	1.15 ± 0.94	2.31 ± 3.64	1.96 ± 2.36	1.33 ± 0.89	0.485
D-dimer	0.45 ± 0.04	0.50 ± 0.12	0.49 ± 0.08	0.50 ± 0.10	0.526
NLR	3.24 ± 1.0	3.42 ± 1.55	3.28 ± 0.76	3.36 ± 1.12	0.976
CRWB (days)	3.21 ± 0.38	3.23 ± 0.78	3.32 ± 0.61	3.4 ± 0.69	0.846
IgG value **	6.49 ± 2.17	6.09 ± 2.61	6.23 ± 2.47	6.70 ± 2.66	0.92
Spearman's Correlation test between each group with CRWB					
Parameters	P-value	IVR + DOX	AZR	HCQ	Symptomatic Rx
NLR		0.303	0.29	0.577	0.437
LDH		0.001*	0.07	0.601	0.001*
CRP		0.03*	0.22	0.203	0.01*
D-dimer		0.04*	0.103	0.521	0.284
AGE		0.07	0.557	0.919	0.035*
BMI		0.311	0.479	0.08	0.456
*Statistically significant at P-value <0.05; **Negative taken as Index <1.0; SD: Standard Deviation; n: Number of Patients; COPD: Chronic Obstructive Pulmonary Disease; BMI: Body Mass Index; IVR + DOX: Ivermectin + Doxycycline; AZR: Azithromycin; HCQ: Hydroxychloroquine; NLR: Neutrophil to Lymphocyte Ratio; LDH: Lactate Dehydrogenase; CRWB: Clinical Response of Well-Being					

Table 2: Analysis and Spearman's Correlation test outcomes.

Discussion

A confirmed COVID-19 case having no evidence of viral pneumonia or hypoxia forms the case definition of mild COVID-19 infection [8]. Treatment of mild COVID-19 has been experimented with almost all available groups of medicine, starting from high dose famotidine to anti-parasitic agent Ivermectin [10,11]. Inhaled nitrous oxide has also not been spared to treat these patients on an experimental clinical trial basis [12]. Working guidelines have taken clues from various ongoing trials and studies and are constantly updating new emerging pieces of evidence. The use of IVR has been well explored as it is presumed to block viral proteins from entering the host cell nucleus [11]. Doxycycline, a tetracycline group of antibiotics, has also been postulated to inhibit SARS-CoV-2 papain-like protease enzyme [13]. Various studies have shown the use of azithromycin and hydroxychloroquine for COVID-19 treatment, though results have been contradictory [14]. Azithromycin, a macrolide-type antibiotic, seems to have multiple properties like anti-inflammatory, immunomodulatory and antiviral effects in

bronchial epithelial cells, through which it affects the virus SARS-COV-2 [15]. Alongside, in-vitro use of HCQ has also been found to demonstrate significant antiviral effects [16]. Numerous such studies, large randomized trials, and critical scientific inputs have been taken into account to form guidelines for treating mild COVID-19 cases.

However, high variations were observed in different guidelines formulated across the globe. While guidelines in Singapore recommended using only supportive therapy for the low-risk group having non-severe COVID-19 and using lopinavir/ritonavir or subcutaneous interferon beta-1B or HCQ or remdesivir on a trial basis in high-risk non-severe cases, the World Health Organization (WHO) recommended only symptomatic treatments for mild infection [17,8]. The US Centers for Disease Control and Prevention (CDC) recommended SARS-CoV-2 neutralizing antibodies available through emergency use authorization (bamlanivimab or acasirivimab plus imdevimab) only for patients having risk for progression [5]. In contrast, a country like India recommended using supportive therapy to use IVR or HCQ depending on patient state [18,6]. IVR as post-exposure prophylaxis within 72 hours has shown significant benefits in some studies. However, a deeper analysis has found that such studies have not reported the secondary outcome of confirmation of RT-PCR positivity and have only considered clinical history as a disease confirmation marker [19]. A trial conducted on health personnel has demonstrated excellent protective results with buccal drops of IVR in addition to regular safety standards followed, with results showing 0% RT-PCR positive cases in IVR arm compared to 11.2% positive cases in standard arm [20].

Multiple studies since the initial days of the pandemic have been conducted in search of defined outcome variables adjudging clinical wellbeing in COVID-19 patients. A study on 74 hospitalized patients showed an NLR of more than four associated with ICU admissions and young age, whereas a value less than three was shown to be associated with clinical improvement [21]. Low levels of lymphocytes, high serum LDH, ferritin, and D-dimer have been associated with poorer outcomes in COVID-19 [22]. A correlation was seen with blood CRP level and mortality amongst hospitalized patients of COVID-19, with a median value of around 40 mg/L in survivors and non-survivors having a median value of 125 mg/L [23].

To assess these varied treatment protocols in mild COVID-19, this retrospective study was conducted to probe any changes in clinical wellbeing, reporting onset timing difference in patients receiving three of the presently available protocols and comparing that to the group who declined any treatments except symptomatic management only. This study showed no change in clinical wellbeing reporting onset timing between all the groups.

However, our study is not devoid of limitations. A record-based, retrospective study has less power to draw any conclusion and comes with few biases. Moreover, the small sample size and single-center set-up hinder data generalizability to a large extent. It was even challenging to state whether patients followed instructions or not and was based on their telephonic response, which invites bias. Inability to perform serial RT-PCR tests to assess the decreasing viral load also added to the limitations of our study.

Conclusion

Publications on COVID-19 have already crossed a few lakhs and have put the treating physicians in a dilemma due to the varied recommendations set by the various guidelines. New therapeutic strategies are continuously being looked into to tackle this new infection in its nascent state.

Many new strains of COVID-19 are emerging with varying modes of presentations, increasing physicians' dilemma to a greater extent. Mild COVID-19 infections can be managed symptomatically in low-risk groups. Only the high-risk groups can be taken into consideration of interventions. This study can help us understand that we might use symptomatic management in mild COVID-19 infections in those who do not progress. These findings need to be further investigated in a larger sample size to reach any conclusion. A study like this can only give us an idea and a conclusion regarding treatment protocols in mild infections must be made after doing large-scale prospective, randomized studies. To ease physicians' dilemma, there must be one universally accepted treatment protocol for these mild infections.

Acknowledgements

This manuscript has been published in a preprint server under the title of “Outcome of Different Therapeutic Interventions in Mild COVID-19 Patients in a Single OPD Clinic of West Bengal: A Retrospective study” (<https://doi.org/10.1101/2021.03.08.21252883>).

Conflicts of Interests

The authors declare that have no competing interest and not any conflict of interest.

Ethics Approval

All the procedures in the study were carried out as per declaration in the ethical standards of the institutional committee and with the 1964 Helsinki Declaration and its later amendments. The study was approved by institutional ethical committee of School of Tropical Medicine, Kolkata (CREC-STM/2020-AS-36).

Consent to Participate/ Consent to Publish

Informed written consent was taken from all the participants to collect their data, analyse them and then, publish for medical knowledge sharing purpose.

Roy S | Volume 2; Issue 2 (2021) | JCIM-2(2)-028 | Research Article

Citation: Roy S, et al. Outcome of Different Therapeutic Interventions in Mild COVID-19 Infection. J Clin Immunol Microbiol. 2021;2(2):1-10.

DOI: <http://dx.doi.org/10.46889/JCIM.2021.2203>

References

1. World Health Organization (2021). WHO COVID-19 dashboard. [Last accessed on August 8, 2021] <https://covid19.who.int/>
2. Lu R, Zhao X, Li J. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* (London, England). 2019;395(10224):565-74.
3. COVID-19 Treatment Guidelines. (n.d.). Clinical Spectrum. [Last accessed on August 8, 2021] <https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/>
4. COVID-19 Treatment Guidelines. What's new | Coronavirus Disease COVID-19. [Last accessed on August 8, 2021] <https://www.covid19treatmentguidelines.nih.gov/whats-new/>
5. Therapeutic Management of Patients with COVID-19. [Last accessed on August 8, 2021] https://files.covid19treatmentguidelines.nih.gov/guidelines/section/section_100.pdf
6. Gov.in. [Last accessed on August 8, 2021] [https://www.wbhealth.gov.in/uploaded_files/corona/WB_Covid_protocol_book_25.09_20\(1\).pdf](https://www.wbhealth.gov.in/uploaded_files/corona/WB_Covid_protocol_book_25.09_20(1).pdf)
7. HealthWorld ET. COVID-19: Health Ministry issues revised home isolation guidelines. PTI. Published July 3, 2020. [Last accessed on August 8, 2021] <https://health.economictimes.indiatimes.com/news/policy/covid-19-health-ministry-issues-revised-home-isolation-guidelines/76767874>
8. Clinical management of COVID-19. Who.int. [Last accessed on August 8, 2021] <https://www.who.int/publications/i/item/clinical-management-of-covid-19>
9. AbhayaIndrayan. Medical biostatistics. Chapman and Hall/Crc. ISBN 9781466513907. 2012;423-43.
10. Janowitz T, Gablenz E, Pattinson D, Wang TC, Conigliaro J, Tracey K, et al. Famotidine use and quantitative symptom tracking for COVID-19 in non-hospitalised patients: a case series. *Gut*. 2020;69(9):1592-7.
11. Ahmed S, Karim MM, Ross AG, Hossain MS, Clemens JD, Sumiya MK, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. *Int J Infect Dis*. 2020;103:214-6.
12. Zamanian RT, Pollack CV Jr, Gentile MA, Rashid M, Fox JC, Mahaffey KW, et al. Outpatient inhaled nitric oxide in a patient with vasoreactive idiopathic pulmonary arterial hypertension and COVID-19 infection. *Am J Respir Crit Care Med*. 2020;202(1):130-2.
13. Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharm Sin B*. 2020;10(5):766-88.
14. Roy S, Mainak Mukhopadhyay. Ventricular arrhythmia risk based on ethnicity in COVID-19 patients on hydroxychloroquine and azithromycin combination: Viewpoint. *SN Compr Clin Med*. 2020;2(8):1-6.
15. Oldenburg CE, Doan T. Azithromycin for severe COVID-19. *Lancet*. 2020;396(10256):936-7.
16. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in-vitro. *Cell Discov*. 2020;6(1):16.
17. Ncid.sg. [Last accessed on August 8, 2021] <https://www.ncid.sg/Health-Professionals/Diseases-and-Conditions/Documents/Treatment%20Guidelines%20for%20COVID-19%20282%20Apr%202020%29%20-final.pdf>
18. Sayak Roy S. Journey so far with COVID 19-a comprehensive review. *Euro J Clin Exp Med*. 2020(4):303-17.
19. Prophylactic ivermectin in COVID-19 contacts. [Last accessed on August 8, 2021] <https://clinicaltrials.gov/ct2/show/results/NCT04422561>
20. Usefulness of topic ivermectin and carrageenan to prevent contagion of COVID 19 - study results. [Last accessed on August 8, 2021] <https://clinicaltrials.gov/ct2/show/results/NCT04425850>
21. Ciccullo A, Borghetti A, Dal Verme LZ, Tosoni A, Lombardi F, Garcovich M, et al. Neutrophil-to-lymphocyte ratio and clinical outcome in COVID-19: a report from the Italian front line. *Int J Antimicrob Agents*. 2020;56(2):106017.
22. Velavan TP, Meyer CG. Mild versus severe COVID-19: Laboratory markers. *Int J Infect Dis*. 2020;95:304-7.
23. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med*. 2020;46(5):846-8.

Roy S | Volume 2; Issue 2 (2021) | JCIM-2(2)-028 | Research Article

Citation: Roy S, et al. Outcome of Different Therapeutic Interventions in Mild COVID-19 Infection. *J Clin Immunol Microbiol*. 2021;2(2):1-10.

DOI: <http://dx.doi.org/10.46889/JCIM.2021.2203>