

# Effectiveness And Safety of Azithromycin in Treatment of Covid-19: A Systematic Review

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**Abstract:- The antiviral effect of Azithromycin has an action of large spectrum antiviral activity. Azithromycin will reduce the virus entry into the cells and also enhance the immune response against viruses. Azithromycin plays an important role in infection control such as sore throat, pneumonia, acute respiratory syndrome. To determine the effectiveness of Azithromycin in the treatment of COVID-19 and its safety as an antiviral therapeutic agent. A literature search was done based using the search keywords ( COVID-19 OR coronavirus 2019) AND (Azithromycin) AND (Treatment). Randomised controlled trials investigating the effect of Azithromycin and safe during the period of hospitalisation in the treatment of COVID 19 and further followed by Cochrane database bias assessment was done. Four randomised controlled trials were included. The usage of Azithromycin, in maintaining the optimal range of respiratory rate, throughout the entire duration of stay of the patients, during hospitalization, were statistically significant (P<0.05) when it is used along with Hydroxychloroquine. The study concludes that Azithromycin, when used along with Hydroxychloroquine, controls the infection in COVID-19.**

**Keywords:- COVID-19 ( coronavirus 2019), Azithromycin, treatment.**

## I. INTRODUCTION

In December 2019, has remarkably high virulence in Wuhan, China become the COVID-19 as pandemic and spreads globally [1]. Disease symptoms resemble a viral pneumonia and genetic analysis of lower respiratory tract samples of early infected patients showed an infection caused by the coronavirus 2019 and named as severe acute respiratory syndrome, which causes COVID-19. The disease rapidly spread throughout China and infected multiple other countries [2].

Due to coronavirus infection in the year 2020, more than 35 million people were infected, and nearly one million people died [3]. In addition to acute respiratory involvement, other organ systems also affected by this virus which includes gastrointestinal, neurological and haematopoietic systems [4,5]. There is no specific pharmacological treatment for the COVID-19 yet [6].

The mechanism of action of Azithromycin in antiviral effect which supports an antiviral spectrum activity. It enhances the immune response against several actions in viruses. It decreases the entry of virus into the body cells.

Azithromycin a macrolide antibiotic, has shown efficacy in preventing infections in patients suffering from viral pneumonia [7]. In vitro studies have demonstrated that it is active against Zika and Ebola viruses [8] and it has a high affinity for the binding interaction site of the SARS-COV-2 spike protein and angiotensin- converting enzyme 2 (ACE2) [9], which is the critical human cell receptor for the SARS-COV-2 virus, and it is believed that blocking this interaction can potentially prevent the infection [10].

Hydroxychloroquine has a better clinical safety in treatment of COVID-19 [11]. Azithromycin has an effect of treating viral diseases the treatment of SARS-COV-2 [12]. So, the aim is to determine the effectiveness of Azithromycin in treatment of COVID-19 and used as a safety of antiviral infection.

## II. MATERIALS AND METHOD

A total of 129 articles were searched using among that 4 articles are included in this study and this systematic review was done using azithromycin in COVID-19. Above 18 years of age groups were included in this study. Azithromycin can be received either as a dose of 500mg once daily followed by 250mg twice daily for 4 days and Hydroxychloroquine with Azithromycin were also included. Below 18 years of age groups and pregnancy patients are excluded in this study.

### A. Eligibility Criteria:

#### ➤ Inclusion criteria:

1. Studies published in English
2. Articles on the effectiveness of Azithromycin
3. Full text articles

#### ➤ Exclusion criteria:

1. Only abstracts available
2. Unrelated articles
3. Animal studies
4. In- vitro studies

**B. Search Engines:**

- PubMed
- Wiley online library
- Cochrane library
- Elsevier science direct
- Prospero
- Cinahl
- Scopus
- OSF

- Ovid Medicine
- Grey literature

After the search using the appropriate mesh terms a total of 129 articles were found from the online databases. After duplicates removal of 106 articles were screened and 93 full-text articles were available. Inclusion-exclusion criteria were applied and finally 4 related articles were selected for further assessment.

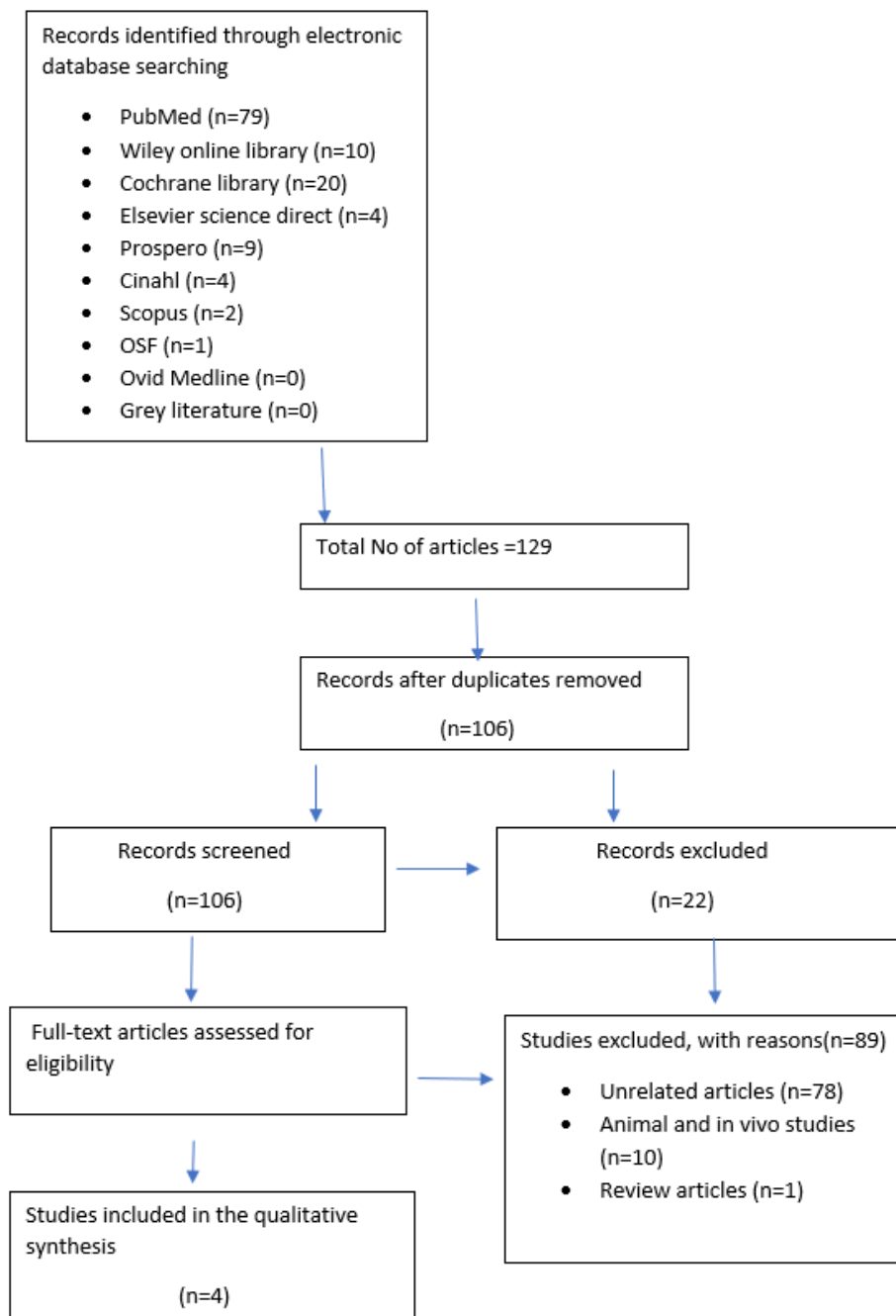


Fig 1:- shows the identified, screened, assessed for eligibility, excluded and included studies in the systematic review

**III. RESULTS**

SL. NO:	AUTHOR	YEAR	PATIENT SELECTION	DURATION	DOSE REQUIRED	INTERVENTION
1	EHSAN SEKHAVATI et al[14]	2020	28 MALES 28 FEMALES	5 DAYS	500 mg	AZITHROMYCIN  HYDROXYCHLOROQUINE WITH AZITHROMYCIN
2	SAMIA ASHRAD et al[15]	2020	62 MALES AND 85 FEMALE PATIENTS	1 DAY 2-5 DAYS	500 mg followed by 250 mg	AZITHROMYCIN  HYDROXYCHLOROQUINE WITH AZITHROMYCIN
3	ELI S. ROSENBERG et al[16]	2020	OUT OF 211 PATIENTS 134 WERE MALES	1 DAY 2-5 DAYS	Not mentioned	AZITHROMYCIN  HYDROXYCHLOROQUINE WITH AZITHROMYCIN
4	VIOLAINE GUERIN et al[17]	2020	OUT OF 34 PATIENTS 14 PATIENTS WERE MALES	1 DAY 2-5 DAYS	500 mg followed by 250 mg	AZITHROMYCIN  HYDROXYCHLOROQUINE AZITHROMYCIN WITH

Table 1:- Characteristics of the interventions in the included studies

Table 1: shows the characteristics of the intervention in the included studies. In all above the effectiveness of Azithromycin was reviewed. Trial duration of azithromycin was 5 days used in each study.

Table 2:- Outcome data as reported in included studies

SL.NO	AUTHOR AND YEAR	STUDY DESIGN	OUTCOME	RESULT
1	EHSAN SEKHAVATI et al 2020[14]	RANDOMISED, OPEN LABEL CONTROLLED TRIAL	HIGHER SPO2 LEVELS, LOWER RESPIRATORY RATE AT THE TIME OF DISCHARGE AND SHORTER DURATION OF HOSPITAL STAY.	THE RESULTS SHOWS LEVEL OF SPO2 IN P VALUE WAS 0.030 WHICH IS NOT STATISTICALLY SIGNIFICANT, RESPIRATORY RATE AT THE TIME OF DISCHARGE, THE P VALUE WAS 0.010 AND DURATION OF HOSPITAL STAY THE PVALUE WAS 0.02, BOTH ARE STATISTICALLY SIGNIFICANT.
2	SAMIA ASHRAD et al 2020[15]	MULTICENTRE, RETROSPECTIVE, OBSERVATIONAL STUDY	MORTALITY, HYPERTENSION, O2 SATURATION (NORMAL, MILD HYPOXEMIA, MODERATE HYPOXEMIA, SEVERE HYPOXEMIA)	THE RESULT SHOWS THE P VALUE IS 0.825 WHICH IS STATISTICALLY NOT SIGNIFICANT.
3	ELI S. ROSENBERG et al 2020[16]	MULTICENTRE, RETROSPECTIVE, OBSERVATIONAL STUDY	RESPIRATORY RATE, BLOOD PRESSURE, O2 SATURATION, HYPOGLYCEMIA, CARDIAC ARREST, ABNORMAL ECG, ARRHYTHMIA, QT PROLONGATION	THE RESULT SHOWS THE P VALUE IS 0.14 WHICH IS NOT STATISTICALLY SIGNIFICANT.
4	VIOLAINE GUERIN et al 2020[17]	SINGLE CENTRE, RETROSPECTIVE, OBSERVATIONAL STUDY	THE OUTCOME SHOWS FASTER RECOVERY TIME IN AZITHROMYCIN AND HAS HIGHER PREVALENCE OF CHILLS AND LOWER PREVALENCE OF ANOSMIA.	THE RESULT SHOWS THE RECOVERY TIME OF P VALUE IS LESS THAN 0.0001 AND SURVIVAL CURVES OF P VALUE IS LESS THAN 0.007 WHICH WAS NOT STATISTICALLY SIGNIFICANT.

Table 2: shows an outcome and result of the effectiveness of Azithromycin in above-mentioned studies.

S.NO	AUTHOR AND YEAR	RANDOM SEQUENCE GENERATION	ALLOCATION CONCEALMENT	SELECTIVE REPORTING	INCOMPLETE OUTCOME DATA	BLINDING OF OUTCOME ASSESSMENT	BLINDING PARTICIPANTS AND PERSONALS
1	EHSAN SEKHAVATI et al 2020 [14]	++	-	++	++	++	-
2	SAMIA ASHRAD et al 2020[15]	++	-	-	++	++	++
3	ELI.S. ROSENBERG et al 2020 [16]	++	-	++	++	++	?
4	VIOLAINE GUERIN et al 2020[17]	++	-	++	++	++	?

Table 3:- Bias analysis of included studies

Table 3: shows the bias analysis of all the included studies. It is categorized as high-risk bias “-“, low risk bias “++” and unclear “?”.

#### IV. DISCUSSION

During rapidly spreading global pandemic period of COVID-19, it is important to have a safe treatment plan. There are several reports on the effectiveness of various medications, but as yet none of them have been proven to be significantly effective [13]. Ehsan Sekhavat et al reported that treatment with Azithromycin had significantly higher SpO<sub>2</sub> levels 93.95% and a lower respiratory rate at the time of discharge 17.42 breaths/min [14]. It is an open label randomised clinical trials with a daily dose of 500 mg for 5 days. In this study the patient who receive Azithromycin in addition to Hydroxychloroquine had a shorter duration of hospitalisation. Here the length of hospital stay was 4.61 days. They show, there is a safety treatment of Azithromycin in COVID 19 patients but it does not show it is an effective. The higher spo<sub>2</sub> levels the p value is 0.030 which is not statistically significant but lower respiratory rate the p value is 0.010 and shorter duration of hospital stay the p value is 0.02 which was statistically significant.

Samia Arshad et al reported that treatment with Azithromycin had significantly decreased mortality hazard ratio by 66% [15]. It is a multi-centre, retrospective, observational study with a dose of 500 mg once daily for 1 day and 250 mg for next 4 days. They show there is a use of Hydroxychloroquine reduced in-patient hospital mortality by 66% and by 71% when combined with Azithromycin. The result shows the p value is 0.0825 which is statistically not significant. Arshad et al also says there is no effective of using Azithromycin alone in treatment of COVID 19.

Eli.S Rosenberg et al reported that treatment with Azithromycin had significantly decreased mortality [16]. It is a multi-centre, retrospective, observational study with a dose of 500 mg once daily for 1 day and 250 mg for next 4 days. In this study they showed a trend towards reduced mortality in use of Azithromycin alone and mortality was 10.9% shown in use of Azithromycin. This is the only study shows that found potential mortality benefit of using Azithromycin in hospitalised patients. Here the result shows the p value is 0.14 which is not statistically significant.

Violaine Guerin et al reported that treatment with Azithromycin had significantly lower respiratory rate at the time of discharge 16 breaths/min [17]. It is a single centre, retrospective, observational study with a dose of 500 mg for 1 day and 250 mg for next 4 days. Early treatment of Azithromycin alone shows shorter time to recover COVID 19 patient infection. This study shows there is a use of Azithromycin early gives safe and effective treatment in COVID 19 patient. The outcome shows faster recovery time and has higher prevalence of chills and lower prevalence of anosmia in Azithromycin. The result shows the recovery time of p value is less than 0.0001 and survival curves of p value is less than 0.007 which was not statistically significant.

The adverse drug effects of using azithromycin are nausea, vomiting, diarrhoea or loose stools, stomach upset or abdominal pain. According to these 4 articles, there is a decreased respiratory rate at the time of discharge. So hence the study shows there is a safety use of Azithromycin and has an effective treatment in COVID-19. But yet, none of the study has showed that there is an effectiveness of Azithromycin in treatment of COVID-19, but many studies show there is a combination of both Hydroxychloroquine and Azithromycin has an effective in treatment of COVID-19.

#### V. LIMITATION OF THE STUDY

Many articles were excluded due to limited accessibility. The other sources should also be considered to get more relevant outcome. Only limited number of studies available and need further studies for research. In the present study, the dosage of Azithromycin is not mentioned.

#### VI. CONCLUSION

Azithromycin is a macrolide antibiotic which kills bacteria and prevents its growth. Azithromycin used as a safe drug and play an important role in treatment of COVID-19. This study concludes that there is an effective treatment to control the infection in COVID-19 patients when it is used with Hydroxychloroquine.

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