# To Determine Safety Profile of Azithromycin in Covid-19 Patients: A Cross Sectional Survey

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**Abstract**

**Objective:** Covid-19 outbreak late in 2019 from Wuhan city of China spread rapidly all over the world and became a pandemic. Corona Virus is RNA virus, major virus that affects respiratory system and can result in acute respiratory distress syndrome, so there emerged several management strategies to combat the challenge of the disease, Azithromycin is one of those treatment options. Azithromycin have been used widely and generally considered as safe medication. The Purpose of this study was to establish its safety profile in this new disease in our part of world.

**Methods:** 80 covid-19 positive in ICU were given Azithromycin along with other standard treatment, Side effects were divided into mild serious and allergic reactions. These were noted down in pre designed proforma. Data analysis was done in SPSS version 25.

**Results:** 80 patients were studied 38 (46.2%) patients experienced side effects , majority of which were mild in nature, Out of 80 patients Abdominal Pain was 37.5% , diarrhea 22.7% nausea 25%, transaminitis 2.5%, anorexia 26.3%, taste perversion 36.3% , dyspepsia 15%, vomiting 17.5% , headache 6.3% and somnolence 1.3% . Only 1 (1.25%) patients had arrhythmia and 1 (1.25%) had urticaria that was successfully treated.

**Conclusion:** After this study this can be concluded that Azithromycin is safe drug as majority of side effects experienced were mild in nature and it can be safely used to treat Covid-19 positive patients.

**Key words:** 2019-nCoV, Azithromycin, SARS-CoV-2. COVID-19.

## Introduction

The Wuhan City of China experienced COVID-19 outbreak for the first time late in December 2019, Which spread rapidly in China and then worldwide in 209 countries, became a pandemic, it has been treated as pneumonia with unknown etiology.[1,2] One of the major target of corona virus is respiratory system of the humans.[3] It was named as 2019-nCoV by Chinese experts[4] and Later, it was named by the International Committee on Taxonomy of Virus as Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2).[5]

Rapid and accurate detection of COVID-19 is crucial to control outbreaks in the community and in hospitals.[6] Current diagnostic tests for coronavirus include reverse-transcription polymerase chain reaction (RT-PCR), real-time RT-PCR (rRT-PCR), and reverse transcription loop-mediated isothermal amplification (RT-LAMP).[7]

The need of an hour is to find effective therapeutic agents for the treatment of COVID-19 whether inpatient or outpatient as the devastating effects of the coronavirus designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) demands an urgent attempt to combat situation.[8]

It has been demonstrated by few studies that hydroxychloroquine sulfate (HCQ) inhibits SARS-CoV-2 in vitro[9] and one of study proves that the combination of HCQ and azithromycin (AZ) inhibits SARS-CoV-2 in vitro.[10]

Azithromycin is a macrolide antibiotic it has a struc-

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ture modified from erythromycin. Like other macrolides, azithromycin has activity against Moraxella catarrhalis and Streptococcus pneumoniae and and also against atypical pathogens, like Mycoplasma pneumoniae, Chlamydia pneumoniae and Legionella pneumophila.[11] It has been showing activity against Zika and Ebola viruses in vitro and has immunomodulatory action as demonstrated by in vivo activity in the prevention of severe respiratory tract involvement in viral infections.[12] Azithromycin works by inhibiting protein synthesis and experimentally reduces viral replication and inflammation possibly because viruses and cytokines are both made of proteins and use cellular ribosomes for protein translation. In addition, inhibiting virus production can reduce viral transmission to others, which is an important additional benefit.[13]

Azithromycin has been used widely and is generally considered a safe antibiotic. Th however, occasional adverse effects may occur[13] like with almost all antibiotics, gastrointestinal symptoms like Nausea, vomiting, diarrhea and headache may ensue, like so occasional urticaria and few other skin eruptions. Serious side effects are uncommon; however, they may occur, including cardiac arrhythmias, which happen especially in the elderly and in those patients with preexisting QT interval prolongation, bradycardia, low serum magnesium or potassium, and in individuals who are taking certain antiarrhythmic drugs.[13,14] However in the search for a safe and effective treatment of individuals with mild or moderate COVID-19, azithromycin remains one of the most promising.[15]

## Objective

The objective of this study is to determine the safety profile of azithromycin in our part of world it may open room for further research as regards treatment of novel corona virus and may establish azithromycin as safe and effective in treatment of Covid-19 positive patients of Asian ethnicity.

## Methods

This Cross Sectional Survey was performed in Intensive Care Unit of Services Hospital Lahore, from1st May to 31st July. Eighty (80) patients were taken through Non probability purposive sampling. Patients were taken according to inclusion criteria that is Covid-19 PCR patients admitted in ICU, Both genders included, Age range was 18 to 85 years, and all grades of severity of disease were included.

The patents who has Documented known allergy to Macrolides. Females who were pregnant, those with prolonged QT interval documented on Baseline ECG. Patients receiving other medicines that are likely to prolong the QT interval and those with a history of arrhythmias, torsade's de pointes or uncompensated cardiac failure, were excluded from study

After Ethical Committee approval of the proposal of the study, patient according to inclusion and exclusion criteria were recruited. After taking informed consent, all patients received a standardized clinical examination, all baseline and specific investigations according to their clinical condition and Baseline ECG at day 0 and they were regularly followed up daily during their stay in hospital. All of them given Tab Azithromycin 500mg oral daily, they were observed and asked questions regarding side effects of Azithromycin and side effects were noted down on tenth day.

The Side effects has been divided in three major groups, Mild Side Effects, Serious Side effects and Allergic Reactions. All findings and self-reported side effects were noted down in pre designed proforma.

Data Analysis was done with SPSS version 25.0, that was used to enter and analyzed the data. Quantitative data like age were presented as means and standard deviation and qualitative data like gender, diarrhea was presented as frequency and percentages.

## Results

Eighty (n=80) patients presented to Covid ICU were studied, all of them were given Azithromycin 500mg daily orally. Their demographic profile is shown in Table 1, there were 56 (80%) male and 24(30%) female patients. Mean Age was 54.9 + 11.28 with Minimum 27 and Maximum 85 years , Out of which 11 (13.7%) were in 18-40 year age group, 46 (57.5%) in 41-60 year age group, 22 (27.5%) in 61-80 years age group and 1 (1.25%) in > 81 year group. All patients were Covid PCR positive 80(100%) and only 4 (5%) were smokers. (Table 1)

Out of 80 patients 11(17.5%) were having mild to moderate Disease, 50(62.5%) patients had sever disease and 16 (20%) were critical. (Table 2)

**Table 1:** *Demographic Profile of Patients*

| Total No. Patients (n) | | 80 |
|---|---|---|
| Male | | 56 (70%) |
| Female | | 24 (30%) |
| **Age Group** | 18-40 | 11 (13.7%) |
| | 41-60 | 46 (57.5%) |
| | 61-80 | 22 (27.5%) |
| | ≥ 81 | 1 (1.25%) |
| **Covid-19 PCR** | | 80 (100%) |
| **Smokers** | | 4 (5%) |

**Table 2:** *Clinical Severity*

| Mild To Moderate Disease | 14(17.5%) |
|---|---|
| Sever Disease | 50 (62.5%) |
| Critical Illness | 16 (20%) |

Out of 80 patients 38 (46.2%) suffered from Side effects, of which 36 (45%) out of 80 and 94.7% out of 38 had Mild Side effects, 1(1.25%) out of 80 and 2.6% out of 38 patient had Sever Adverse reaction and 1(1.25%) out of 80 and 2.6% out of 38 patient had Allergic reaction .Table 3(a)

**Table 3(a):** *Side Effect Profile of Azithromycin in 80 Patients*

| 1 | Occurrence Of Adverse Events | 38 (46.2%) out of 80 patients |
|---|---|---|
| 2 | Mild Side Effects | 36 (45%) out of 80 and 94.7% out of 38 |
| 3 | Sever Adverse Events | 1(1.25%) out of 80 and 2.6% out of 38 |
| 4 | Allergic Reaction to Azithromycin | 1(1.25%) out of 80 and 2.6% out of 38 |

Amongst Patients having mild side effects 30(37.5%) out of 80 and 78.9% out of 38 had Abdominal Pain. 22(27.5%) out of 80 and 57.8% out of 38had Diarrhea,

20(25%) out of 80 and 52.6% out of 38 had Nausea, 2(2.5%) out of 80 and 5.2% out of 38 had Elevated ALT AST, 21(26.3%) out of 80 and 55.2% out of 38 had Anorexia, 29(36.3%) out of 80 and 76.3% out of 38 experienced Taste perversion

12(15%) out of 80 and 31.5% out of 38 had Dyspepsia.14(17.5%) out of 80 and 36.8 % out of 38 had Vomiting. 5(6.3%) out of 80 and 13.1% out of 38 had Headache. 1(1.3%) out of 80 and 2.6% out of 38 had Somnolence.

**Table 3(b):** *Side Effect Profile of Azithromycin*

| | | Mild side effects |
|---|---|---|
| 1 | Abdominal Pain | 30(37.5%) out of 80 and 78.9% out of 38 |
| 2 | Diarrhea | 22(27.5%) out of 80 and 57.8% out of 38 |
| 3 | Nausea | 20(25%)out of 80 and 52.6% out of 38 |
| 4 | Elevated ALT AST | 2(2.5%) out of 80 and 5.2% out of 38 |
| 5 | Anorexia | 21(26.3%) out of 80 and 55.2% out of 38 |
| 6 | Taste Perversion | 29(36.3%) out of 80 and 76.3% out of 38 |
| 7 | Dyspepsia | 12(15%) out of 80 and 31.5% out of 38 |
| 8 | Vomiting | 14(17.5%) out of 80 and 36.8 % out of 38 |
| 9 | Headache | 5(6.3%) out of 80 and 13.1% out of 38 |
| 10 | Somnolance | 1(1.3%) out of 80 and 2.6% out of 38 |
| **Serious Adverse Reaction** | | |
| 11 | Arrythmia | 1(1.25%) out of 80 and 2.6% out of 38 |
| 12 | Hypotension | None |
| 13 | QT Prolongation | None |
| 14 | Torsade's de Point | None |
| 15 | Renal and Hepatic Failure | None |
| 16 | Convulsions | None |
| 17 | Neutropenia, Leucopenia and Thrombocytopenia | None |
| **Allergic Reactions to Azithromycin** | | |
| 18 | Arthralgia | None |
| 19 | Edema | None |
| 20 | Urticaria | 1(1.25%) out of 80 and 2.6% out of 38 |
| 21 | Angioedema | None |

Only 1(1.25%) out of 80 and 2.6% out of 38 had Arrythmia as serious adverse event and 1(1.25%) out of 80 and 2.6% out of 38 had Urticaria, Amongst Allergic reaction. Table 3(b)

Out of 80 patients, 38 (47.5%) had Co Morbid Conditions in the form of Diabetes 28 (35%) out of 80 (73.6% out of 38). Hypertension was present in 19 (23.7%) out of 80 (50% out of 38) and 5(6.25%) out of 80 (13.1% out of 38) had Ischemic Heart Disease. Table 4.

**Table 4:** *Co Morbid Conditions*

| 1 | Co Morbid Conditions | 38 (47.5%) out of 80 |
|---|---|---|
| 2 | Diabetes | 28 (35%) out of 80 and 73.6% out of 38 |
| 3 | Hypertension | 19 (23.7%) out of 80 and 50% out of 38 |
| 4 | Ischemic Heart Disease | 5(6.25%) out of 80 and 13.1% out of 38 |

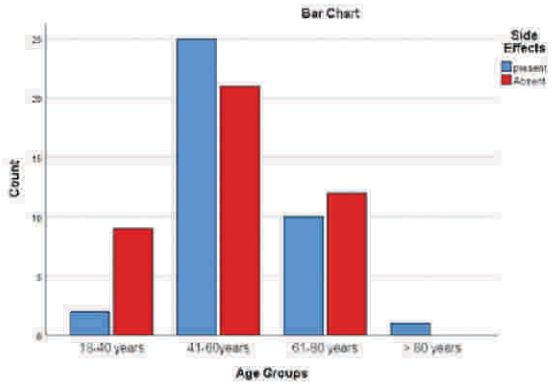


**Figure 1:** *Showing Frequency of Side Effects According to Age Groups*

Figure 1 is bar chart showing frequency of occurrence of side effects was more in Age group 41-60 years that is 25 patients. 2 patients from 18-40 years, 10 from 61-80 years and 1 from > 81 years experienced adverse reaction.

## Discussion

Azithromycin is a broad-spectrum macrolide antibiotic having bacteriostatic activity against many Gram-negative and Gram-positive bacteria[16] Azithromycin is the prototype of an antimicrobial agent which falls in the class of azalides derived from the macrolides[17] Azithromycin has good tolerance in general, but relatively common adverse effects (1–5 % of patients) include gastrointestinal upset, headache and dizziness.[18]

Compared to study done by Barbara A. Brown Mean age was 66 years compared to 54.9 in our study. He noted adverse events in 33 of 39 patients (85%) while receiving Azithromycin compared to 38(46.2%) patients in our study which is quite less. The majority of these were GI events (82%) in Barbara's study, GI symptoms included diarrhea (62%) compared to (27.5%) in ours, abdominal pain (41%) compared to (37.5%) in ours, anorexia (33%) compared to (26.3 %) in ours, unusual taste sensation (33%) compared to (36.3%) in ours, nausea (28%) compared to (25%) in ours , vomiting (18%) compared to (17.5%) in ours and abdominal bloating or dyspepsia (~IO%) compared to (15%) in our study.[19]

The retrospective cohort study was performed using national Department of Veterans Affairs' administrative data, it did not reach statistical significance in regards cardiac arrhythmias (25.8 vs 26.0%; OR: 0.99, 95% CI: 0.95 – 1.02) compared to only one patient (1.25%) having Arrhythmia in our study.[20]

Hence it is demonstrated that generally, Azithromycin remained safe drug option to use in covid positive, ICU admitted patients in Pakistan, majority of side effects were mild and tolerable and resulted in completion of antibiotic course, one patient had episode of arrhythmia, he had multiple co morbid conditions as well, that episode was successfully treated and does not resulted in fatality.

Further research with larger sample size however will definitely enable us to better manage this potentially fatal Novel Corona Virus.

## Conclusion

After this study this can surely concluded that Azithromycin is a safe drug as demonstrated by results only 38 (46.2%) out of 80 patients experienced side effects , majority of which were mild in nature. Only 1 (1.25%) patients had arrhythmia and one (1.25%) has allergic reaction that was successfully treated.

## Author's Contribution

**SZ, MI:** Data compilation and writing
**MJA:** Review Article
**MH, SMAN, AM:** Data Collection

**Conflict of Interest:** None

## References

1. A.Waris, U. K. Atta, M. Ali, A. Asmat and A. Baset. COVID-19 outbreak: current scenario of Pakistan. New Microbes and New Infections. 2020; 35: 100681
2. A.R. Sahin, A. Erdogan, P.M. Agaoglu, Y. Dineri, A.Y. Cakirci, M.E. Senel, A.M. Tasdogan. 2019 novel coronavirus (COVID-19) outbreak: a review of the current literature. EJMO, 4 (1) (2020):1-7
3. S Hoehl , H Rabenau ,A Berger ,M Kortenbusch , J Cinatl, D Bojkova, P Neumann. Evidence of SARS-CoV-2 infection in returning travelers from Wuhan, China. New England J Med 2020;382(13):1278–80.
4. N Zhu et al. A novel coronavirus from patients with pneumonia in China 2019. New England J Med 2020; 382(8):727
5. ZY Zu et al. Coronavirus disease 2019 (COVID-19): a perspective from China. Radiology 2020; 200490-200490.
6. W K Kelvin et al. Consistent Detection of 2019 Novel

Coronavirus in Saliva. Clinical Infectious Diseases 2020; 71(15):841–843.

7. C L Chih et al. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease- 2019 (COVID-19).The epidemic and the challenges. Elsevier International Journal of Antimicrobial Agents 2020; 55(3):105924
8. Schwartz, RA, Suskind, RM. Azithromycin and COVID-19: Prompt early use at first signs of this infection in adults and children, an approach worthy of consideration. Dermatologic Therapy. 2020; e13785. https://doi.org/10.1111/dth.13785
9. Y Xueting et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clinical Infectious Diseases 2020; 71(15) 732–739. https://doi.org/10.1093/cid/ciaa237
10. J Andreani, BM Le , I Duflot ,P Jardot , C Rolland ,M Boxberger, et al. In vitro testing of combined hydroxychloroquine and azithromycin on SARS-CoV-2 shows synergistic effect. Microb Pathog 2020: 104228
11. P Xu ,L Zeng , T Xiong , et al. Safety of azithromycin in paediatrics: a systematic review protocol .BMJ Paediatrics Open 2019; 3:e000469. doi: 10.1136/bmjpo-2019-000469
12. DH Tran, R Sugamata , T Hirose et al. Azithromycin, a 15-membered macrolide antibiotic, inhibits influenza A(H1N1)pdm09 virus infection by interfering with virus internalization process. J Antibiot (Tokyo). 2019; 72(10): 759- 768.
13. A Gérard, S Romani, A Fresse et al. French network of pharmacovigilance centers. "Off-label" use of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine in COVID-19: a survey of cardiac adverse drug reactions by the French network of pharmacovigilance centers. Therapies 2020; 32418730. https://doi.org/10.1016/j.therap. 2020. 05.002.
14. E Asensio , R Acunzo , W Uribe, EB Saad, LC Sáenz. Recommendations for the measurement of the QT interval during the use of drugs for COVID-19 infection treatment. Updatable in accordance with the availability of new evidence. J Interv Card Electrophysiol. 2020; 16: 1- 16. https://doi.org/10.1007/s10840-020-00765-3.
15. PK Jr Carlton, J Johanigman, EJ Janniger, RA Schwartz. COVID-19 and the urgent need to render spaces safer. Global Policy. 2020; 11(2). https://www.globalpolicyjournal.com/blog/15/05/2020/covid-19-and-urgent-need-render-spaces-safer.
16. MJ Parnham, H V Erakovic, EJ Giamarellos-Bourboulis, G Perletti, GM Verleden, R Vos. Azithromycin: mechanisms of action and their relevance for clinical applications. Pharmacol Ther. 2014;143(2):225-245. doi:10.1016/j.pharmthera.2014.03.003
17. G Panteix, B Guillaumond , R Harf, et al. In-vitro concentration of azithroMycin in human phagocytic cells. J Antimicrob Chemother 1993; 3 1:1-4.
18. JM Zuckerman , F Qamar , BR Bono . Macrolides, ketolides, and glycylcyclines: azithromycin, clarithromycin, telithromycin, tigecycline. Infect Dis Clin North Am. 2009;23(4):997-x. doi:10.1016/j.idc.2009.06.013
19. AB Barbara et al. Relationship of Adverse Events to Serum Drug Levels in Patients Receiving High-Dose Azithromycin for Mycobacterial Lung Disease. Clinical Infectious Diseases 1997;24(5):958-964. https://doi.org/10.1093/clinids/24.5.958
20. EM Mortensen et al. Association of azithromycin with mortality and cardiovascular events among older patients hospitalized with pneumonia. JAMA. 2014;311(21):2199–208.