

OBSERVATIONAL STUDY OF COVID-19 CASES AND OFF-LABEL DRUGS TO MANAGE COMPLICATIONS DURING FIRST AND SECOND WAVE

ABSTRACT

Background: Initially Covid-19 complication treatment was almost nil and focused only on supportive measures. Various off-label drugs were utilized globally to obtain better outcomes; the same was practiced by the Indian healthcare fraternity. We have aimed to review the utilization of off-label medicines like Vitamin C, Azithromycin, Ivermectin, Doxycycline, Low Molecular Weight Heparin, Zinc, Remdesivir, Dexamethasone, etc. prescribed in Covid-19 nodal hospital of Telangana state, India.

Methodology: A retrospective review and prospective observational study were conducted in the Covid-19 units of Gandhi medical college and hospital, Secunderabad between December 2020 and May 2021. The study was conducted after obtaining the necessary permission. In a retrospective review; previously published reports were analyzed to correlate the off-label medicine prescription for Covid-19 complications. Prospective case analysis was performed to access the outcome of drugs prescribed in Covid-19 complication and identified as off-label. **Results:** A total of 60 prescriptions were analyzed. Among these; Vitamin-C, Dexamethasone, and Azithromycin were prescribed in 67%, 43%, and 37% cases respectively. The study further revealed that hypertension and diabetes mellitus were the two most common comorbidities that lead to hospitalization and subsequently required aggressive treatment to manage the Covid-19 related complications. Bilateral pneumonia was the most frequently appearing complication and therefore Dexamethasone and Azithromycin were listed as top off-label drugs to manage the same. **Conclusion:** Due to the lack of specific treatment available initially to manage

Covid-19 complications, off-label medicines not only aided enormously in recovering from the complication but also demonstrated to the world that the right choice of off-label medicine can greatly reduce the risk.

Keywords: Covid-19 complications, off-label drugs, recovery, Remdesivir, Dexamethasone, Ivermectin, Doxycycline.

INTRODUCTION

During the first emergence of the Covid-19 pandemic during the last month of 2019 and early months of 2020, specific treatment was very minimal or almost nil to counter the disease. Instead, treatment was mainly focused on the supportive measure rather than the eradication of the virus. While doing so, various off-label drugs were administered to the patients to obtain enhanced patient care in various countries. A similar practice was also observed in India where various off-label drugs were prescribed to provide supportive care to the Covid-19 positive hospitalized patients. During the early stages of a pandemic, in particular, empirical use of antiviral and anti-inflammatory drugs such as Hydroxychloroquine (HCQ)(antimalarial – Quinolone), Lopinavir, Ritonavir, Remdesivir, and Monoclonal antibodies was widespread globally in the absence of formal guidelines.¹ Dexamethasone is an immune modulator that modulates inflammation-mediated lung injury and further reduces progression to respiratory failure and death and it also has greater benefit in terms of managing endothelial injury.^{2,3} Remdesivir is a broad-spectrum antiviral that inhibits the severe acute respiratory syndrome coronavirus 2(SARS COV-2) in-vitro and in-vivo. Early treatment with Remdesivir in hospitalized Covid-19 patients reduces the length of stay of the patient.^{4,5} Patients with Zinc deficiency have developed more complications and the deficiency was associated with a prolonged hospital stay and increased mortality.⁶ Aspirin is used in association with reduced risk of mechanical ventilation, ICU admission, and hospital mortality. Heparin/low molecular weight heparin is an anticoagulant agent that inhibits bradykinin formation both via inhibition of heparinase (HPSE) activity and to bind with high molecular weight and

further reduces the local inflammation and vascular leakage in Covid-19 patients.⁷ The efficacy of HCQ in patients with Covid-19 results of a randomized clinical trial and effects on viral diseases must also be taken seriously; Retinopathy is one of the major adverse reactions of long-term therapy with HCQ.⁸ Azithromycin administration had a significantly shorter hospital stay as well as significantly higher SpO₂ and lower respiratory rate at discharge. However, a risk scoring system should be utilized before initiating treatment to prevent QT prolongation, especially for high-risk patients.⁹ Widespread use of Vitamin C in covid-19 patients minimizes the effect of oxidative stress and cytokine, it helps in intensive care management.¹⁰ Zinc Supplements is used for prophylaxis, the zinc ions (Zn⁺²) are closely involved in the normal development, differentiation, and function of immune cells, thus considered critical for generating both innate and acquired (humoral) antiviral response.¹¹ Vitamin B is used in the prevention of the covid-19 pandemic as it plays a vital role in cell functioning, energy metabolism, and maintaining a proper immune function.¹² Vitamin D is used in the prevention and treatment of the Covid-19 pandemic, as it poses as an anti-viral, immune-modulatory, and anti-inflammatory action.¹³ The efficacy of Vitamin D, as it maintains the epithelial barrier integrity by restoring tight junctions, gap junctions, and adherence junctions.¹⁴ Vitamin D is a steroidal hormone and may influence the immune response in covid-19, and is found to decrease the incidence of viral respiratory tract infection, especially in Vitamin D deficiency.^{15,16} Use of O₂ therapy for n-Corona virus patients that could disrupt virus replication by decreasing hypoxia-inducible factor 1- α . O₂ therapy could regulate autoimmunity, decrease (angiotensin-converting enzyme 2) expression in tissues, and be given as a therapeutic option for patients under home quarantine.¹⁷ When Lopinavir/Ritonavir was given and it was found that reduced viral loads and improved clinical symptoms during the treatment so Lopinavir /Ritonavir can be recommended to relatively high-risk groups of covid-19 pneumonia from the early stage.¹⁸ The antiviral activity of Doxycycline shows anti-inflammatory effects by decreasing the expression of various pro-inflammatory cytokines.¹⁹ Ivermectin for the treatment of Covid-19 may reduce the duration of illness and reduces the viral load faster thus may help block disease transmission in the general population.²⁰ and the use of Ivermectin for treatment of Covid-19, although larger trials are conducted to understand the effects of Ivermectin on clinically relevant outcomes.²¹ Cocktail antibody therapies hold greater promise to control disease and prevent drug resistance. Cryo-electron microscopy analysis of two highly potent antibodies in complex with the SARS-

CoV2 spike protein suggested there may be particularly useful when combined in a Cocktail therapy.²² The prolonged low dose of Methylprednisolone is demonstrated as a 71% reduction in mortality and the achievement of the secondary endpoints such as an increase in ventilation support and further treats severe pneumonia and high levels of systemic inflammation.²³ Covid-19 affects Cobalamine metabolism and therefore contributes to symptoms of Cobalamine deficiency. Covid-19 patients need to be checked for vitamin B12 deficiency and treated in time to prevent possible deterioration.²⁴

MATERIALS AND METHODS

This retrospective review and prospective case observational study was conducted in the various Covid-19 units of Gandhi medical college and hospital, Secunderabad, India for six months between December 2020 and May 2021. The study was conducted after obtaining Institutional Ethical Committee clearance and permission from the hospital (CMRCP/IEC/2020-21/001, Date: 18/02/2021). The study was carried out by considering the following inclusion and exclusion criteria; patients of both gender and all ages diagnosed as Covid-19 positive, admitted to the hospital were included in the study. Patients with incomplete information or patient transferred to other hospitals were excluded from the study. The study was conducted in the following method: In retrospective review; various previously published literature and reports related to off-label drugs used for Covid-19 complications were thoroughly reviewed to assess the actual outcome in terms of the effectiveness of those identified drugs. A similar review was done to identify off-label drugs prescribed in the Indian scenario to highlight the dose strength administration guidelines scheduled or any other changes in their labeling. We also cross verified with national and local guidelines.

In the prospective case analysis approach; we visited the Covid-19 wards in the hospital and collected the cases to identify prescribed off-label drugs. Once identified, a utilization review of those identified off-label drugs was performed to assess the outcome. Simultaneously we discussed with the doctors regarding the prescription of these drugs and try to comprehend the need for the administration of particular drugs for the particular patient as the prescription was not uniform instead it was patient and complication specific.

RESULTS

A total of 60 cases were collected during the study period after satisfying the inclusion criteria. Age-wise categorization of admitted cases shows that the age group between 41 and 60 years has a higher appearance (52%) compared to other age groups. **FIGURE 1.**

Gender-wise categorization of admitted cases shows that the gender group of male above 40 years (58%) were more infected when compared to that of the female (42%). **FIGURE 2.**

Out of 60 collected cases, existing comorbidities includes 36% of cases with no existing comorbidities, 28% of cases with both hypertension and diabetes mellitus, 20% of cases with only hypertension, 12% of cases with only diabetes mellitus, and the remaining 2% with seizures and intestinal obstruction.

FIGURE 3.

Complications during the hospital stay highlight bilateral pneumonia as the single most complication developed in almost half of the cases (48%). Various lab diagnostics tests were performed during the hospital stay. **FIGURE 4.**

Out of the collected 60 cases, oxygen saturation (SPO₂%) was measured in 54 cases. Rest 6 cases were not required to measure the SPO₂ as they do not exhibit shortness of breath. Out of 54 cases, nearly half the cases (40%) had SPO₂ levels above 95%, 27% of cases had SPO₂ ranges between 91 and 95%. Almost 1/3 of the cases had SPO₂ levels below recommendation. **FIGURE 5.**

Out of the collected 60 cases, 72% cases had up to 6 lit/min O₂ administration, the remaining 22% cases had 7- 8 lit/min O₂ administration and 6% of cases had above 8 lit/min O₂ administration. **FIGURE 6.**

Out of the collected 60 cases, 67% cases had prescribed Vitamin C, 43% cases had prescribed with Dexamethasone, 37% cases had prescribed with Azithromycin, 30% cases had prescribed with Vitamin B and Ivermectin, 28% cases had prescribed with Doxycycline, 27% cases had prescribed Low Molecular Weight Heparin and other drugs such as Zinc, Oseltamivir, Vitamin D and Calcium, Remdesivir and Methylprednisolone had also prescribed in some of the cases. **FIGURE 7.**

DISCUSSION

Cases were obtained from the covid-19 units for this prospective study, with a total of 60 cases collected during the study period. The outcome was not identified in a few cases, and we were forced to leave such outcomes due to constraints in entry to the Covid-19 unit. Male were somewhat more likely to be infected

with Covid-19 illness compared to females and those over the age of 40 were more likely to be hospitalized. According to our findings, we identified that respiratory problems such as shortness of breath and cough were present in virtually all patients along with fever as a clinical presentation is collected cases during admission.²⁵ We also learned from this study that hypertension and diabetes mellitus are two of the most common pre-existing co-morbidities that were predominant in Covid-19 infection cases being hospitalized.²⁶ our study outcome indicates that people with hypertension and diabetes mellitus should be more cautious and must take necessary prevention measures to avert getting infected. As we have previously identified that respiratory complications remain in the front position in Covid-19 cases during hospital admission, a similar trend was also identified as complications developed during the hospital stay and bilateral pneumonia was the uppermost condition in this list.²⁶ Our data show that except for a few cases, oxygen saturation and oxygen administration were nearly normal in most cases and the use of oxygen therapy for SARS-CoV-2 infected patients could disrupt virus replication by decreasing hypoxia-inducible factor 1- α and in most of the cases oxygen therapy could regulate autoimmunity, decrease angiotensin-converting enzyme-2 expressions in tissues and be given as a therapeutic option for patients under home quarantine.¹⁷ We discovered that the results of the study were rather positive, as a substantial proportion of patients were discharged after testing negative with no further issues. The results of our research suggest that a considerable number of off-label medications were used to treat Covid-19 problems. Some of these drugs were eventually discontinued by the government, and others had their usage restricted. Vitamin C was the most commonly used of all.¹⁰ Because there was no definitive treatment for Covid-19, doctors tried a variety of drugs to prevent the accompanying problem, Surprisingly Vitamin C acts as an immune booster and it also minimizes the effect of oxidative stress and cytokine, which further helps in intensive care management.¹⁰ Azithromycin and Dexamethasone were the other two most commonly prescribed medications on the list. Since the Covid-19 complications wreaked havoc on the respiratory system, these two medications played a key role in the treatment of secondary respiratory infection and inflammation.⁹ In addition to this, utilization outcome of Ivermectin and Remdesivir has shown significant outcomes in managing Covid-19 complications but later Government of India restricted the usage of Remdesivir.²⁸ There were some reports of clotting difficulties as a result of Covid-19 infection, and Low molecular weight heparin (LMWH)

was also used for these purposes.⁷ This study identified that the Zinc ions are closely engaged in the normal development, differentiation, activity of immune cells are thus regarded as crucial for generating both innate and acquired (humoral) antiviral responses and these supplements are also used as prophylaxis.¹¹ In some patients, the use of low-dose Methylprednisolone results in a 71% reduction in mortality and the achievement of secondary objectives such as increased ventilation support as well as treating severe pneumonia and high levels of systemic inflammation.²³ Finally, Multivitamin and Multi-mineral supplements played a key role in the therapy of numerous Covid-19 problems.¹³ In a few patients; Covid-19 affects Cobalamine metabolism and therefore contributes to symptoms of Cobalamine deficiency and needs to be checked for Vitamin B12 deficiency and subsequent treatment in time to prevent deterioration.²⁴ There are few reports of Vitamin D insufficiency as a result of covid-19. Vitamin D is used to avoid the occurrence of viral respiratory tract infection and to improve immunological response.¹⁶ Vitamin C boost up immune system functions such as lymphocyte proliferation, antimicrobial activity, anti-natural killer cell activity.²⁸ SARS-CoV-2 impacts on the levels of vitamin C due to stress in Covid-19 patients, as a result vitamin C is mandatory for SARS-CoV-2 infected patients.²⁹

FIGURES:

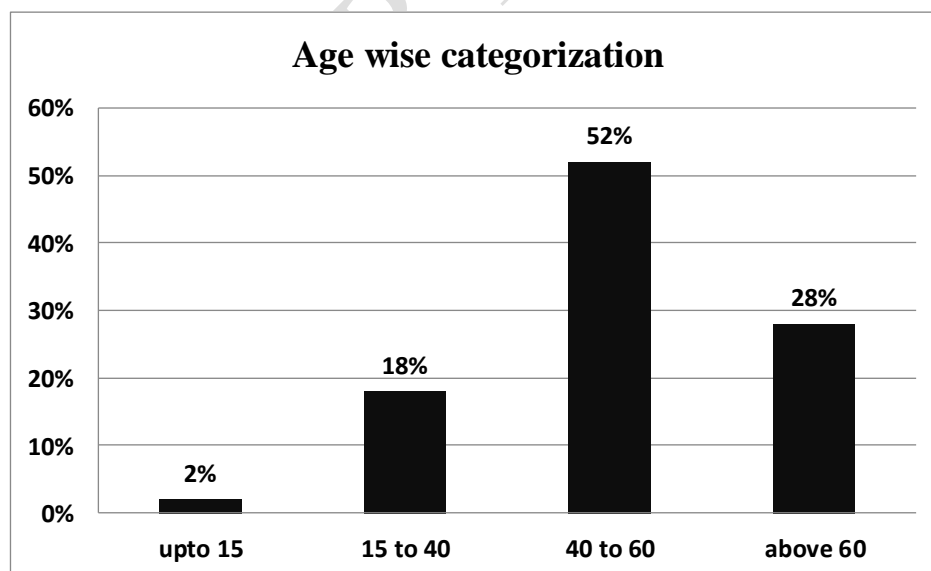


Figure 1. Age-wise categorization of Collected Cases

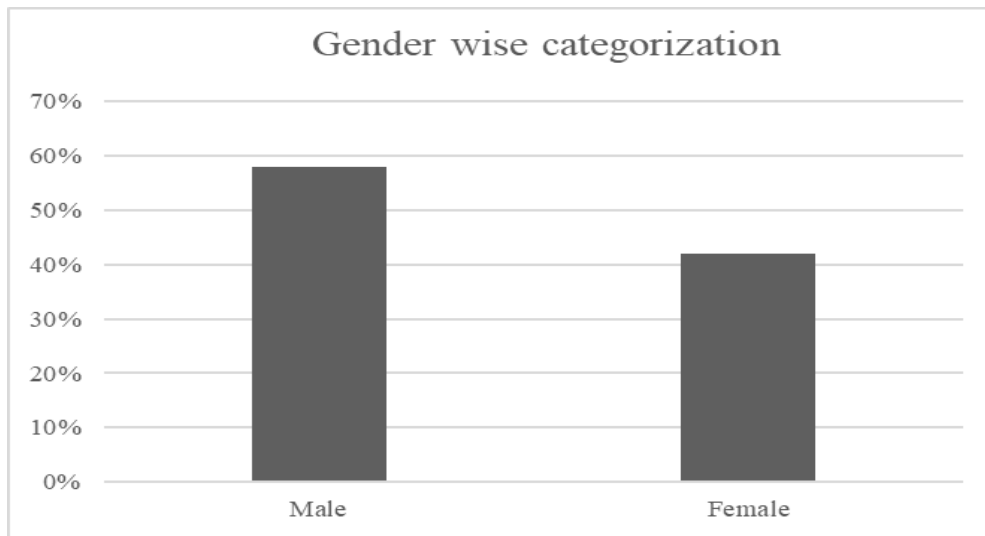


Figure 2. Gender wise categorization of collected cases

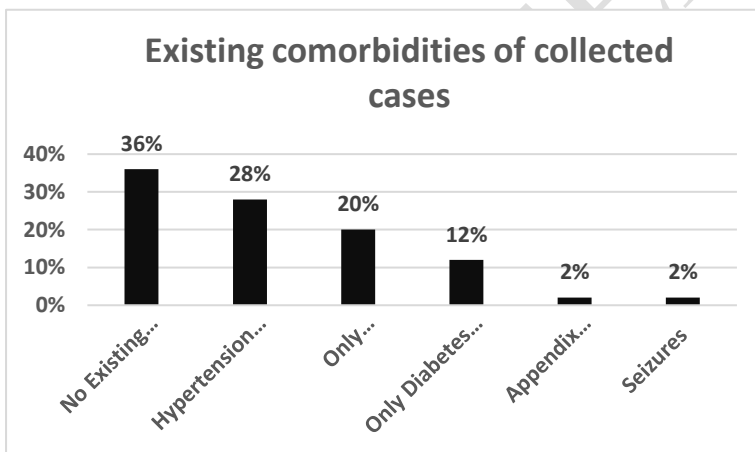


Figure 3. Existing comorbidities of collected cases

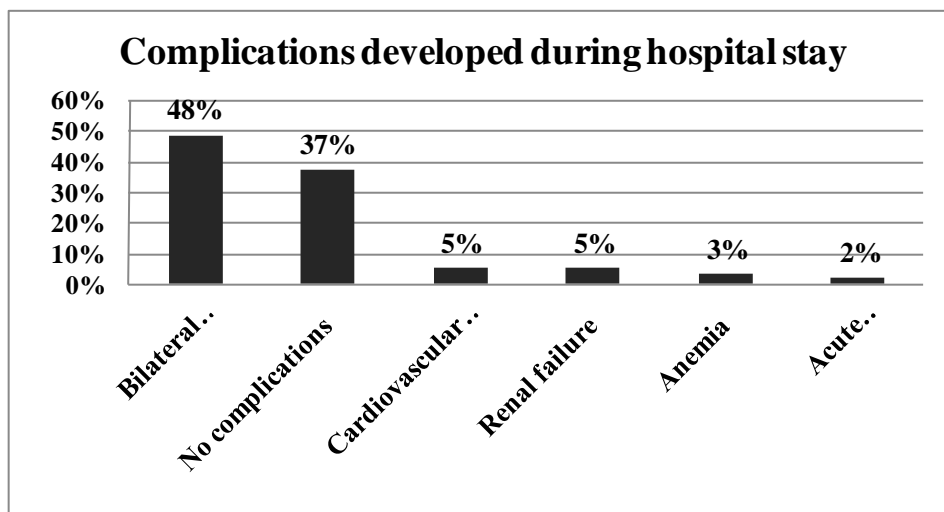


Figure 4. Complications develop during the hospital stay

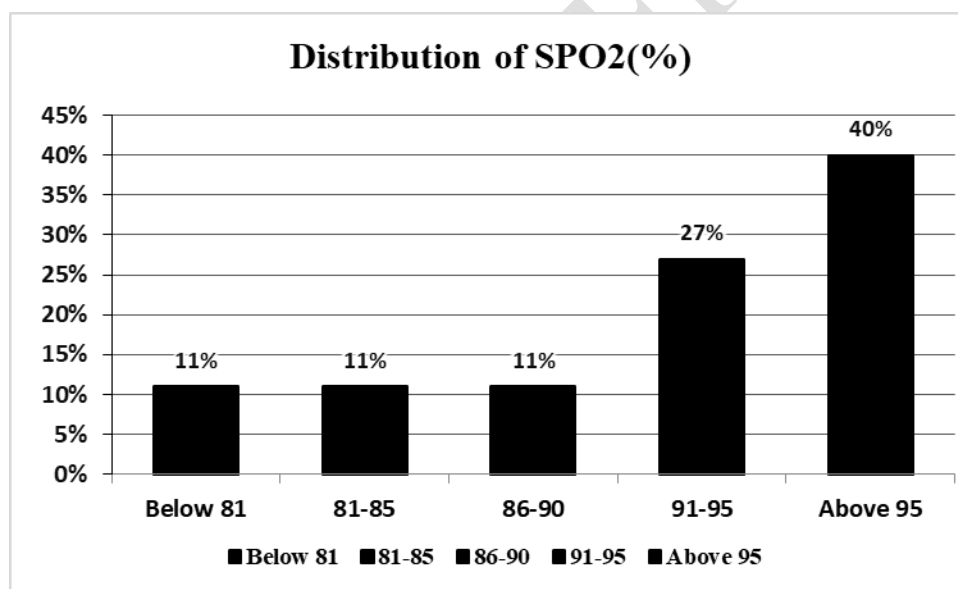


Figure 5. Distribution of SpO₂(%)

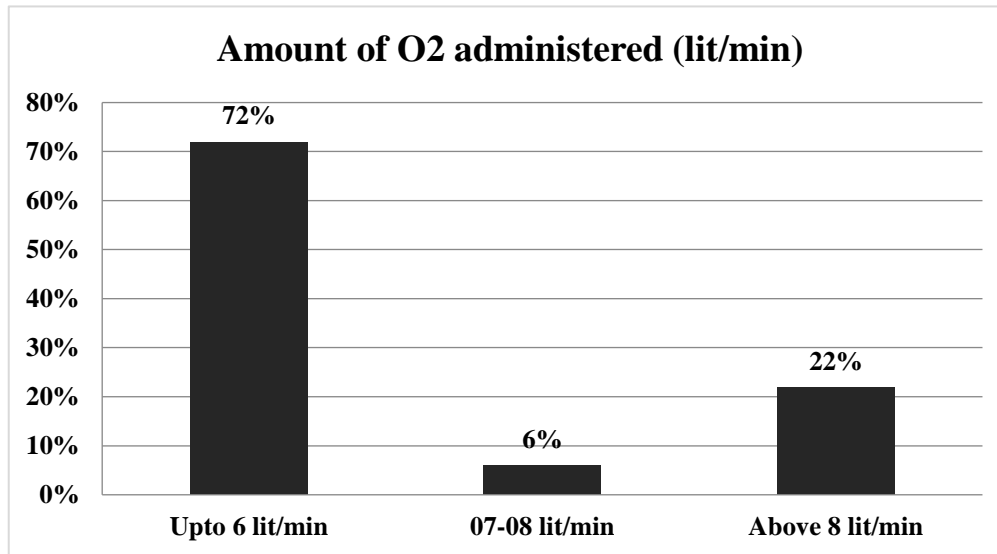


Figure 6. Amount of O₂ administered (lit/min)

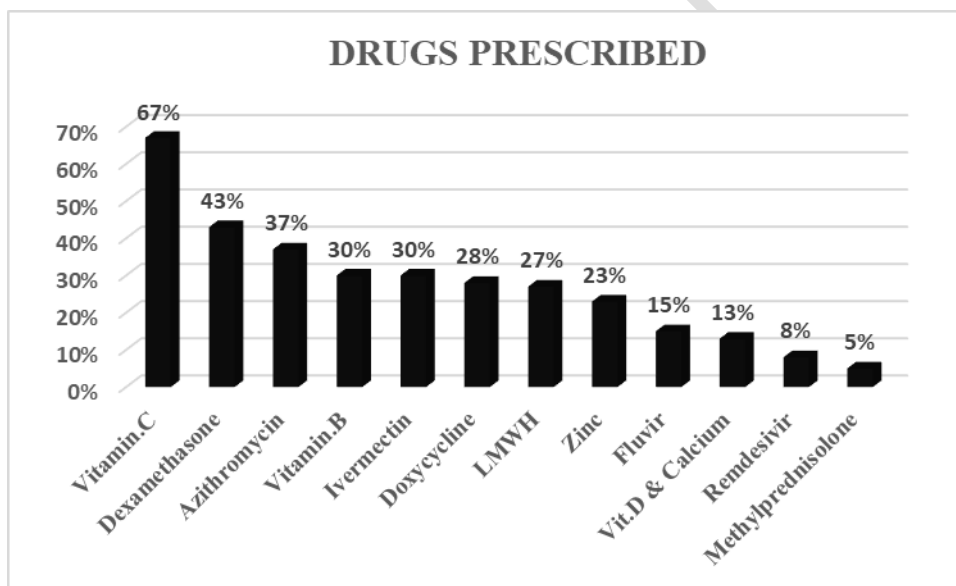


Figure 7. Various Off-label Drugs Prescribed

CONCLUSION

Covid-19 has hit hard on the Indian population and healthcare system. With the second-largest populated country in the world having a huge number of people over 40 years of age and having both hypertension and diabetes mellitus as common pre-existing comorbidity, patients were left with no possible survival options as was seen in other advanced countries. But a motivated healthcare system with great pharmaceutical support and vast medical research experience, India choose the medicines in the right manner to prevent Covid-19 complications. For therapy and associated with a wide range of complications, these medicines not only help the patients to recover in great numbers but also show the way to the world that careful selection of off-labeled medicine can greatly minimize the fatality.

Ethical Approval:

The study was conducted after obtaining Institutional Ethical Committee clearance and permission from the hospital (CMRCP/IEC/2020-21/001, Date: 18/02/2021).

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