

# Adverse Drug Reactions in COVID-19 patients admitted to Intensive care unit: Analysis of individual case study reports

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## Research

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# Abstract

## Background

Occurrence of adverse drug reactions in COVID-19 patients has not been extensively studied. Thus the present study was conducted to analyze the pattern of suspected Adverse Drug Reactions in COVID-19 patients admitted in Intensive Care Unit.

## Methods

In this observational study, all the individual case study reports of patients admitted to the COVID ICU from August to October 2020 were analyzed. The type of ADR, the system involved, drug history, the suspected drug, reaction time and time to revert and management of ADR were recorded. ADRs were classified as serious and non-serious and causality was assessed using the WHO-UMC scale. The severity of ADRs was determined using Hartwig Scale.

## Results

From 395 patients admitted to the COVID ICU during the study period, 44 individual case reports were received of 36 patients. Dermatological manifestations were the most frequent ADRs reported in this study, followed by gastrointestinal. Remdesivir was the most common drug associated with ADRs. The female gender, use of more than 5 drugs and presence of comorbidities were the independent risk factors for the occurrence of ADRs in patients with COVID-19.

## Conclusion

The use of many of these drugs in this pandemic is experimental and so far the data available in the literature does not guarantee the safety and efficacy for COVID-19 treatment. Therefore, during these times of uncertainty, the results from present study reinforce the importance of monitoring patients. Early diagnosis and management of ADRs is warranted.

## Background:

With the increasing burden of Corona Virus Disease-19 (COVID-19) cases, there has been a drastic upsurge in patients requiring admission in Intensive Care Unit. With the evolving knowledge on the pathophysiology of the disease, drug regimens are constantly being updated and modified, adding more numbers to the existing list of drugs being used, especially in severe cases. Hydroxychloroquine, Ivermectin, Doxycycline, Favipiravir and multivitamins were recommended for treatment of mild (to moderate) category COVID patients. Convalescent Plasma therapy, anti-inflammatory drugs (such as methylprednisolone or dexamethasone), antivirals, immunomodulators, anticoagulants (UFH or LMWH),

thiamine, vitamin C and antimicrobials and or antifungals as per local antibiotic policy were recommended for COVID-19 patients who progressed to the inflammatory phase (moderate/ severe category) of the disease [1]. While the occurrence of adverse drug reactions (ADRs) in COVID 19 patients has not been extensively studied, findings from retrospective trials in non-COVID cases indicate that it is likely to be high [2–3]. ADRs, when encountered, add to the complexity of the management of patients with COVID-19. In the COVID era, use of multiple drug therapy, complex presentations, and above that COVID restriction, make diagnosis and treatment of ADRs more challenging in the ICU setting.

ADRs can range from mild to fatal, with both short- and long-term repercussions. As a result, drug safety must be prioritized while maintaining efficacy. An increased incidence of ADRs has been reported in COVID patients as compared to non-COVID [4]. However, the prevalence of ADRs in critically ill COVID-19 patients is poorly understood, if precisely estimated, could help with the determination of the burden caused by multiple pharmacological therapies. Literature search did not retrieve any study reporting ADRs in patients admitted to COVID ICU. Hence, this study was planned to estimate the pattern of Adverse Drug Reactions in COVID-19 patients admitted in the Intensive care unit.

## Methods:

This observational study was carried out at the COVID ICU of a 300 bedded tertiary care teaching hospital in western Uttar Pradesh. All the individual case study reports (ICSR) of patients admitted to the COVID ICU from August to October 2020 submitted to the ADR monitoring centre were analyzed. Demographic characteristics, associated comorbid conditions and relevant data on drugs prescribed were recorded. The data on adverse drug reaction included type of ADR, the system involved, drug history, the suspected drug, time of onset and ablation, information on challenge and dechallenge, management and outcome of ADR. Drug induced hepatic dysfunction was defined as S. Bilirubin > 2mg/dl and liver enzymes > 3 X ULN (Upper limit of normal). Drug induced kidney injury was defined as S. Creatinine > 1.5mg/dl and Blood Urea > 50 mg/dl. Random Blood Glucose > 250mg/dl was taken as hyperglycemia.

Causality was assessed using the WHO-UMC scale that determines the relationship between the suspected ADR and the medicine used [5]. The ADRs were classified as serious and non-serious, where serious ADR were considered as any reaction that resulted in death, threat to life, causing hospitalization or prolonging hospitalization, resulting in disability, persistent or significant, or congenital anomaly [6]. The severity of ADRs was determined using Hartwig Scale [7].

## Results:

A total of 395 COVID-19 positive patients were admitted in ICU during the study period. The general characteristics of these patients are shown in Table 1. Forty-four ADRs were reported in 36 patients. The general characteristics of the patients are given in Table 1. The various drugs associated with ADRs have been summarized in Table 2.

**Table 1** General characteristics of the study population (with and without ADR)

Characteristics of patients	Total number of patients	Patients with ADR (n)
<b>Age (years)</b>		
<65	289 (73.2)	30
>65	106 (26.8)	06
<b>Gender</b>		
Male	285 (72.5)	16
Female	110 (27.8)	20
<b>Comorbidities*</b>		
	<b>167</b>	<b>34</b>
Diabetes	102	23
Cardiovascular Disease/Hypertension		
Bronchial Asthma/COPD	55	20
Hepatic disorders		
Renal disorders	20	10
Epilepsy	06	03
Allergic hypersensitivity	03	01
	11	03
	02	-

\* Many patients presented with more than one comorbidity.

**Table 2** Name and route of administration of the Drugs causing ADR

S.N.	Name of the drug	Number of patients who developed ADRs (%)	Route of administration	Manifestations
1.	Clindamycin	4 (11.2)	Intravenous	Diarrhoea
2.	Enoxaparin	4(16.7)	Subcutaneous	Hematuria, deranged KFT
3.	Heparin	2 (5.6)	Subcutaneous	Hematuria, melena
4.	Methylprednisolone	4 (11.2)	Intravenous	Hyperglycemia
5.	Remedesivir	8 (22.3)	Intravenous	Urticaria, deranged KFT & LFT
6.	Hydroxychloroquine	6 (16.7)	Oral	Rash
7.	Plasma therapy	6 (16.7)	Intravenous	Anaphylaxis (allergic reaction)

Among the patients who developed adverse events, the onset of ADR ranged from 0 to 8 days, with dermatological manifestations being the most common symptom reported by the patients. Majority (91%) of the patients recovered. In eight of these cases, the association between the drug and the ADR was categorized as 'Certain' (Table 3).

**Table 3** Characteristics of Adverse Drug Reactions according to the onset, manifestations, severity, seriousness, causality assessment and use of > 5 drugs.

S.No.	Characteristics of Adverse Drug reaction	Pattern/trends - number (percent)
1.	Onset	Immediately – 02 (5.5)
		0 day – 06 (16.6)
		1-3 day – 08 (22.2)
		4-8 day – 20 (55.5)
2.	Manifestations	Dermatological – Rash (10), urticaria (06)
		Gastrointestinal - Diarrhoea (04), melena (02), deranged LFT (04), hematemesis (02)
		Urinary – Hematuria (02), deranged KFT (05)
		Metabolic – Raised Blood Glucose (04)
		Hypersensitivity reactions – 05
3.	Severity	Mild – 30 (68.2)
		Moderate – 08 (18.2)
		Severe – 06 (13.6)
4.	Seriousness	Non-serious – 28 (63.6)
		Prolongation of hospitalization – 09 (20.5)
		Life-threatening– 03 (6.8)
		Death – 04 (9.1)
5.	Causality assessment	Certain – 08 (18.2)
		Probable – 06 (13.6)
		Possible – 30 (68.2)
6.	Patients on multiple medications	<5 drugs – 06 (16.6)
		>5 drugs – 30 (83.3)

Evaluation of factors associated with ADRs showed that COVID-19 patients admitted in ICU who had comorbidities (OR= 17.74; CI=2.34-134.6) and were on more than 5 drugs (OR=1.17; CI=0.45-3.02) were more likely to develop ADRs. The Association of all the factors with ADRs is given in table 4.

**Table 4** The level of significance was <0.05. P-value was calculated using Chi-square test. For parameters with at least one frequency <5, Fischer's exact test# was used.

S.No.	Factors associated with ADR	Odds Ratio (CI)	p-value
1.	Age	0.51 (0.21-1.3)	0.15
2.	Gender	2.3 (1.1-4.5)	0.02
3.	Comorbidities	32.6 (7.7 - 138)	<0.0001#
4.	Polypharmacy (>5 drugs)	3.75 (1.5-9.2)	0.004#

## Discussion:

Adverse drug reactions (ADRs) in patients admitted in medical wards and ICU have shown to be a major cause of morbidity and mortality [2, 3]. Unavailability of specific medication for COVID-19 has led to inadvertent use of multiple drugs. This may lead to possible drug interactions and potential adverse drug reactions. Additionally, complex pathophysiology of the disease per se has predisposed the patients to an increased risk of drug reactions.

In the present study, adverse drug reactions were observed in 9.2 % of patients admitted to COVID ICU. Similar studies could not be found for comparing the data among the Indian population. However, few previous studies from other countries have reported a much higher incidence of ADRs among COVID patients admitted in wards [8, 9]. The possible reason could be under reporting of ADRs by the treating physicians due to increased workload, pandemic stress and hesitation to report the adverse effects.

In the present study, no significant association was observed between age and the occurrence of ADR. This is in concordance with the findings of Sun et al, 2020 [9]. Previous studies on non-Covid-19 patients have also reported a significant association between age and occurrence of ADR [10, 11]. The study showed significant association between female gender and occurrence of ADRs (OR: 2.3; 95% CI 1.1–4.5; P = 0.02). On the contrary, Zekarias et al, 2020 showed a significant association of ADR patterns with gender among COVID-19 patients, with male predominance [12]. Analysis of Adverse drug reactions in patients with COVID-19 in Brazil also showed male predominance [8]. The present study has revealed use of more than 5 drugs as an independent risk factor for the occurrence of ADRs in patients with COVID-19 (OR: 3.75; 95% CI 1.5–9.2; P = 0.004). Presence of comorbidities was also an independent risk factor (OR: 32.6; 95% CI 7.7–138; P < 0.0001). These findings are consistent with the results of other studies which have shown polypharmacy and co-morbidity to be important risk factors for ADRs [4, 8, 9]. This association has been observed in non-COVID patients also [13, 14].

Most of the ADRs reported in our study affected the dermatological system followed by the gastrointestinal and hepatobiliary system. A study done by Sun et al reported hepatobiliary and gastrointestinal symptoms as the main manifestations of ADRs [9]. However, in the case series by Crescioli et al, 2020, it was concluded that the ADRs related to cardiovascular, psychiatric and gastrointestinal disorders were the most frequent [15].

The time of onset of the majority of ADRs was 4–8 days and only 1 reaction was reported immediately. Similarly, Sun et al reported the majority of ADRs within the first week of admission (79.8%) [8].

The causal relationship as assessed by the WHO UMC scale was found to be possible in 68.2% and probable in 13.6% of the total suspected ADR cases. In contrast to the present study Sun et al found 55.3% of the suspected ADR cases to be probable [8], while Crescioli et al (2021) reported 74% of ADRs to be probable and 26% as possible [15].

In the current study, maximum ADRs were associated with the use of Remdesivir, followed by Enoxaparin and hydroxychloroquine. The use of Remdesivir led to deranged kidney and liver functions. A similar causal association between Remdesivir and kidney disorders has also been reported by Chouchana et al (2021) [16]. Majority of ADRs in this study presented as rash and urticaria. As skin changes are visible, these can be diagnosed early and notified frequently during spontaneous reporting. A systematic review on treatment-related mucocutaneous reactions in COVID-19 patients have also shown dermatological findings as common ADRs [17].

## **Limitations:**

The duration of the study was short (3 months). Additionally we cannot be oblivious to the under reporting of adverse reactions. In view of the contagious nature of the disease, the data was not collected by active surveillance; it was based on spontaneous reporting of ADR by the treating physician.

## **Conclusion:**

In an era where medication misinformation is rampant, quality pharmacovigilance has become more important than ever. This study has shown that muco-cutaneous and gastrointestinal manifestations are the commonly observed adverse effects with these drugs. Similar to the non-COVID patients, the occurrence of ADRs increases proportionately with increase in the number of drugs being used and presence of comorbidity. The use of drugs in this pandemic is experimental and so far the data available in the literature does not guarantee the safety and efficacy for COVID-19 treatment. Therefore, during these times of uncertainty, the results from present study reinforce the importance of monitoring patients.

## **Abbreviations**

COVID-19: Corona Virus Disease-19; ADR - Adverse Drug Reactions; ICU - Intensive Care Unit; ICSR- Individual Case Study Report; OR – Odds Ratio

## **Declarations**

**Ethics approval and consent to participate:** Ethical approval was obtained from Institutional Ethics Committee for using patients' data and reports submitted to Pharmacovigilance Centre for publication.

**Consent for publication:** Not applicable

**Availability of data and materials:** The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

**Competing interests:** The authors declare that they have no competing interests" in this section.

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