INTRODUCTION

On December 31, 2019, a new respiratory viral disease identified in Wuhan, China. The disease was caused by a novel coronavirus named with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On March 12, 2020, the World Health Organization (WHO) declared a new pandemic all over the world because cases of Coronavirus Disease (COVID-19) infection rapidly increase outside China [1,2]. According to Data taken from WHO, on February 21, 2021, confirmed cases were 110.7 million and over 2.4 million deaths occurred since the start of the pandemic [3]. The SARS-CoV-2 virus, which is an enveloped and single-stranded RNA virus belonging to the Coronaviridae family causes multiple organ system diseases in humans and animals. The signs and symptoms of COVID-19 can vary from asymptomatic to severe symptoms. There is a difficulty to identify effective and safe treatments for COVID-19 disease. With the rapid spread of covid-19 disease in all over the world, the scientific authorities have developed treatment algorithms to treat COVID-19 infection. The treatment algorithms of COVID-19 are composed of medicinal drugs which have been utilized in preceding pandemics and the medications that have been thought potentially effective [4]. In response, National Institute of Health (NIH) provides guidelines to treat COVID-19. Antimicrobial drugs like hydroxychloroquine, azithromycin, remdesivir, ritonavir/ lopinavir, favipiravir used as antiviral drugs, immune-based drugs such as tocilizumab and corticosteroids and convalescent plasma with adjunctive therapy such as anticoagulants, Vitamin C, zinc were used [5]. These drugs are recommended as therapeutic drugs against COVID-19 infection, using those drugs in pandemic is experimental, and even compassionate use may pose health risks due to the potential to cause unfavorable adverse reactions [6,7]. Adverse drug reactions (ADRs) are a serious public health problem and contribute to increased morbidity and mortality in addition to prices for each sufferer and health systems. Prolong hospitalization of the patient, and increase difficulties to get bed in the hospital for new infected patients also associated with ADRs [7]. Considering the limited amount of safety information for the treatment of COVID-19, the study aims to evaluate the ADR profile in patients with the COVID-19 disease.

MATERIALS AND METHODS

Study design and population
This is a descriptive, cross-sectional, prospective as well as retrospective type of study conducted at COVID-19 hospital of tertiary care teaching hospital, Rajkot after ethically approved by the institutional ethics committee. The population consisted of COVID-19 confirmed hospitalized patients who presented with ADRs and were notified by ADR monitoring Center, Rajkot between April 2020 and March 2021.

Data collection
All data about ADRs such as demographic profile, travel history, past medication history and details about ADRs, suspected medications and relevant tests will be collected from COVID-19 hospital and was filled in special suspected ADR reporting form for drugs used in prophylaxis/treatment of COVID-19 provided by Indian Pharmacopoeia Committee, Ghaziabad.

Outcome variables
Analysis of ADRs according to demographic profile, system organ classification (SOC), seriousness and outcome, related to travel history,
COVID-19 test and comorbidity, Drug–drug interaction, etc. Reaction terminology was confirmed with Medical Dictionary for Regulatory Activities (MedDRA) in vigiflow. Drug–drug interaction checked with https://reference.medscape.com/drug-interactionchecker. Suspected ADRs were assessed for causality, preventability, and severity using the WHO causality assessment scale and Naranjo algorithm, modified Schumock and Thornton’s criteria, and modified Hartwig’s criteria, respectively [8-11].

Statistical analysis
The results are represented as Mean±SD and percentage and number using Microsoft Excel (office version 2019).

RESULTS
Total 100 ADR reports were collected. Out of them, there were 60 males and 40 females. The mean age of patients was 52.65±13.95 years. As shown in Table 1 majority of ADRs noted between the age group of 50–70 years. Majority have reverse transcription-polymerase chain reaction (RT-PCR) test positive (78%) as compared to rapid antigen test, no travel history (96%) and majority have non-serious illness (51%). About 54% of patients were without comorbidity and among comorbidity Diabetes Type-2 and Hypertension were the most common. About 4% ADR considered to be due to drug interaction and among them one interaction occurred with Enoxaparin and Aspirin (Fig. 1).

As shown in (Table 2) majority of ADRs were suspected with single medication (69%) as compared to two medications (30%) and three medications (1%). Among single drug therapy, most common on drug was methylprednisolone and among two drugs azithromycin was common. Most common concomitant medication prescribed were paracetamol, chlorpheniramine, Vitamin C, and multivitamins.

According to the WHO causality score, 70% ADRs were probable and 30% were possible (Fig. 2). Considering Naranjo’s scale 64% were possible and 36% were probable. Based on the modified Hartwig severity scale, most of the reactions were categorized as mild (44%), moderate (39%), and severe (17%) in nature. According to Modified Schumock and Thornton’s criteria, majority of reactions were definitely preventable (86%) followed by probably preventable (14%) (Table 3). Regarding management of ADRs, among suspected single drug medication 26 reactions were subsided on withdrawal of drug, 39 without dose modification, and 4 on dose reduction. Among suspected two drugs, 3 reactions were subsided on withdrawal of both suspected drugs and 22 without dose modification and 5 reactions were subsided with one drug withdrawal while other suspected drug continued

| Parameters | Number of ADRs (%) (n=100) |
|------------|-----------------------------|
| Sex        |                             |
| Male       | 60 (60%)                    |
| Female     | 40 (40%)                    |
| Age (years) |                             |
| 21–30      | 10 (10%)                    |
| 31–40      | 15 (15%)                    |
| 41–50      | 16 (16%)                    |
| 51–60      | 25 (25%)                    |
| 61–70      | 28 (28%)                    |
| 71–80      | 6 (6%)                      |
| Type of COVID-19 test |         |
| RT-PCR    | 78 (78%)                    |
| Rapid antigen test | 22 (22%)                |
| Travel history |                             |
| Yes       | 04 (4%)                     |
| No        | 96 (96%)                    |
| Co-morbid conditions |                         |
| Yes       | 46 (46%)                    |
| No        | 54 (54%)                    |
| Drug interaction |                             |
| Yes       | 4 (4%)                      |
| No        | 96 (96%)                    |

Table 2: Distribution of ADRs according to suspected medication

| Type of suspected drug therapy | No. of ADRs (%) (n=100) | Type of suspected drugs |
|-------------------------------|--------------------------|-------------------------|
| Single drug therapy           | 69 (69%)                 | Methylprednisolone (27) |
|                               |                          | Azithromycin (23)       |
|                               |                          | Enoxaparin (5)          |
|                               |                          | Dexamethasone (3)       |
|                               |                          | Ceftriaxone (3)         |
|                               |                          | Hydroxychloroquine (2) |
|                               |                          | Heparin (2)             |
|                               |                          | Favipiravir (1)         |
|                               |                          | Piperacillin+Tazobactam (1) |
|                               |                          | Tocilizumab (1)         |
|                               |                          | Remdesivir (1)          |
| Two drug therapy              | 30 (30%)                 | Azithromycin (24)       |
|                               |                          | Dexamethasone (21)      |
|                               |                          | Hydroxychloroquine (5)  |
|                               |                          | Enoxaparin (3)          |
|                               |                          | Aspirin (2)             |
|                               |                          | Remdesivir (2)          |
|                               |                          | Metoprolol (1)          |
|                               |                          | Methylprednisolone (1)  |
|                               |                          | Dexamethasone (1)       |
| Three drug therapy            | 1 (1%)                   | Azithromycin (1)        |
|                               |                          | Heparin (1)             |
|                               |                          | Ceftriaxone (1)         |

Table 3: Distribution of ADRs according to causality, severity, and preventability

| Parameters                      | No. of ADRs (%) (n=100) |
|---------------------------------|-------------------------|
| Causality (Naranjo scale)       | 64 (64%)                |
| Probable                        | 36 (36%)                |
| Severity (Modified Hartwig scale) |                             |
| Mild                            | 44 (44%)                |
| Moderate                        | 39 (39%)                |
| Severe                          | 17 (17%)                |
| Preventability (Modified Schumock and Thornton’s criteria) |         |
| Definitely preventable          | 86 (86%)                |
| Probable preventable            | 14 (14%)                |
Among them, Diarrhea was the most common symptom and suspected medication was antibiotics (19.8%) and antivirals (12.1%). Antivirals were mostly used in the initial phase of infection to treat mild symptoms, whereas antibiotics were used for severe infections. Hyperglycemia was the most common adverse effect of the drugs used in COVID-19, affecting 22% of patients. Other common adverse effects included gastrointestinal issues (35%), metabolic disorders (41%), and respiratory symptoms (26%).

The pharmacovigilance program of India (PvPI) has been instrumental in monitoring ADRs in COVID-19 patients. The PvPI program has reported an increased number of cases of ADRs during the COVID-19 pandemic, with 62.3% recovered and 21.7% fatal cases. The male predominance (60%) in COVID-19 ADR reporting is steady with the consequences of an observed increase in mortality in men. The mean age of patients for ADRs was 52.65±13.95 years. Most comparable end result visible with a study done by Sun et al. [16] in which our result confirmed that the majority of patients were tested positive for RT-PCR and no travel history. Elderly populations are followed through comorbidity and polypharmacy leading to increases in unfavorable drug reactions (ADRs) [17]. Our result confirmed that the majority of ADRs occurred in patients whose age was between 50 and 70 years. Possible reasons could be the changes in pharmacokinetics with advancing age or disease presentation-older age group patients were developing complications or leading to hospital admissions.

Drug-drug interactions occurring in the course of COVID-19 treatment and co-morbidities could lead to ADRs, which causes increasing the risk of hospitalization, prolonged time to recovery, or death on some cases [18]. In our observation, comorbidity has been found in 46% of cases of ADR and drug-drug interaction was observed in 4% of cases.

According to SOC most common ADRs associated with GIT disorders (41%), which is inconsistent with the results of a study performed by Crescioli et al. [19]. Among them, Diarrhea was the most common symptom and suspected medication was antibiotics that is established that diarrhea is common adverse effect of antibiotics [20]. Other study reported that ADRs cited with two or more suspected drug therapy [19]. In comparison to this, our result confirmed that ADRs cited with single suspected medication (69%) were higher than two (30%) and three (1%) suspected drug therapy. Methylprednisolone is more common with single suspected and azithromycin is more common with two suspected drug therapy. Steroids are the principle motive of drug-induced hyperglycemia. They not only exacerbate hyperglycemia in patients with known diabetes mellitus but also cause DM in patients without documented hyperglycemia before the initiation of glucocorticoids therapy [21,22]. Also in our study metabolic disorders noted the second most common ADRs and among them, hyperglycemia was the most common symptom.

CONCLUSION

Comorbid and elderly patients should be closely monitored for ADRs to avoid harmful consequences in this COVID-19 pandemic situation. The pharmacovigilance program of India (PVPI) will work as important tool to help physicians to choose their therapy sensibly and decrease chances of mortality in this pandemic era.

**DISCUSSION**

Since COVID-19 influences multi-organ systems, the infection and its treatment may also induce many adverse effects instead of side effects [4]. There is a determined want to pick out powerful treatment for coronavirus disorder. Most drugs recently used in this COVID-19 pandemic are repurposed antiviral and immunomodulatory drugs [12]. WHO in addition to the European Medicines Agency (EMA) have indicated the shortage of proof helping the efficacy and safety of any medicine in COVID-19 [13,14]. Hence, this study examined ADR occurred with experimental drugs used in COVID-19 and association between comorbidity and severity of ADRs.

According to our observations, most of the unfavorable drug reactions were categorized as mild (44%) and moderate (39%). Only 17% of ADRs have been categorized as severe ADRs. According to Preventability (Modified Schumock and Thornton’s) criteria majority have been actually definitely preventable ADRs (86%). Considering management, we found that the majority of ADRs abated on without dose modification whether suspected medication was single or two drugs. Finally, concerning final results of ADRs majority were recovered (51%) and recovering phase (33%). Similar result observed in study performed by Melo et al. wherein 62.3% recovered and 21.7% in recovering phase.

**CONCLUSION**

Comorbid and elderly patients should be closely monitored for ADRs to avoid harmful consequences in this COVID-19 pandemic situation. The pharmacovigilance program of India (PVPI) will work as important tool to help physicians to choose their therapy sensibly and decrease chances of mortality in this pandemic era.

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**Table 4: Distribution of ADRs according to type of management**

| Suspected medication | Reaction abated on | No. of ADRs (%) | n=100 |
|----------------------|--------------------|----------------|-------|
| Single drug          | Without dose       | 39 (39%)       |       |
|                      | modification       |                |       |
|                      | withdrawal         | 26 (26%)       |       |
|                      | Dose reduction     | 4 (4%)         |       |
| Two drugs            | Without dose       | 22 (22%)       |       |
|                      | modification       |                |       |
|                      | With reduced dose  | 5 (5%)         |       |
|                      | withdrawal         |                |       |
| Three drugs          | Without dose       | 3 (3%)         |       |
|                      | modification       | 1 (1%)         |       |

**Fig. 2: Distribution of adverse drug reactions according to WHO causality scale**

**Fig. 3: Outcome of adverse drug reaction**

**Table 4: Distribution of ADRs according to type of management**
AUTHOR’S CONTRIBUTIONS
Dr. Ridhdhi H. was involved in data collection, data organization, data interpretation, data analysis, preparation, reviewing, and editing of the manuscript. Dr. Bharti K. was involved in data interpretation, data analysis, preparation, and reviewing of article. Dr. Anil and Dr. Aarti were involved in reviewing and guiding this article.

CONFLICT OF INTEREST
None.

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