



Distribution and Determinants of Suspected Adverse Events among COVID like Illness (CLI) Patients with Different Comorbidities



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Abstract

Background: Several drugs were administered to patients with COVID-19, focusing on their antiviral, immunomodulatory, or anti-inflammatory actions, which could potentially present risk since most of these medicines have the potential to cause numerous adverse effects. **Objective:** This study aimed to observe the incidence of suspected adverse events of selected medicines among COVID-like ill (CLI) patients. **Methodology:** A prospective analysis was performed from February 15, 2021, to June 15, 2021, upon 223 CLI patients. CLI patients were enrolled from the National Institute of Diseases of the Chest and Hospital. The incidence of suspected adverse events were assessed among CLI patients, the laboratory investigations values of SGPT, RBS, serum electrolytes, and serum creatinine of day one and day five and interpreted the 12-lead ECG tracing paper of the same days assessed hepatotoxicity, nephrotoxicity, cardiotoxicity, and metabolic disorders. **Results:** The result showed the incidence of adverse events was 21.5% in CLI patients. Only the incidence of hepatotoxicity was more (12.55%) among CLI patients but statistically not significant ($p > 0.05$). In CLI patients who had co-morbidities, the incidence of adverse events was relatively less and only a significant difference was seen among diabetes mellitus patients ($p \leq 0.05$). **Conclusion:** This study showed that the rate of adverse events was present in CLI patients when treated with the same specific drug of interest in addition to other medicines they received. [*Journal of National Institute of Neurosciences Bangladesh, January 2023;9(1):35-41*]

Keywords: Distribution and Determinants; Suspected Adverse Events; COVID like Illness (CLI) Patients; Different Comorbidities

Introduction

Initially, to handle this pandemic situation, for the first time, the US FDA, on March 30, 2020, issued Emergency Use Authorization (EUA) for hydroxychloroquine and chloroquine when a clinical trial was unavailable¹, or participation in a clinical trial was not feasible. Based on scientific data on June 15, 2020, the FDA revoked chloroquine, and hydroxychloroquine considers the balance of risks versus benefits of treatments for COVID-19². The FDA's fourth emergency use authorization was tocilizumab, specifically for hospitalized adults and children aged two years and older

under some special conditions¹.

The National Guidelines on Clinical Management of COVID-19 (9th Version) Bangladesh, treatment is recommended according to the category of COVID 19 patients. For asymptomatic patients only supportive care and home Isolation³. For mild cases without comorbidities and with controlled comorbidities only symptomatic management, home isolation and monitored with finger pulse oximetry. Mild cases with multiple uncontrolled comorbid and prothrombotic state such as high risk-pregnancy and active malignancy etc. should receive thromboprophylaxis (LMWH) along with

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symptomatic management and should be admitted. For moderate cases along with standard of care patients are treated with LMWH, steroid, remdesivir, and oral antibiotic as amoxicillin Clavulanic acid or doxycycline may be given if bacterial infection is suspected. Severe cases are treated as like moderate cases; here IV broad spectrum antibiotic is recommended⁴.

Up-to-date, for acute management of COVID-19, evidence-based guidelines are mandatory to guide the clinicians in this pandemic situation⁵. In Ireland, a study⁶ was performed a retrospective analysis to assess clinical outcomes and adverse drug events among hospitalized COVID-19 patients who were treated with off-label hydroxychloroquine and azithromycin. The researchers' observation was that these drugs did not help clinical improvement rather than to cause significant toxicity like hypoglycemia, elevated liver function tests, and QT prolongation, highlighting the importance of monitoring all repurposed agents for adverse events.

Several clinical trials are ongoing to investigate the efficacy and safety of the selected drugs like ritonavir, lopinavir, remdesivir, chloroquine, interferon β , and azithromycin in the treatment of the coronavirus infection has already been registered and used for the treatment of other diseases. However, the available clinical data regarding the most often reported toxic effects of these medicines were hepatotoxicity, retinal damage, nephrotoxicity, and cardiotoxicity⁷.

Several clinical observations indicated a temporal relationship between viral infections and the simultaneous or subsequent development of drug rashes as virus-infected cells might be more sensitive to drugs and drug metabolites than normal cells⁸. The underlying viral infections may increase infected patients' susceptibility to adverse drug reactions. However, the mechanisms whereby viral infections might induce or contribute to the development of drug-induced adverse effects are currently unknown⁹. This study aimed to observe the incidence of suspected adverse events of selected medicines among COVID-like ill (CLI) patients.

Methodology

Study Design and Population: This study was a multicenter prospective observational study. The study was conducted and supervised in the Department of Pharmacology of Bangabandhu Sheikh Mujib Medical University to partially fulfill the Doctor of Medicine (MD) degree in Pharmacology. This study was conducted in the COVID unit of Bangabandhu Sheikh Mujib Medical University, Dhaka Medical College Hospital, Mugda Medical College Hospital, Shahid

Suhrawardy Medical College Hospital, and non-COVID unit of the National Institute of Diseases of the Chest and Hospital. This study was carried out from October 2020 to July 2021 (actual enrollment started after getting approval from IRB, i.e., February 2021). The study populations were the hospitalized COVID-19 and COVID-like illness (CLI) patients who met the selection criteria. Inclusion criteria were age more than 18 years and below 65 years of both sex, COVID-19 patients who were treated with any two drugs of amoxicillin-clavulanic acid combination, steroid, and montelukast, in addition to standard of care with medications and COVID-like illness (CLI) patients who were treated with any two drugs of amoxicillin-clavulanic acid combination, steroid, and montelukast, in addition to standard of care with medications. Exclusion criteria were age less than 18 years and more than 65 years, Pregnant and lactating mother, Patients who were previously diagnosed with chronic kidney disease and chronic liver disease or patients who were treated with anti-tubercular medicines. Purposive sampling was applied to collect the data.

Study procedure: For documentation, the information about particulars of patient, complete diagnosis of the disease, details about the prescription sheets, random blood sugar (RBS), liver function test (serum glutamic pyruvic transaminase or SGPT), renal function test (serum electrolytes, serum creatinine), and interpretation of Electrocardiogram (ECG) on the day of admission and 5th day after dose administration during the hospitalization for both groups of patients, a data collection sheet was prepared. The information was recorded in two separate data collection forms for COVID-19 and CLI patients by the following heading:

Patients' enrollment: Patients who met the selection criteria were diagnosed as a case of confirmed COVID-19 according to the National Guidelines on Clinical Management of COVID-19, Bangladesh, and received any two drugs from the drug of interest along with other medications as needed. COVID-like illness patients who met the selection criteria were admitted to the hospital for their COVID-like symptoms (fever, cough, breathlessness) and diagnosed as COVID-19 negative according to the National Guidelines on Clinical Management COVID-19 and received any two drugs of the drug of interest along with other medications as needed.

Data Collection: After taking the written informed consent (Appendix X), filled the data collection form from patients' hospital admission papers and treatment

sheets on the day of admission. On the second day, the data collection form was filled with the reports of hematological parameters and tracing paper of the ECG as of baseline value before drug administration on the first day of admission. The patients were advised to repeat the same hematological parameters and ECG on the 5th day after dose administration during the hospitalization and filled the rest of the data collection form after the reports were available. To detect adverse drug events during the treatment period, reviewed baseline and repeat data. All the documents were documented as photographs in distinct patient folders.

Assessment of Adverse Event: Assessed the incidence of existing known adverse events, whether it was worsening or not, or emerged any new adverse events that occurred concurrent to COVID-19 drug therapies. SGPT/ALT values of days one and five were compared and assessed with the internationally accepted standard reference value given in the patients' investigation paper for hepatotoxicity. The normal value of SGPT is 7 to 56 U/L and three times the upper limit of normal was considered as hepatotoxicity. Serum creatinine values of days one and five were compared and assessed with the internationally accepted standard reference value given in the patients' investigation paper to evaluate nephrotoxicity. The normal value of serum creatinine is 0.74 to 1.35 mg/dL for men and 0.59 to 1.04 mg/dL for women. An increase of serum creatinine of 0.3 mg/dL then the normal value was considered as nephrotoxicity. RBS values of day one and day five were compared and assessed with the internationally accepted standard reference value to evaluate metabolic disorder. According to the American Diabetes Association, the normal value of RBS is 4.4 to 10 mmol/L. In this study < 4.4 mmol/L was considered hypoglycemia and > 10 mmol/L was considered hyperglycemia. Serum electrolytes (Na⁺, K⁺) values of days one and five were compared and assessed with the internationally accepted standard reference value given in the patients' investigation paper to evaluate electrolytes imbalance. The normal value of Na⁺ is 135 to 145 mmol/L. In this study < 135 mmol/L was considered as hyponatremia and 145 mmol/L was considered as hypernatremia. The normal value of K⁺ is 3.5 to 5.5 mmol/L. In this study < 3.5 mmol/L was considered as hypokalemia and > 5.5 mmol/L was considered as hyperkalemia. By interpreting the 12-lead ECG tracing paper, assessed cardiotoxicity focus upon QT interval (i.e., >500 ms is prolonged QT). Except for this finding, cardiac abnormalities like old myocardial infarction, left ventricular hypertrophy, right bundle branch block,

right axis deviation, p-pulmonale, and tachycardia were also observed and assessed for adverse events concerning these.

Assessing possible drug-related ADRs: Since ADRs may act through the same physiological and pathological pathways as different diseases, they are difficult and sometimes impossible to distinguish. According to the guide of WHO, "Safety of Medicines - A guide to detecting and reporting adverse drug reactions," the following step-wise approach may be helped to assess possible drug-related adverse events: Ensure that the medicine ordered was the medicine received and taken by the patient at the dose advised, Verify that the onset of the suspected adverse event was after the drug was taken, not before, Determine the time interval between the beginning of drug treatment and the onset of the Event.

Causality assessment: Causality assessment is the evaluation of the relationship between drug treatment and the occurrence of adverse events. It also evaluates and checks that the particular treatment is the cause of observed adverse events or not and estimates the strength of the relationship between drug(s) exposure and occurrence of adverse events. The WHO-Uppsala Monitoring Centre (WHO-UMC) system was used to perform causality assessment for all suspected adverse events as this system is a universally accepted method. The relationship between the adverse events and drugs was categorized as certain, probable, possible, unlikely, conditional/unclassified, or unassessable/unclassifiable and the criteria for diagnosis of these categories were mentioned in the appendix.

Severity assessment of Adverse Event: The severity of adverse events was assessed by the Adverse Event severity grading scale mentioned in the National Guidelines on the Pharmacovigilance System in Bangladesh, 2018- mild, moderate, severe, fatal.

Statistical Analysis: All raw data were recorded, processed, and analyzed using SPSS (Statistical Package for Social Science) version 20. An appropriate statistical test (chi-square (x²), independent sample t-test, mann-whitney U test, and spearman rank correlation) was used to analyze the data. The data were expressed as mean ± standard deviation (SD) and median for continuous variables and frequency and percentage for categorical variables. The chi-square (x²) test was employed to compare categorical data between groups. To compare the continuous data between groups, using an independent sample t-test or mann-whitney U test where applicable. Results were presented in tables & figures. Calculated 'p' value <0.05

was considered significant because all analysis was done at a 95% confidence level.

Ethical Consideration: Submitted the research protocol to the Institutional Review Board (IRB) of Bangabandhu Sheikh Mujib Medical University to review the scientific and ethical issues related to the research to obtain the required approval. After reviewing the protocol, the Institutional Review Board of BSMMU issued a Clearance Letter Memo No. BSMMU/2021/956 dated 02/02/2021.

Results

Total 861 cases were enrolled in this study after meeting inclusion and exclusion criteria. Among them, 638 (74.1%) cases were COVID-19 positive and were admitted in different COVID dedicated hospitals in Dhaka, and 223 (25.9%) cases were admitted in NIDCH, Dhaka for their COVID like symptoms were enrolled in this study.

Demographic Characteristics of Study Subjects

The average age for hospitalized COVID-19 patients who had adverse events was (53 ± 10 years; 43 to 63 years) and who had no adverse events was (50 ± 12 years; 38 to 62 years). The independent sample t- test was done where the comparison between adverse events and age was significant ($p \leq 0.05$). Adverse events occurred more with increased age among COVID-19 positive cases and more adverse events was occurred in the age group of 51 to 60 years. The spearman Rank correlation test was done where the correlation between age group and adverse events was significant ($p \leq 0.05$). Among the 638 COVID-19 hospitalized patients 386 (60.5%) patients were male and 252 (39.5%) patients were female. Adverse events occurred 42.5% in male and 34.9% in female. The chi-square test was done to assess sex difference in the adverse events occurred which was not significant ($p > 0.05$). The average age for hospitalized COVID like illness (CLI) patients who had adverse events was (50 ± 12 years; 43 to 63 years) and who had no adverse events was (50 ± 12 years; 38 to 62 years). The independent sample t- test was done where the comparison between adverse events and age was significant ($p \leq 0.05$). Adverse events occurred more with increased age among COVID-19 positive cases and more adverse events was occurred in the age group of 51 to 60 years. The spearman Rank correlation test was done where the correlation between age group and adverse events was significant ($p \leq 0.05$). Among

the 638 COVID-19 hospitalized patients 386 (60.5%) patients were male and 252 (39.5%) patients were female. Adverse events occurred 42.5% in male and 34.9% in female. The chi-square test was done to assess sex difference in the adverse events occurred which was not significant ($p > 0.05$) (Table 1).

Table 1: Demographic Characteristics of Study Subjects in Hospitalized COVID like Illness Patients (n=223)

Characteristics	Adverse event		Total	P value
	Yes	No		
Age in Years; (Mean±SD)	50.3±12.12	48.7±12.34	-	0.273a
Age Groups				
≤30 Years	4(13.8%)	25(86.2%)	29(100.0%)	
31 to 40 Years	4(20.0%)	16(80.0%)	20(100.0%)	0.281b
41 to 50 Years	12(24.5%)	37(75.5%)	49(100.0%)	
51 to 60 Years	11(18.3%)	49(81.7%)	60(100.0%)	
>60 years	17(26.1%)	48(73.9%)	65(100.0%)	
Gender				
Male	28(18.8%)	121(81.2%)	149(100.0%)	
Female	20(27.0%)	54(73.0%)	74(100.0%)	0.159c

n: Total number of cases; SD: standard deviation; %: percentage, all percentage was calculated as row percentage; p-value: probability value; Here, p-value calculated from a = independent sample t- test, b = Spearman Rank correlation test, c = Chi-Square test and

The correlation of adverse event with age were measured. The spearman rank correlation test was done where compared between age and incidence of adverse events in COVID-19 patients was significant ($p \leq 0.05$) (Table 2).

Table 2: Correlation of adverse event with age in COVID-19 and CLI patients

Study population	r value	P value*
CLI	0.070	0.298

*Spearman Rank correlation test was done to measure the level of significance.

Co-morbidities of study subjects of hospitalized CLI patients:

The adverse events were occurred more in diabetics' patients (45.0%) than the patients who had no diabetics' (16.4%). The association between diabetes mellitus and adverse events was significant ($p \leq 0.05$). Diabetics' patients were 2.75 times more at risk for developing adverse events. The association between adverse events and diabetes mellitus of hospitalized CLI patients were assessed. The adverse

Table 1: Demographic Characteristics of Study Subjects in Hospitalized COVID like Illness Patients (n=223)

Co-morbidities	Adverse event		Total	RR	P value
	Yes	No			
Diabetes mellitus					
• Present	18(45.0%)	22(55.0%)	40(100.0%)	2.75	<0.001
• Absent	30(16.4%)	153(83.6%)	183(100.0%)		
Hypertension					
• Present	9(33.3%)	18(66.7%)	27(100.0%)	1.68	0.111
• Absent	39(19.9%)	157(80.1%)	196(100.0%)		
Ischemic Heart Disease					
• Present	3(20.0%)	12(80.0%)	15(100.0%)	0.92	0.882
• Absent	45(21.6%)	163(78.4%)	208(100.0%)		
Bronchial Asthma					
• Present	9(22.5%)	31(77.5%)	40(100.0%)	1.06	0.868
• Absent	39(21.3%)	144(78.7%)	183(100.0%)		
COPD					
• Present	3(20.0%)	12(80.0%)	15(100.0%)	1.34	0.205
• Absent	21.6%	78.4%	208(100.0%)		

RR = Relative Risk

Discussion

The research described 252 adverse events in 638 hospitalized COVID-19 patients from February 15, 2021, to June 15, 2021, and 48 adverse events in 223 hospitalized CLI patients of the same duration. The drug of interest were systemic steroids, amoxicillin-clavulanic acid combination, and montelukast respectively. In this study, the rate of suspected adverse events was 39.5% in COVID-19 patients and 21.5% in CLI patients. Thus, the detected adverse event was 1.83 fold higher in COVID-19 patients than CLI patients during the same period. In addition, the most reported reaction for COVID-19 patients was nephrotoxicity (9.2%), hyperglycemia (28.2%), hyponatremia (18.3%), and for CLI patients' hepatotoxicity (12.55%), and hypokalemia (9.0%). Though there was no cardiotoxicity occurred but the patients who had cardiac abnormalities according to their ECG, the incidence of adverse events was more among them.

The mean age of the patients with ADRs and without ADRs group was 45.2 ± 17.5 and 46.0 ± 16.2 years, respectively⁹. In another study in Brazil, the most affected age group was 45-64 years (36.8%), with a mean age of 60.5 years \pm 1.8 years. In this study, the mean age of COVID-19 with and without adverse events was 53 ± 10 and 50 ± 12 years, respectively and this value was nearer the previous study. On the other side, the mean age of CLI patients with or without

adverse events was 50 ± 12 and 48 ± 12 years which was also similar to the previous study. The correlation between increased age and adverse events was statistically significant among COVID-19 patients.

The male predominance in COVID-19 ADR reporting is consistent with observations of a greater risk of COVID-19 in males than in females¹⁰. In Ghana's June 2020 interim report on the descriptive analysis of COVID-19-related spontaneous reports from VigiBase, more males (55.7%) were reported to have ADRs than 38.8% in females¹¹. In this study, males were also predominant than females in both groups but this difference concerning adverse events was not statistically significant.

More than 50.0% of the patients presented other diseases or risk factors, such as hypertension, diabetes, and cardiovascular diseases¹². In this study, among the co-morbid conditions diabetes mellitus, hypertension, and bronchial asthma were more in COVID-19 patients, and in CLI patients mostly reported comorbidities were diabetes mellitus and bronchial asthma. The association between adverse events and co-morbidities was significant in both groups for diabetes mellitus and hypertension.

In Brazil and Ghana, adverse drug reactions were observed among COVID-19 patients with hydroxychloroquine, azithromycin, and chloroquine. In China, the most observed drugs for adverse drug reactions were lopinavir/ritonavir, and chloroquine. In

Spain, the most frequently related drugs were tocilizumab, dexamethasone, azithromycin, lopinavir/ritonavir, dexamethasone, and chloroquine and hydroxychloroquine. In this study, the drug of interest was an amoxicillin-clavulanic acid combination, systemic steroid, and montelukast. The use of montelukast was highest among the two groups though the SARS-CoV-2 virus is responsible for COVID-19 disease. In this situation, the irrational use of medicines was observed. Steroid was also used more in COVID-19 patients and amoxicillin-clavulanic acid combination was more used in CLI patients. The association between adverse events and the use of these three medicines was statistically significant in both groups.

Medication reconciliation is necessary at transitions of care to decrease medication discrepancies, potential adverse effects, and ADEs in especially the high-risk group of patients receiving polypharmacy (WHO, 2020). The treatment of COVID-19 patients with co-morbidities may result in problematic polypharmacy and an increased risk of drug-drug interactions¹³. The consequence of polypharmacy among the aged population is often correlated with poor compliance, drug-drug interactions, medication errors, and adverse drug reactions¹⁴. In this study, the patients who were treated with more than 4 drugs, the incidence of adverse events occurred more among them in both groups and the association between adverse events and polypharmacy was statistically significant in both groups.

All previous studies regarding adverse drug reactions or events were related to the drugs like chloroquine and hydroxychloroquine, azithromycin, lopinavir/ritonavir, remdesivir, anti-inflammatory medications (such as corticosteroids and other compounds). In one study, drug-induced gastrointestinal disorders and liver disorders were predominant among the detected adverse events¹⁵. A retrospective analysis in China showed that ADRs in patients with COVID-19 were mainly characterized by gastrointestinal reactions, liver injury, rash, and hyperlipidemia (Sun et al., 2020). A cross-sectional study was done in another study¹⁶. The main sites of manifestation of the reactions they noticed in their research were: cardiac, gastrointestinal, skin, and hepatobiliary systems.

As the drug of interest for observing the suspected adverse events was different from other previous studies so, the results of this study showed that the most observed adverse events among COVID-19 were nephrotoxicity, hyperglycemia, and hyponatremia. A

probable reason may be the incidence of acute renal injury¹⁷⁻¹⁸ significantly increases with COVID-19 infection though the reason was not clearly understood and increased use of systemic steroids. The incidence of hepatotoxicity was observed more among CLI patients and the possible cause was the patients were chronically ill and treated over a period of time with multiple drugs.

Cardiotoxicity was common among all the previous studies conducted in different countries where the researchers specify QT prolongation as cardiotoxicity. In this study, no QT prolongation was observed. A significant number of patients had other cardiac abnormalities according to their ECG tracing paper. These patients have experienced more adverse events than the patient who had normal ECG tracing paper in both groups.

The majority of the ADRs were rated as possible, indicating that there could be alternative causes of the reactions apart from the suspected drug¹⁹. In another study, more than 80% of the reactions were classified as probable or possible. This is due to the complexity of evaluating a causal relationship between a drug and an adverse reaction. This is because there are multiple approaches and different scenarios that can bring uncertainties regarding the causal link of the reaction, including the underlying disease itself as a confounding factor, competing with the drug for the cause of the reaction¹².

A causality assessment of the current study was done. For both groups, possible was more than unlikely. The causality assessment of the present study supports the findings of previous studies in some aspect. The study of adverse drug reactions in Ghana showed that 3 (5.7%) were serious (life-threatening) and the rest non-serious²⁰. Another study showed that in total, 56.4% of reactions were classified as severe¹². But in this study, only a mild assessment was possible because there was a lack of proper continuous follow-up and proper documentation regarding patients' conditions.

Conclusion

The incidence rate of adverse events in the CLI patients are detected. In this study suspected adverse events were observed for the drugs which are common among most prescribed medicines for the treatment of CLI patients. Hepatotoxicity was observed more in CLI patients. Cardiotoxicity was absent but the patients who had cardiac abnormalities regarding ECG were experienced more adverse events. In addition, this study provides support for best practices in

pharmacovigilance, which can contribute to effective and safe regulatory decision-making for patients.

Acknowledgements

None

Conflict of interest: There is no conflict of interest relevant to this paper to disclose.

Financial Disclosure

This research project was partially funded by Bangladesh Medical Research Council (BMRC).

Contribution to authors: Mohith MT, Marnush M, Hussain MN had involved in protocol preparation, data & sample collection and literature search and manuscript writing. Sarwar S, Rahman MS, Begum T were involved in manuscript preparation and revision. All the authors have read and approved the final version of the manuscript.

Data Availability

Any inquiries regarding supporting data availability of this study should be directed to the corresponding author and are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Ethical approval for the study was obtained from the Institutional Review Board. As this was a prospective study the written informed consent was obtained from all study participants. All methods were performed in accordance with the relevant guidelines and regulations.

How to cite this article: Sarwar S, Mohith MT, Marnush M, Hussain MN, Rahman MS, Begum T. Distribution and Determinants of Suspected Adverse Events among COVID like Illness (CLI) Patients with Different Comorbidities. *J Natl Inst Neurosci Bangladesh*, 2023;9(1):35-41

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Article Info

Received on: 7 October 2022

Accepted on: 24 December 2022

Published on: 1 January 2023

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