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Original article

Incidence and risk factors of adverse drug reactions in patients with coronavirus disease 2019: A pharmacovigilance experience utilizing an ADR trigger tool

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ABSTRACT

Background: Since the World Health Organization declared coronavirus disease (COVID-19) as a pandemic, most countries started treating their patients with various therapies. However, the data regarding their safety and effectiveness is still lacking.
Objectives: We aimed to evaluate the adverse drug reactions (ADRs) incidence and their predisposing factors among COVID-19 patients.
Methods: A retrospective observational study that was conducted at a tertiary academic hospital from March – June 2020. Patients were included if they were ≥ 18 years old, inpatient, had a reverse transcriptase-polymerase chain reaction (PCR) positive for COVID-19, and were treated with; (lopinavir-ritonavir, hydroxychloroquine, chloroquine, favipiravir, ribavirin, or interferon-ß) either as monotherapy or combination therapy for three days or longer. The data of eligible patients were retrieved from the electronic medical records. A standardized data collection form was designed to collect patient demographics, COVID-19 severity based on the Saudi Ministry of Health management protocols, antiviral therapies, duration of therapy, and length of stay (LOS). The ADRs were identified via conducting a comprehensive review using predefined triggers and were evaluated using Naranjo Score.
Results: A total of 155 patients were included of which 123 (79.4%) were males. In our sample, the incidence proportion of ADRs per patient was 72.3%. A total of 287 ADRs were identified most of them were hepatic (n = **101**, 35.2%), gastrointestinal (n = **59**, 20.6%), hematological (n = **47**, 16%), and endocrine (n = **45**, 15%). Hydroxychloroquine was the most common drug associated with ADRs (n = **155**). The length of stay (10 – 20 days) was the only statistically significant with the ADR incidence (p-value = 0.008; 95 %CI 1.216:3.568).
Conclusions: The ADRs are prevalent among COVID-19 patients, which assure the importance of implementing active hospital-based pharmacovigilance systems.

1. Introduction

At the end of December 2019, reports of a new coronavirus strain causing respiratory infection in Wuhan, China, were detected. The first documented case in the kingdom of Saudi Arabia was confirmed on March 2nd, 2020. Consecutively on March 11th, 2020, the World Health Organization (WHO) declared coronavirus disease 2019 (COVID-19) as a pandemic (World Health Organization, 2020). Data provided by the WHO Health Emergency Dashboard (June 14th 2021, 10:56 am CEST) reports 175,541,600 confirmed cases of COVID-19 worldwide since the beginning of the pandemic and 3,798,361 deaths. This number might be under-

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estimated as many countries have faced shortages or unavailability of testing (Richterich, 2020). From the time of its spread, unified efforts across the globe attempted to find potential therapies to help alleviate its deleterious impact on patients. Despite the lack of approved medications for treating COVID-19 patients by the US Food and Drug Administration (FDA), many agents are being utilised, and some are authorised for emergency use. The proposed options are based on previous experiences with similar coronavirus management and limited studies (Venkatasubbaiah and Reddy, 2020). Chloroquine, hydroxychloroquine, remdesivir, lopinavir/ritonavir, tocilizumab, dexamethasone, triple therapy (lopinavir/ritonavir, ribavirin, and interferon-beta), intravenous immunoglobulins (IVIg), and favipiravir have been used in practice (Sanders et al, 2020). However, the safety profile of these medications in COVID-19 infected patients has not been assessed prudently, and sufficient information has not been established except in a small number of studies (Rhodes et al, 2021; Lu et al, 2020; Naksuk et al, 2020). The optimisation of the balance between the therapeutic effectiveness of medications and their adverse effects is a critical pillar that potentially assures a positive impact on patient outcomes. For decades, adverse drug reactions (ADRs) persist in being a significant concern that might compromises patient's safety and pharmaceutical care plans (Abdul Hadi et al, 2017; Coleman and Pontefract, 2016).

It has been shown in a retrospective study on the incidence of ADRs in COVID-19 infected patients that the length of hospital stay, number of drugs used during hospitalisation, and the underlying diseases were independently predisposing patients to the development of ADRs (Sun et al, 2020).

The documentation and assessment of ADRs are essential when dealing with unapproved indications. It might help identify severe reactions, assure the safety of new investigational therapy, evaluate risk factors, and distribute information among health care providers (HCPs) (Visacri et al, 2015). As no studies have been published yet with this regard on a national level, this study would highlight the risk factors that might predispose patients with confirmed COVID-19 infection to the development of ADRs in light of the scarcity of evidence on the management. Hence, it would promote the provision of tailored therapy and more insights in regard to the safety profile. Moreover, it would potentially contribute to the implementation and expansion of an active hospital-based pharmacovigilance system.

2. Aims

- To evaluate the incidence of ADRs and their predisposing risk factors among COVID-19 patients when using different pharmacological agents as a therapeutic option.
- To assess the effectiveness of the ADRs' trigger tool.

3. Material and methods

3.1. Study design and setting

This is a retrospective observational study that was conducted from a sample of a tertiary care teaching hospital. The academic hospital serves around 500 beds. The data of patients with confirmed COVID-19 infection in the period of March 2020 – June 2020 were retrieved from the medical record system (QuadraMed).

3.2. Study population

All Adult patients (aged 18 years or older) who were admitted to the hospital with confirmed COVID-19 infection by reverse transcription-polymerase chain reaction (RT-PCR), and treated with any of the following medications: lopinavir-ritonavir, hydroxychloroquine, chloroquine, favipiravir, ribavirin, interferon-beta, or IVIg either as monotherapy or combination therapy for three days or greater were included in the study.

3.3. Outcome measures

The primary outcome is the incidence of ADRs of medications used to manage patients with RT-PCR-confirmed COVID-19 infection. Moreover, the ADRs' severity, probability, outcomes, and the potential predisposing risk factors are considered secondary outcomes.

3.4. Study procedures

3.4.1. ADR triggers tool

All medications used in the management of patients of COVID-19 that are available at our institution were selected in the study. A positive trigger tool items for ADRs we used to initially define the triggers (**Supplementary Table S1**) we further specified them for each medication (**Supplementary Table S2 – S8**) based on information retrieved through a literature review, information from the US FDA, and global trigger tool white paper (Griffin and Resar, 2009).

3.4.2. Evaluation and assessment of ADRs

The data of patients in the period of [March – June 2020] who met the eligibility criteria were retrieved from the electronic-based medical records (eMR). The incidence of ADRs was evaluated thoroughly via conducting a comprehensive review of the patients' electronic medical records (eMR**),** i.e., laboratory data and HCPs' daily notes.

The Naranjo ADR-probability scale was utilised to assess the causality between the ADRs and the suspected drug. The Naranjo scale is a 10-item ADR-probability scale that classifies ADRs into definite ($\geq$9 points), probable (5 – 8 points), possible (1 – 4 points), and doubtful (0 points) (Naranjo et al, 1981). Only possible, probable, and definite ADRs were reported. The severity of the ADRs was evaluated and classified into minor (i.e., no medical treatment was needed), moderate (i.e., medical treatment was administered or hospitalisation was prolonged), and severe (i.e., life-threatening, resulted in permeant damage or death) (Petrova et al, 2017; Kramer, 1979). Furthermore, the outcome of the ADRs was reported as (resolved with no sequel, resolving, ongoing, permeant damage/death, or unknown).

3.5. Data collection

After obtaining ethical approval from the research committee at Imam Abdulrahman bin Faisal University – Dammam, Kingdom of Saudi Arabia (IRB-2021–05-206), the data collection was commenced.

The data collection was conducted by 2 of the investigators (i.e., a clinical pharmacist and pharmacy resident) in which the eMR of patients who met the study inclusion criteria were reviewed. A standardised form was used for collecting the retrieved data.

3.5.1. Data collection form

A standardised data collection form is constructed of five main domains; patient-related, admission-related, therapeutic management-related, ADR-related, and overall patient outcome-related information domains were used to collect the data.

The first domain was designed to collect patient-related information that includes patient's demographics (i.e., age, gender, allergies, weight, and body mass index (BMI)), comorbidities (i.e., diabetes mellitus, hypertension, heart failure, chronic kidney

disease, chronic obstructive pulmonary disease (COPD)/asthma, cancer, and others), and renal function (i.e., baseline renal function; serum creatinine and estimated creatinine clearance (eCrCl) and the presence of an acute kidney injury).

The second domain contains the admission-related information such as the admitting speciality and admission to intensive care unit (ICU) (i.e., critical versus general isolation wards) and the disease severity status based on the Saudi Ministry of Health (MOH) classification (i.e., mild to moderate, severe, and critical) (Saudi Ministry of Health and Saudi Center For Disease Prevention and Control, 2020).

The therapeutic management-related information domain includes the administered antiviral agents/other agents for the management of COVID-19 (i.e., lopinavir-ritonavir, hydroxychloroquine, chloroquine, favipiravir, ribavirin, interferon-beta, and IVIg), the number of days these agents were administered, and the total number of concomitant agents (i.e., antimicrobials versus non-antimicrobials).

The fourth domain was designated to incorporate ADR-related information (i.e., ADRs' incidence, severity, probability, and outcome, and the number of days between administering the drug and the development of the ADR).

Lastly, the overall patient outcome-related information domain included the length of hospital stay in days and the mortality.

3.5.2. Data collection form validity and reliability

A data collection form was developed based on reviewing the relevant literature published in the field of ADRs and COVID-19 infection (Rhodes et al, 2021; Abdul Hadi et al, 2017; Coleman and Pontefract, 2016; Visacri et al, 2015). All of the research objectives and aims were highlighted while designing the form. Moreover, the data collection sheet was piloted initially.

3.6. Statistical analysis

Data were summarised using frequencies and percentages. An initial univariate analysis was performed using the Chi-square test where the outcome was the presence of an ADR or not. Furthermore, a negative binomial regression model was employed with the number of ADR as the outcome variable to determine the risk factors of ADR. Relative risk (RR) and its 95% confidence level (CI) were reported. A p-value of<0.05 was considered statistically significant. All analyses were carried out using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA).

4. Results

4.1. Baseline characteristics

A total of 155 patients were included in the study (Fig. 1: Flow-chart on patient selection). Among the participants, nearly 80% were males, 31% were aged 60 years or older, and 34% were obese. Approximately two-thirds (n = 102) had a comorbidity condition, and one-third had more than one comorbidity. Diabetes mellitus and hypertension were the more prevalent comorbidities among the participants. The Charlson comorbidity index was less than three among 66%.

The severity of COVID-19 was severe-critical among 62.3%. The majority of patients, 127 (81.9%), were admitted to the general isolation wards, out of which 44 (34.6%) were transferred to the ICU as their disease state had worsened. Most of the patients (n = 71; 45.8%) had a hospital length of stay of 10 – 20 days (Table 1). Mortality had occurred in 36 (23.2%) of patients.

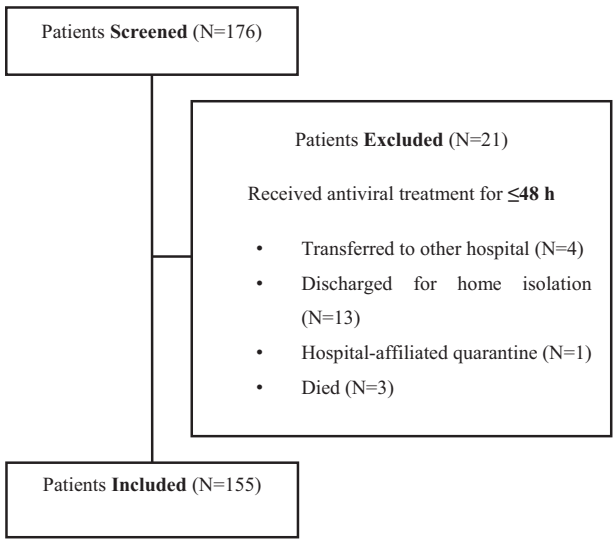

Fig. 1. Flow-chart on the selection of patients.

4.2. Antiviral therapies used

The number of patients who received hydroxychloroquine alone, a **combination of hydroxychloroquine and lopinavir-ritonavir**, lopinavir-ritonavir alone, or a combination of hydroxychloroquine and favipiravir was **39** (25.2%), **98** (63.2%), **5** (3.1%), and **11** (7.1%), respectively (Table 2).

4.3. Outcomes

4.3.1. Primary outcome

4.3.1.1. Incidence of ADRs among COVID-19 patients. A total of 287 ADRs were reported among 115 (74.2%) patients during the study period. Characteristics of these patients are detailed in (Table 1).

The identified ADRs were hepatic (n = 101, 35.2%), gastrointestinal (n = 59, 20.6%), hematological (n = 47, 16%), and endocrine (n = 45, 15%) (Table 3). Hydroxychloroquine and lopinavir-ritonavir were the most common drugs associated with a total ADRs of 156 and 113, respectively (Table 4).

4.3.2. Secondary outcomes

4.3.2.1. Adrs' severity, probability, outcomes. Most of the ADRs were minor in severity (n = 257, 89.5%) and (n = 154, 53.7%) of ADRs have resolved. Importantly, 84% of patients who received hydroxychloroquine had an ADR with an average of 1.4 events per patient. Further, most of the moderate-severe ADRs (25/30) were associated with hydroxychloroquine. Average time to onset of ADR after the medication was lowest for lopinavir-ritonavir, with an average of 3.9 days (Table 5).

4.3.2.2. Predisposing risk factors. The negative binomial regression model (Table 6) indicated that having more than ten days of hospitalisation was significantly associated with the occurrence of an ADR (relative risk = 2.06 and 2.18 if the length of stay was 10–20 days and more than 20 days, respectively).

5. Discussion

The availability of enriched safety and monitoring data of the proposed therapies in COVID-19 infected patients would potentially enhance the decision-making process while providing optimal care. To the best of our knowledge, limited evidence on ADRs' incidence and risk factors in patients with COVID-19 has

Table 1
Baseline characteristics of The Study Participant and Patients who Developed an Adverse Drug Reaction (ADR).

Characteristics			All Participants (N=155)	Patients who developed ADR (N=115)	
			n (column %)	n (row %)	p-value
Patient Demographics	Age				
		<40 years	32 (20.6)	18 (56.3)	0.034
		40-59 years	75 (48.4)	59 (78.7)	
		≥60 years	48 (31.0)	38 (79.2)	
	Gender				
		Female	32 (20.6)	20 (62.5)	0.090
		Male	123 (79.4)	95 (77.2)	
Comorbidities	DM				
		No DM	78 (50.3)	58 (74.4)	0.396
		Controlled DM	26 (16.8)	17 (65.4)	
		Uncontrolled DM[a]	39 (25.2)	29 (74.4)	
		Untreated DM[b]	12 (7.7)	11 (91.7)	
	HTN		64 (41.3)	45 (70.3)	0.354
	HF		6 (3.9)	3 (50.0)	0.167
	CAD		16 (10.3)	11 (68.8)	0.599
	ESRD		9 (5.8)	7 (77.8)	0.800
	Asthma		7 (4.5)	4 (57.1)	0.291
	Active cancer		2 (1.3)	1 (50.0)	0.387
Charlson comorbidity index		0 - 2	102 (65.8%)	76 (74.5%)	0.718
		3 - 4	41 (26.5%)	32 (78%)	
		≥5	12 (7.7%)	7 (58.3%)	
BMI		Normal	16 (20.8%)	12 (75%)	0.27
		Overweight	27 (35.1%)	19 (70.4%)	
		Obese	34 (44.2%)	27 (79.4%)	
Renal function	eCrCl[c]				
		≥90	68 (43.9%)	47 (69.1%)	0.149
		60 - 89	51 (32.9%)	42 (82.4%)	
		30 - 59	24 (15.5%)	16 (66.7%)	
		<30 or Dialysis	12 (7.7%)	10 (83.3%)	
	AKI[d]				
		Yes	40 (27.4%)	33 (82.5%)	0.001
		No	106 (72.6%)	75 (70.8%)	
Level of care and disease severity	Admitting Speciality				
		General Isolation Ward	127 (81.9%)	92 (72.4%)	0.288
		Critical care	28 (18.1%)	23 (82.1%)	
	ICU admission		72 (46.5%)	63 (87.5%)	<0.001
	Disease severity				
		Mild-to-moderate	58 (37.4%)	34 (58.6%)	0.002
		Severe	66 (42.6%)	54 (81.8%)	
		Critical	31 (20.0%)	27 (87.1%)	
Length of Stay (Days)					
		<10 days	40 (26.1%)	25 (62.5%)	0.008
		10-19 days	69 (45.1%)	49 (71%)	
		≥20 days	44 (28.8%)	40 (90.9%)	

Abbreviations: ADR: adverse drug reaction; AKI: acute kidney injury; BMI: body mass index; CAD: coronary artery disease; DM: diabetes mellitus; eCrCl: estimated creatinine clearance; ESDR: end-stage renal disease; HF: heart failure; HTN: hypertension; ICU: intensive care unit

[a] Haemoglobin A1C of ≥ 7% was considered as uncontrolled DM based on the American Diabetes Association guidelines (American Diabetic Association, 2020).

[b] Patients were considered to have untreated DM if they were diagnosed with DM upon their admission to the hospital with COVID-19 disease.

[c] The eCrCl was calculated using the Cockcroft-Gault formula (Cockcroft and Gault, 1976).

[d] The AKI was defined according to the Kidney Disease Improving Global Outcomes (Khwaja, 2012).

Table 2
Antiviral Therapies Used.

Antiviral Therapy	No. of Patients	%
Hydroxychloroquine	39	25.2
Hydroxychloroquine + Lopinavir/Ritonavir	88	56.7
Hydroxychloroquine + Favipiravir	11	7.1
Hydroxychloroquine + Lopinavir/Ritonavir + Interferon-beta + IV Immunoglobulin	10	6.5
Lopinavir/Ritonavir	5	3.2
Chloroquine + Lopinavir/Ritonavir	1	0.7
Favipiravir	1	0.7
Total	155	100.0

been published (Rhodes et al, 2021; Cai et al, 2020; Elbeddini et al., 2020a,b; Olry et al, 2020; Ren et al, 2020). We reported a total of 287 ADRs among 115 (74.2%) patients during the study period. This is higher than what was reported in a study conducted in China that discussed the incidence, type, and risk factors associated with ADRs among patients with COVID-19 infection by Hospital Pharmacovigilance System (CHPS) (37.8%) (Sun et al, 2020). Moreover, the same study reported that the length of hospital stays, the number of drugs used during hospitalisation, and the underlying diseases were independently predisposing patients to the development of ADRs (Sun et al, 2020). Our study confirmed that the length of hospital stay was a predisposing risk factor for ADR development (p-value = 0.008; 95 %CI 1.216:3.568). Length of hospital stay is evidently associated with negative consciences like increase medical cost, recurrent hospital infections, prescribed unnecessary prescription medications, and delirium among the older adult population. Such complications should be avoided among COVID-19 patients to minimise all the previous factors.

In addition, other studies have shown that gastrointestinal (GI) disorders, liver disorders that are hepatocellular and or cholestatic,

Table 3
Incidence of ADRs per System.

System	ADR	Total	HydroxychloroquineN (%)	Lopinavir/RitonavirN (%)	RibavirinN (%)	FavipiravirN (%)
CNS	Agitation	1	1 (0.68)			
	Headache	6	5 (3.38)	1 (0.90)		
	Dizziness	2	2 (1.35)			
	Insomnia	2	1 (0.68)	1 (0.90)		
	Fatigue	1	1 (0.68)			
	Weakness	2		2 (01.92)		
CVS	SVT	1	1 (0.68)			
	QT Prolongation	4	4 (2.70)			
	Hypotension	2	2 (1.35)			
Endocrine	Hyperglycemia	27		27 (25.10)		
	Hypertriglyceridemia	3		3 (02.88)		
	Increased GGT	15		15 (14.42)		
Hematological	Anemia	32	29 (19.60)		3 (30.00)	
	Thrombocytopenia	12	7 (4.73)	4 (03.85)	1 (10.00)	
	Lymphocytopenia	3			3 (30.00)	
Hepatic	Drug-induced liver injury (AST/ALT/ALP)	89	52 (03.51)	28 (27.00)	5 (50.00)	4 (33.33)
	Increased TBili	12		11 (10.58)	1 (10.00)	
GI	Nauseas	12	8 (05.41)	4 (03.85)		
	Anorexia	1	1 (0.68)			
	Vomiting	20	10 (06.76)	10 (09.62)		
	Diarrhea	26	18 (12.16)	7 (06.73)		1 (08.33)
Renal	Renal insufficiency	14	14 (09.51)			
Total number of ADRs		287	156	113	13	5

Table 4
Incidence of ADRs per Drug.

Drug which caused an ADR	Number of patients received	Number of patients who experienced an ADR	% of patients experienced an ADR	Number of ADRs	Number of ADR per patient
Favipiravir	8	5	63	5	0.6
Hydroxychloroquine	111	93	84	156	1.4
Lopinavir/Ritonavir	85	63	74	113	1.3
Ribavirin	11	7	64	13	1.2

Abbreviations: ADR: adverse drug reaction.

Table 5
Probability, Severity, and Outcomes of ADRs.

Suspicious drug	Number of ADRs	Probability		Severity			Outcome				Average time to ADR
		Possible	Probable	Minor	Moderate	Severe	Ongoing	Resolved	Resolving	Unknown	Time between drug administration and ADR onset (days)
Hydroxychloroquine	156	142	14	131	23	2	31	79	16	30	4.7
Lopinavir Ritonavir	113	100	13	110	3		21	66	14	12	3.9
Ribavirin	13	13		11	2		3	6	1	3	5.1
Favipiravir	5	4	1	5				3	1	1	4.8
Grand Total	**287**	259	28	257	28	2	55	154	32	46	4.4

Abbreviations: ADRs: adverse drug reactions.

endocrine disorders, and expanded to include cardiac disorders (i.e., QTc interval prolongation and arrhythmias) were the most common reported ADRs among COVID-19 patients (Rhodes et al, 2021; Olry et al, 2020; Sun et al, 2020; Tang et al., 2020). Our data has similar results in which out of a total of 287 ADRs that were identified most of them were hepatic (n = 101, 35.2%), gastrointestinal (n = 59, 20.6%), hematological (n = 47, 16%), and endocrine (n = 45, 15%).

Table 6
Predisposing Factors For ADR.

Factors		Relative risk [95% CI]	p-value
Age (Years)	≥60	1.24 [95 %CI 0.67:2.28]	0.490
	40–59	1.3 [95 %CI 0.74:2.26]	0.359
Gender	Female	0.68 [95 %CI 0.39:1.17]	0.161
Severity of disease	Critical	1.35 [95 %CI 0.63:2.91]	0.440
	Severe	1.19 [95 %CI 0.68:2.07]	0.550
ICU admission	Yes	1.06 [95 %CI 0.57:1.96]	0.851
Length of Stay (Day)	greater than20	2.18 [95 %CI 1.14:4.14]	0.018
	10 to 20	2.06 [95 %CI 1.2:3.54]	0.009

Reference groups: Age (age < 40 years); Gender (male); Severity of disease (mild); ICU admission (no admission); length of stay (<10 days)
Abbreviations: ADR: adverse drug reaction; CI: confidence interval; ICU: intensive care unit; Ref: reference.

The incorporation of a Pharmacovigilance Program by Laboratory Signals to identify the incidence of suspected ADRs in COVID-19 patients was also reported at a tertiary care hospital in Spain. They stated that the incidence rate of serious ADRs detected in patients with COVID-19 was 4.75-fold higher than that of the non-COVID-19 patients. The most frequently related drugs were tocilizumab (59.84%), dexketoprofen (13.93%), azithromycin (8.43%), lopinavir-ritonavir (7.35%), dexamethasone (7.62%), and chloroquine/hydroxychloroquine (6.91%). Thus, they recommended cautious use when prescribing these medications for COVID-19 patients (Ramírez et al, 2020). In regard to hydroxychloroquine, our study has similar findings.

We reported that lopinavir-ritonavir was also among the most common drugs associated with ADRs in our patient population. The percentage of reports was 39% of the identified ADRs. Chouchana et al. performed a therapeutic drug monitoring (TDM) of serum levels of lopinavir-ritonavir in 24 COVID-19 patients and compared it to the average plasma concentrations in patients infected with human immunodeficiency virus (HIV) (Chouchana et al, 2021). Higher lopinavir plasma concentrations were documented in COVID-19 patients, increasing by 4.6- to 8-fold (IQR: 3.6–6.2). They explained that lopinavir-ritonavir level increases in inflammatory settings, which is an expected state for COVID-19 patients. Hence, Chouchana et al. concluded that cautious use is recommended as ADR and safety concerns might occur due to this high serum level (Chouchana et al, 2021).

The highest detected ADRs in our study was hepatic abnormalities accounting for 35.2% of identified ADRs, elevated liver function test (LFT) seen in COVID-19 patients could be attributed to many factors, including drugs used for the treatment, pre-existing liver disease, the effect of the virus itself and complicated disease course (Alqahtani and Schattenberg, 2020). The virus might cause direct or indirect damage to liver tissue by many proposed mechanisms, including the influence of angiotensin-converting enzyme 2 (ACE2), systemic inflammatory response, and hypoxic liver injury (Clark et al, 2021; Olry et al, 2020). Nevertheless, in our study, we took this into account and monitored LFT trends before and after starting and stopping the agents in question. When LFTs quickly decreased after discontinuing the suspected agent, we considered this as a probable causality of the treatment.

Detecting and reporting ADRs of mediations used in managing patients with COVID-19 could not be more critical because many of the agents used are off-label indications. A systematic review reported that using off-label indications is associated with higher ADR rates compared to agents used as labelled indications due to a substantial lack of strong evidence (Eguale et al, 2016).

The WHO defines ADRs self-reporting as "the reporting of a suspected adverse reaction on the initiative of the health professional who becomes aware of the problem, or on the patient's initiative". They further state the fact that the success or failure of any pharmacovigilance activity depends on the reporting of suspected adverse reactions (World Health Organization, 2006). Hence, this might be subjected to underreporting.

Aldryhim et al. conducted a questionnaire-based cross-sectional survey that targeted both hospital and community pharmacies in Saudi Arabia. They surveyed 1870 pharmacists and reported that only 10.2% and 26.8% of community and hospital pharmacists, respectively, have never reported an ADR (Aldryhim et al, 2019). Therefore, this has highlighted the issue of ADRs' underreporting in the Kingdom of Saudi Arabia.

Other methods of identifying ADRs include intensive monitoring by an expert team via a prospective review and conducting a prospective or retrospective chart review. Moreover, using computerised systems that generate ADR signals which then undergo evaluation and review by an expert (Miguel et al, 2013).

Underreporting would have a greater impact since COVID-19 has subjected the health care system to stress and understaffing (Mehta et al, 2021). The reporting of ADRs with an active hospital-based pharmacovigilance system is an attractive tool, especially in the era of COVID-19, and would help with the underreported overlooked events. Trigger tool could be useful in detecting preventable ADRs among COVID-19 patients. Such a tool has been used successfully in this patient population (Elbeddini et al., 2020a,b; Ramírez et al, 2020; Sun et al, 2020). Although our study was conducted in a single centre with a small sample size, we highlighted the importance of implementing an active hospital-based pharmacovigilance system in detecting and evaluating possible ADRs. Furthermore, though we tried to eliminate factors other than the medication in question, we cannot exclude it entirely as the disease status might also cause a similar effect.

6. Conclusions

Finding from our study shows that ADRs are common in COVID-19 patients and significantly related to the prolonged hospital stay. Using trigger tools may help health care practitioners to identify preventable ADRs in the ICU settings compared to traditional ADR methods. More studies with a large sample size are needed to confirm our hypothesis. Furthermore, it highlighted the importance of implementing an active hospital-based pharmacovigilance system.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jsps.2022.01.021.

References

Alqahtani, S.A., Schattenberg, J.M., 2020. Liver injury in COVID-19: The current evidence. United European Gastroenterol. J. 8 (5), 509–519. https://doi.org/10.1177/2050640620924157.

American Diabetic Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes—2020, **2020**. Diabetes Care. 43,S66-S76. https://doi.org/10.2337/dc20-S006

Aldryhim, A.Y., Alomair, A., Alqhtani, M., Mahmoud, M.A., Alshammari, T.M., Pont, L. G., Kamal, K.M., Aljadhey, H., Mekonnen, A.B., Alwhaibi, M., Balkhi, B., Alhawassi, T.M., 2019. Factors that facilitate reporting of adverse drug reactions by pharmacists in Saudi Arabia. Expert Opin. Drug Saf. 18 (8), 745–752. https://doi.org/10.1080/14740338.2019.1632287.

Abdul Hadi, M., Neoh, C.F., Zin, R.M., Elrggal, M.E., Cheema, E., 2017. Pharmacovigilance: pharmacists' perspective on spontaneous adverse drug reaction reporting. Integr. Pharm. Res. Pract. 6, 91–98. https://doi.org/10.2147/IPRP.S105881.

Chouchana, L., Boujaafar, S., Gana, I., Preta, L.-H., Regard, L., Legendre, P., Azoulay, C., Canouï, E., Zerbit, J., Carlier, N., Terrier, B., Kernéis, S., Batista, R., Treluyer, J.-M., Zheng, Y.i., Benaboud, S., 2021. Plasma Concentrations and Safety of Lopinavir/Ritonavir in COVID-19 Patients. Ther. Drug Monit. 43 (1), 131–135. https://doi.org/10.1097/FTD.0000000000000838.

Clark, R., Waters, B., Stanfill, A.G., 2021. Elevated liver function tests in COVID-19: Causes, clinical evidence, and potential treatments. Nurse Pract. 46 (1), 21–26. https://doi.org/10.1097/01.NPR.0000722316.63824.f9.

Cai, Q., Huang, D., Yu, H., Zhu, Z., Xia, Z., Su, Y., Li, Z., Zhou, G., Gou, J., Qu, J., Sun, Y., Liu, Y., He, Q., Chen, J., Liu, L., Xu, L., 2020. COVID-19: Abnormal liver function tests. J. Hepatol. 73 (3), 566–574. https://doi.org/10.1016/j.jhep.2020.04.006.

Coleman, J.J., Pontefract, S.K., 2016. Adverse drug reactions. Clin. Med. (Lond) 16 (5), 481–485. https://doi.org/10.7861/clinmedicine.16-5-481.

Cockcroft, D.W., Gault, M.H., 1976. Prediction of creatinine clearance from serum creatinine. Nephron 16 (1), 31–41. https://doi.org/10.1159/000180580.

Elbeddini, A., Yeats, A., Lee, S., 2020a. Amid COVID-19: the importance of developing an positive adverse drug reaction (ADR) and medical device incident (MDI) reporting culture for Global Health and public safety. J. Pharm. Policy Pract. 13 (1). https://doi.org/10.1186/s40545-020-00219-1.

Elbeddini, A., Yeats, A., Lee, S., 2020b. Correction to: Amid COVID-19: the importance of developing an positive adverse drug reaction (ADR) and medical device incident (MDI) reporting culture for Global Health and public safety. J. Pharm. Policy Pract. 13 (1). https://doi.org/10.1186/s40545-020-00231-5.

Eguale, T., Buckeridge, D.L., Verma, A., Winslade, N.E., Benedetti, A., Hanley, J.A., Tamblyn, R., 2016. Association of Off-label Drug Use and Adverse Drug Events in an Adult Population. JAMA Intern. Med. 176 (1), 55. https://doi.org/10.1001/jamainternmed.2015.6058.

Griffin, F.A., Resar, R.K., **2009**. IHI Global Trigger Tool for Measuring Adverse Events (Second Edition). http://www.ihi.org/resources/Pages/IHIWhitePapers/IHIGlobalTriggerToolWhitePaper.aspx. (Accessed 1 June 2020).

Khwaja, A., 2012. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin. Pract. 120 (4), 179–184. https://doi.org/10.1159/000339789.

Kramer, M. S., Leventhal, J. M., Hutchinson, T. A., Feinstein, A. R., **1979**. An Algorithm for the Operational Assessment of Adverse Drug Reactions: I. Background, Description, and Instructions for Use. JAMA. 242(7),623–632. Htts://doi.org/10.1001/jama.1979.03300070019017

Lu, C.C., Chen, M.Y., Lee, W.S., Chang, Y.L., 2020. Potential therapeutic agents against COVID-19: What we know so far. J. Chin. Med. Assoc. 83 (6), 534–536. https://doi.org/10.1097/JCMA.0000000000000318.

Mehta, S., Machado, F., Kwizera, A., Papazian, L., Moss, M., Azoulay, É., Herridge, M., 2021. COVID-19: a heavy toll on health-care workers. Lancet Respir. Med. 9 (3), 226–228. https://doi.org/10.1016/S2213-2600(21)00068-0.

Miguel, A., Azevedo, L.F., Lopes, F., Freitas, A., Pereira, A.C., 2013. Methodologies for the detection of adverse drug reactions: comparison of hospital databases, chart review and spontaneous reporting. Pharmacoepidemiol. Drug Saf. 22 (1), 98–102. https://doi.org/10.1002/pds.3348.

Naksuk, N., Sorin, L., Peeraphatdit, T.B., 2020. Cardiac safety of off-label COVID-19 drug therapy: a review and proposed monitoring protocol. Eur. Heart J. Acute Cardiovasc. Care 9 (3), 215–221. https://doi.org/10.1177/2048872620922784.

Naranjo, C.A., Busto, U., Sellers, E.M., Sandor, P., Ruiz, I., Roberts, E.A., Janecek, E., Domecq, C., Greenblatt, D.J., 1981. A method for estimating the probability of adverse drug reactions. Clin. Pharmacol. Ther. 30 (2), 239–245. https://doi.org/10.1038/clpt.1981.154.

Olry, A., Meunier, L., Délire, B., Larrey, D., Horsmans, Y., Le Louët, H., 2020. Drug-Induced Liver Injury and COVID-19 Infection: The Rules Remain the Same. Drug Saf. 43 (7), 615–617. https://doi.org/10.1007/s40264-020-00954-z.

Petrova, G., Stoimenova, A., Dimitrova, M., Kamusheva, M., Petrova, D., Georgiev, O., 2017. Assessment of the expectancy, seriousness and severity of adverse drug reactions reported for chronic obstructive pulmonary disease therapy. SAGE Open Med. 5. https://doi.org/10.1177/2050312117690404.

Rhodes, N.J., Dairem, A., Moore, W.J., Shah, A., Postelnick, M.J., Badowski, M.E., et al., 2021. Multicenter point-prevalence evaluation of the utilisation and safety of drug therapies for COVID-19. Am. J. Health Syst. Pharm. 78 (7), 568–577. https://doi.org/10.1093/ajhp/zxaa426.

Ramírez, E., Urroz, M., Rodríguez, A., González-Muñoz, M., Martín-Vega, A., Villán, Y., Seco, E., Monserrat, J., Frías, J., Carcas, A.J., Borobia, A.M., 2020. Incidence of Suspected Serious Adverse Drug Reactions in Corona Virus Disease-19 Patients Detected by a Pharmacovigilance Program by Laboratory Signals in a Tertiary Hospital in Spain: Cautionary Data. Front. Pharmacol. 11. https://doi.org/10.3389/fphar.2020.602841.

Ren, L., Xu, W., Overton, J.L., Yu, S., Chiamvimonvat, N., Thai, P.N., 2020. Assessment of Hydroxychloroquine and Chloroquine Safety Profiles: A Systematic Review and Meta-Analysis. Front. Pharmacol. 11. https://doi.org/10.3389/fphar.2020.562777.

Richterich, P., **2020**. Severe underestimation of COVID-19 case numbers: effect of epidemic growth rate and test restrictions. medRxiv [preprint]. https://doi.org/10.1101/2020.04.13.20064220

Sanders, J.M., Monogue, M.L., Jodlowski, T.Z., Cutrell, J.B., 2020. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. JAMA 323 (18), 1824–1836. https://doi.org/10.1001/jama.2020.6019.

Saudi Ministry of Health, Saudi Center For Disease Prevention and Control. COVID-19 Coronavirus Disease Guidelines (version 2), **2020**. COVID-19 Coronavirus Disease Guidelines - Public Health Authority (cdc.gov.sa) (Accessed 01 June 2020)

Sun, J.i., Deng, X., Chen, X., Huang, J., Huang, S., Li, Y., Feng, J., Liu, J., He, G., 2020. Incidence of Adverse Drug Reactions in COVID-19 Patients in China: An Active Monitoring Study by Hospital Pharmacovigilance System. Clin. Pharmacol. Ther. 108 (4), 791–797. https://doi.org/10.1002/cpt.1866.

Tang, W., Cao, Z., Han, M., Wang, Z., Chen, J., Sun, W., et al, **2020**. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ. 369. https://doi.org/10.1136/bmj.m1849

Venkatasubbaiah, M., Reddy, P.D., Satyanarayana, S.V., 2020. Literature-based review of the drugs used for the treatment of COVID-19. Curr Med Res Pract 10 (3), 100–109. https://doi.org/10.1016/j.cmrp.2020.05.013.

Visacri, M.B., de Souza, C.M., Sato, C.M.S., Granja, S., de Marialva, M., Mazzola, P.G., Moriel, P., 2015. Adverse Drug Reactions and quality deviations monitored by spontaneous reports. Saudi Pharm J. 23 (2), 130–137. https://doi.org/10.1016/j.jsps.2014.06.008.

World Health Organization. Coronavirus Disease, **2020**. https://www.who.int/health-topics/coronavirus#tab=tab_1 (Accessed 23 March 2020)

World Health Organization. The safety of medicines in public health programmes: pharmacovigilance, an essential tool, **2006**. https://apps.who.int/iris/handle/10665/43384 (Accessed 03 January 2021)