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Evaluation of Drug-Drug Interactions and Side Effects in COVID-19 Patients in an Intensive Care Unit

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ABSTRACT

BACKGROUND/AIM: Considering comorbidity rates in patients diagnosed with coronavirus disease 2019 (COVID-19), polypharmacy will be inevitable when the treatment for COVID-19 is added to the treatment of existing chronic disease conditions. In our study, we evaluated the effects of comorbidities, drug-drug interactions and complications on the clinical course of the disease in COVID-19 patients.

MATERIALS AND METHODS: This study was conducted retrospectively with thirty five COVID-19 patients of various age and gender groups who had been admitted to the intensive care unit in a university hospital in March and April, 2020. The demographic, laboratory and clinical data were collected.

RESULTS: In our study, the average number of days intubated in patients with acute respiratory distress syndrome and sepsis was found to be statistically significantly higher than those without complications. serious-use alternative interaction was detected in 85.7% of the patients, monitor closely interaction in 60%, and minor interaction in 34.3%. In 88.6% of the patients, at least one of these interactions was observed, while all three interactions occurred at the same time in 20% of them.

CONCLUSION: According to the results of this study, managing the risks, interventions such as drug dosage adjustment, and drug changes and monitoring of any parameters that may indicate drug side effects for the patient may be necessary.

Keywords: COVID-19, intensive care unit, drug-drug interactions, comorbidities, complications

INTRODUCTION

On April 10, 2020, the World Health Organization (WHO) identified the coronavirus disease 2019 (COVID-19) disease as a pandemic, and an estimated 2.3% of patients needed tracheal intubation. Death rates of up to 60% have been reported in critically intubated patients. According to the results of large studies conducted in the United States, 12 to 24 percent of hospitalized patients required mechanical ventilation due to respiratory-related complications.[1]

There is no accepted standard treatment to be applied for the pharmacological treatment of patients with COVID-19 to date. The fact that the treatment strategies are not clearly defined causes confusion about the management of this disease in intensive care units, and when the presence of comorbidities and polypharmacy in patients are added, the situation becomes more complex.[2]

Acute respiratory distress syndrome (ARDS), sepsis, septic shock, arrhythmia, myocarditis, cardiogenic shock and acute kidney injury are conditions that requires patients to be taken into intensive care, and all of them are among the complications of COVID-19.[3]

It is important to pay attention to the pharmacological effects and number of drugs administered to manage a patient's condition. Although those who work in intensive care units are specialist healthcare professionals, some errors may still occur in some cases. Some of the

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main reasons underlying these errors are polypharmacy, inadequate compliance with the principles of rational drug use and drug-drug interactions. Furthermore, the most important factor causing drug-drug interactions is polypharmacy. When the literature is reviewed, it is observed that as the number of drugs used by the patient increases, the rate of drug-drug interaction increases. When the number of drugs used by the patient is more than 5, the drug interaction rate increases by 21%, when this number increases to 10 or above, the interaction rate reaches 100%.[4]

It is a common fact that the use of hydroxychloroquine concomitantly with other drugs that prolong the QT period should be avoided. However, our knowledge about the potential drug-drug interactions that can be caused by drugs used in the treatment of COVID-19, especially antiviral drugs, is limited.[5]

Our study was conducted retrospectively with COVID-19 patients who were admitted to the intensive care unit of a university hospital in March and April, 2020. In our study, we evaluated the effects of comorbidities, drug-drug interactions and complications on the clinical course of the disease in COVID-19 patients.

MATERIALS AND METHODS

The study was approved by the research Ethics Committee of the İstanbul Medipol University (10840098-604.01.01-E.17838). Our study was conducted retrospectively with 35 COVID-19 patients of various age and gender groups who were admitted to an intensive care unit in a university hospital in March and April, 2020. Patients with stage 4 and 5 renal failure or liver failure were not included in this study. The laboratory results of the patients and the drug lists (orders) used in the hospital were collected in order to evaluate the interactions of favipiravir, hydroxychloroquine, azithromycin and tocilizumab used for the treatment of COVID-19 with those drugs used routinely in the intensive care unit as well as any side effects arising from their use. While evaluating interactions and examining side effects, Medscape, Liverpool COVID-19 Interactions, drugs.com, and up-to-date applications were used. The severity of drug interactions was evaluated in three separate categories, namely; serious-use alternative interaction, monitor closely interaction and minor interaction; and the rate at which each type of interaction occurred in patients was also calculated. As a result of these evaluations, the parameters that should be monitored to avoid interactions were determined. Among the variables which were found in all patients, electrocardiograms (ECGs) and laboratory values were examined respectively to check for QT prolongation and to monitor electrolyte levels. The relationship of drug-drug interactions and complications occurring in those patients with existing comorbidities were examined. The effect of complications on the number of days that patients were intubated was evaluated.

Statistical Analysis

SPSS statistics for Windows version 15 (SPSS Inc. Chicago, IL, USA) was used for the statistical analysis. Descriptive statistics are given as number and percentage for categorical variables; mean, standard deviation, minimum, maximum, median, interquartile range are given for numerical variables. The proportions were compared with the chi-square test in independent groups. Independent group comparisons of numerical variables were made using the Mann–Whitney U test for the normal distribution condition. A statistical significance level of alpha was accepted as $p<0.05$.

RESULTS

A total of 35 patients with a mean age of 63.7±13.7 years, a minimum of 30, a maximum of 94 years of age, 23 males (65.7%) 12 females (34.3%) were included in this study. The mean body mass index of the patients was 31.1±4.8 kg/m^2. 91.4% of the patients had additional comorbid diseases. The most common comorbidities were determined to be hypertension (HT) at a rate of 57.1%, Diabetes mellitus (DM) at a rate of 34.3%, Asthma at a rate of 20%, Congestive heart failure (CHF) at a rate of 17.1%, and Coronary artery disease (CAD) at a rate of 14.3%. One patient had cardiac arrest and one patient had hepatotoxicity. Complications developing in patients and their rates were found to be 85.7% ARDS, 22.9% sepsis and 8.6% septic shock. 68.6% of the patients were intubated. The mean time that the patients were intubated was 7.1±5.6 days, and the median was 5 days (Table 1).

The average number of days intubated in patients with ARDS and sepsis was found to be statistically significantly higher than those without complications ($p=0.004$, $p=0.039$) (Table 2).

Serious-use alternative interaction was detected in 85.7% of the patients, monitor closely interaction in 60%, and minor interaction in 34.3%. In 88.6% of the patients, at least one of the interactions was observed, while all three interactions occurred at the same time in 20% of them. The number of serious-use alternatives observed in the patients was found to be a maximum of 9 and a median of 3 [interquartile range (IQR): 1–4], the number of monitor closely Interactions was a maximum of 8 and a median of 1 (IQR: 0–2), and minor interaction was a maximum of 3 and a median of 0 (IQR: 0–1) (Figure 1).

The serious-use alternative interaction rates in patients are summarized in Table 3 in order of frequency. The first column represents the drug combination showing interactions, the second column represents the percentage ratio of the number of patients administered, and the last column indicates the interaction type and parameters to be monitored. Accordingly, the most common parameter to be monitored in the patients is QT prolongation with a rate of 57.14%, which can occur with the simultaneous use of hydroxychloroquine and azithromycin. The combination of drugs that should be avoided and alternative drugs that can be preferred are azithromycin and enoxaparin (37.14%).

The monitor closely interaction rates detected in patients are summarized in Table 4. The most frequent three monitor closely interactions in patients were detected between propofol and midazolam with 11.43%, azithromycin and piperacillin with 8.57%, pantoprazole and clopidogrel with 8.57%.

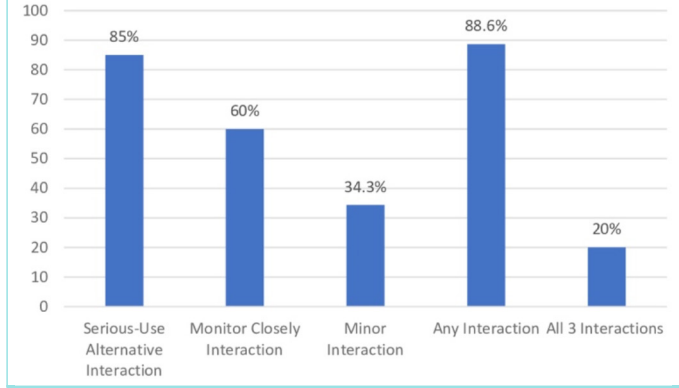

Figure 1. Rates of interaction types observed in patients.

The minor interaction rates determined in patients are summarized in Table 5 in order of frequency. The most frequent minor interaction rate was found between paracetamol and enoxaparin with a rate of 4.76%.

There was no statistically significant change in glomerular filtration rate (EGFR), aspartate aminotransferase (AST)-alanine transaminase (ALT), and SPO_2 values depending on the treatment applied (Table 6).

No statistically significant difference was found in the rates of serious-use alternative Interaction occurrence in patients with comorbidity (Table 7).

Table 1. Categorical variables reflecting the clinical characteristics of the patients

		n
Age, mean ± SD (min-max)		63.7±13.7 (30–94)
Gender, n (%)	Male	23 (65.7%)
	Female	12 (34.3%)
BMI, mean ± SD (min-max)		31.1±4.8 (21.2–43)
Comorbidity, n (%)		32 (91.4%)
Hypertension		20 (57.1%)
Diabetes		12 (34.3%)
Asthma		7 (20.0%)
CHF		6 (17.1%)
CAD		5 (14.3%)
HL		3 (8.6%)
Kidney failure		3 (8.6%)
Ca		3 (8.6%)
Hypothyroidism		2 (5.7%)
BPH		2 (5.7%)
Hypothyroidism		1 (2.9%)
AF		1 (2.9%)
Parkinson/Alzheimer		1 (2.9%)
Meningitis/Encephalitis		1 (2.9%)
Arrhythmia		1 (2.9%)
Panic attack		1 (2.9%)
Neurogenic bladder		1 (2.9%)
Goiter		1 (2.9%)
Cardiac arrest, n (%)		1 (2.9%)
Hepatotoxicity, n (%)		1 (2.9%)
Severe hypoxia, n (%)		0 (0.0%)
Complication, n (%)	ARDS	30 (85.7%)
	Sepsis	8 (22.9%)
	Septic shock	3 (8.6%)
Intubation, n (%)		24 (68.6%)
Number of days intubated, mean ± SD (min–max)		7.1±5.6 (1–26)

BMI: body mass index, CHF: chronic heart failure, CAD: chronic artery disease, HL: hyperlipidemia, Ca: cancer, BPH: benign prostate hyperplasia, AF: atrial fibrillation, ARDS: acute respiratory distress syndrome, SD: standard deviation, min: minimum, max: maximum, n: number.

No statistically significant difference was found between the rates of complications in those patients with or without serious-use alternative, monitor closely and minor interactions (Table 8).

DISCUSSION

In a retrospective study conducted by Mitra et al.[6], on 117 intensive care patients diagnosed with COVID-19, 73.5% of the patients had comorbidity. In our study, it was observed that 91.4% of the patients had additional comorbid diseases.

In our study, similar to the results of Nandy et al.[7] and Rodriguez-Morales et al.[8], the most common comorbidity was determined to be hypertension, but its incidence rate was found to be relatively much higher (57.1%). In our results, hypertension is followed by type II DM (34.3%), asthma (20%), congestive heart failure (17%) and coronary artery disease (14.3%).

Similar to the results of some other studies, the data obtained from our study show that the most common complication seen in our patients is ARDS with a rate of 85.7%. The complications following ARDS were found to be sepsis (22.9%) and septic shock (8.6%).[2,9,10]

Unlike the retrospective cohort study by Manolis et al.[11], cardiac arrest occurred in only 1 patient and no other cardiac damage was detected.

Unlike some studies, there was no significant increase in AST and ALT levels in the patients who were included in our study, and hepatotoxicity developed in only one patient.[12-14]

According to a study by Leung et al.[12], kidney involvement is also common in patients with COVID-19. The incidence of acute kidney injury was found to be around 0.5% to 29%. Acute kidney injury was found in 20% to 40% of COVID-19 patients in need of intensive care in Europe and the USA. In the study of Chen et al.[14], five out of 51 patients had acute kidney injury. Unlike these results, none of our patients developed acute kidney injury.

Compared with the results of the case series examined by Grasselli et al.[10] and the study conducted by Bhatraju et al.[15], the number of patients who needed intubation in our study was low (68.6%).

In the study of Petrilli et al.[1], 23.6% of 5,279 COVID-19 patients needed mechanical ventilation and 60.4% of these patients died.

The results we obtained seem to be consistent with the results of that study (58.3%), but they were significantly higher than the results of

Table 2. The number of days intubated in patients with or without complications

Median (IQR)		Number of days intubated	p-value*
ARDS	None	0 (0–0)	0.004
	Present	5 (1.75–8)	
Sepsis	None	2 (0–6)	0.039
	Present	6.5 (4.25–8.75)	
Septic shock	None	3.5 (0–6.75)	0.112
	Present	8 (5–9)	

*Mann–Whitney U test, ARDS: acute respiratory distress syndrome, IQR: interquartile range.

Mitra et al.[6] (15.4%) and Hur et al.[16] (15.2%).

In the study by Petrilli et al.[1], the most common comorbidities associated with decreased oxygen saturation were determined to be heart failure and chronic kidney disease. Consistent with that study, the fact that at least one comorbidity was seen in 87% of the patients who needed intubation in our study shows that oxygenation is affected by comorbidities in patients with COVID-19.

The fact that the average number of days intubated in patients with ARDS and sepsis in our study was statistically higher than those without complications confirms the results of the study by Lakoh et al.[17].

In our study, the mean duration of intubation of the patients was found to be 7.1±5.6 days, and this result seems similar to the results of the study by Hur et al.[16].

The meta-analysis conducted by Awortwe and Cascorbi[5] advocated that attention should be paid to symptoms that may indicate drug side effects, particularly cardiac arrhythmias, through drug-drug interactions

Table 3. Serious-use alternative interaction rates in patients and the variables to be followed

Serious-use alternative interaction	Number	%	To be followed
Hydroxychloroquine + azithromycin	20	57.14	Qt prolongation
Azithromycin + enoxaparin	13	37.14	Avoid or use alternate drug
Favipiravir + paracetamol	9	25.71	Paracetamol doses should be monitoring
Hydroxychloroquine + metoprolol	6	17.14	Qt prolongation
Hydroxychloroquine + insulin	5	14.29	Decrease doses insulin maybe required
Hydroxychloroquine + rocuronium	5	14.29	Monitor and adjust rocuronium as needed
Azithromycin + amlodipine	4	11.43	Qt prolongation
Hydroxychloroquine + amlodipine	4	11.43	Qt prolongation
Hydroxychloroquine + furosemide	4	11.43	Qt prolongation/electrolyte monitoring
Azithromycin + metoprolol	3	8.57	Qt prolongation
Hydroxychloroquine + propofol	3	8.57	Qt prolongation
Hydroxychloroquine + tocilizumab	3	8.57	Avoid or use alternate drug
Azithromycin + furosemide	2	5.71	Qt prolongation/electrolyte monitoring
Azithromycin + hydrochlorothiazide	2	5.71	Qt prolongation/electrolyte monitoring
Azithromycin + propofol	2	5.71	Qt prolongation
Hydroxychloroquine + hydrochlorothiazide	2	5.71	Qt prolongation/electrolyte monitoring
Hydroxychloroquine + clopidogrel	2	5.71	Use cautiously
Hydroxychloroquine + metoclopramide	2	5.71	Qt prolongation
Piperacillin + enoxaparin	2	5.71	Avoid or use alternate drug
Propofol + norepinephrine	2	5.71	Avoid or use alternate drug
Azithromycin + amiodarone	1	2.86	Qt prolongation
Azithromycin + dexmedetomidine	1	2.86	Qt prolongation
Azithromycin + digoxin	1	2.86	Qt prolongation
Azithromycin + heparin	1	2.86	Avoid or use alternate drug
Azithromycin + ondansetron	1	2.86	Qt prolongation
Digoxin + metoprolol	1	2.86	Avoid or use alternate drug
Heparin + cilostazol	1	2.86	Avoid or use alternate drug
Hydroxychloroquine + amiodarone	1	2.86	Qt prolongation
Hydroxychloroquine + dexamethasone	1	2.86	Use with caution
Hydroxychloroquine + dexmedetomidine	1	2.86	Qt prolongation
Hydroxychloroquine + digoxin	1	2.86	Qt prolongation
Hydroxychloroquine + ondansetron	1	2.86	Qt prolongation
Ketamine + norepinephrine	1	2.86	Use cautiously
Metoprolol + furosemide	1	2.86	Use cautiously
Ceftriaxone + enoxaparin	1	2.86	Avoid or use alternate drug
No interaction	5	14.29	-

Table 4. Monitor closely interaction rates detected in patients

	Monitor closely interaction	
	n	%
Propofol + midazolam	4	11.43
Azithromycin + piperacillin	3	8.57
Pantoprazole + clopidogrel	3	8.57
Enoxaparin + aspirin	2	5.71
Metoprolol + furosemide	2	5.71
Metoprolol + potassium citrate	2	5.71
Midazolam + norepinephrine	2	5.71
Norepinephrine + midazolam	2	5.71
Amiodarone + metoprolol	1	2.86
Aspirin + potassium citrate	1	2.86
Azithromycin + rocuronium	1	2.86
Azithromycin + tolvaptan	1	2.86
Dexamethasone + enoxaparin	1	2.86
Dexamethasone + finasteride	1	2.86
Dexmedetomidine + morphine	1	2.86
Doxazosin + metoprolol	1	2.86
Enocaparin + clopidogrel	1	2.86
Enoxaparin + ibuprofen	1	2.86
Enoxaparin + clopidogrel	1	2.86
Enoxaparin + ramipril	1	2.86
Enoxaparin + ketoprofen	1	2.86
Epinephrine + azithromycin	1	2.86
Epinephrine + furosemide	1	2.86
Furosemide + aspirin	1	2.86
Ketamine + midazolam	1	2.86
Clopidogrel + aspirin	1	2.86
Meropenem + digoxin	1	2.86
Methylprednisolone + enoxaparin	1	2.86
Methylprednisolone + midazolam	1	2.86
Methylprednisolone + rocuronium	1	2.86
Metoprolol + aspirin	1	2.86
Metoprolol + digoxin	1	2.86
Metoprolol + norepinephrine	1	2.86
Metoprolol + propofol	1	2.86
Metoprolol + tolvaptan	1	2.86
Midazolam + epinephrine	1	2.86
Midazolam + norepinephrine	1	2.86
Midazolam + tramadol	1	2.86
Norepinephrine + furosemide	1	2.86
Pentobarbital + midazolam	1	2.86
Pentobarbital + propofol	1	2.86
Pentobarbital + tramadol	1	2.86
Potassium citrate + epinephrine	1	2.86
Potassium citrate + furosemide	1	2.86
Potassium citrate + insulin	1	2.86
Propofol + tramadol	1	2.86
Ramipril + doxazosin	1	2.86
Ramipril + potassium citrate	1	2.86
Telmisartan + insulin	1	2.86
Tolvaptan + digoxin	1	2.86

n: number.

Table 5. Minor interaction rates detected in patients

	Minor interaction	
	n	%
Paracetamol + enoxaparin	5	4.76
Amlodipine + rocuronium	1	0.95
Amlodipine + rocuronium	1	0.95
Ascorbic acid + aspirin	1	0.95
Ascorbic acid + aspirin	1	0.95
Dextroz + magnesium sulphate	1	0.95
Enoxaparin + paracetamol	1	0.95
Ibuprofen + acyclovir	1	0.95
Levetiracetam + paracetamol	1	0.95
Norepinephrine + furosemide	1	0.95
Pentobarbital + pantoprazole	1	0.95
Ceftazidime + aspirin	1	0.95

n: number.

Table 6. Change in EGFR, AST-ALT-SPO_2 values depending on the treatment applied

		Mean ± SD (min-max)	Median (IQR)
EGFR	First day	78.2±34.2 (30–160)	84 (48–107)
	Median day	80.7±45.8 (21–201)	82 (44–109)
	The last day	77.1±38.3 (12–136)	79 (42–108)
	p-value*	0.774	-
AST	First day	50.5±34.0 (10.9–193)	40.7 (28.9–63.3)
	Median day	97.9±172.8 (11.2–900.7)	46.4 (27.6–76.4)
	The last day	63.5±49.4 (11.4–204.3)	48.3 (25.8–85.3)
	p-value#	0.074	-
ALT	First day	35.1±23.8 (4.2–112.7)	32 (17.3–42)
	Median day	86.1±190.0 (3.7–1041)	34.1 (21.3–52.1)
	The last day	64.8±81.4 (3.4–337)	38.1 (22.2–69)
	p-value#	0.165	-
SPO_2	First day	87.8±6.1 (73–100)	88 (84–92)
	Median day. lowest	88.1±12.5 (19–96)	90 (87–93)
	Last day. lowest	87.3±13.6 (20–99)	91 (85–94)
	p-value#	0.592	-
SPO_2	First day	95.8±3.6 (85–100)	96 (93–99)
	Median day. highest	95.3±12.4 (25–100)	98 (96–99)
	Last day. highest	94.7±12.2 (27–100)	98 (95–99)
	p-value#	0.091	-

*Repeated measures ANOVA, #Friedman test.

EGFR: glomerular filtration rate, AST: aspartate aminotransferase, ALT: alanine aminotransferase, SPO_2: oxygen saturation, min: minimum, max: maximum, SD: standard deviation, IQR: interquartile range.

Table 7. Serious-use alternative drug interactions in comorbidities

		Serious-use alternative interaction		p-value
		n	%	
Comorbidity	None	3	100.0%	1.000
	Present	27	84.4%	
Asthma	None	24	85.7%	1.000
	Present	6	85.7%	
Hypertension	None	13	86.7%	1.000
	Present	17	85.0%	
Type I DM	None	29	85.3%	1.000
	Present	1	100.0%	
Type II DM	None	20	83.3%	1.000
	Present	10	90.9%	
Ca	None	27	84.4%	1.000
	Present	3	100.0%	
Neurogenic bladder	None	29	85.3%	1.000
	Present	1	100.0%	
Goiter	None	29	85.3%	1.000
	Present	1	100.0%	
Hypothyroidism	None	29	87.9%	0.269
	Present	1	50.0%	
CAD	None	26	86.7%	0.561
	Present	4	80.0%	
CHF	None	24	82.8%	0.561
	Present	6	100.0%	
Parkinson/ Alzheimer	None	29	85.3%	1.000
	Present	1	100.0%	
BPH	None	28	84.8%	1.000
	Present	2	100.0%	
HL	None	27	84.4%	1.000
	Present	3	100.0%	
Hypothyroidism	None	30	88.2%	0.143
	Present	0	0.0%	
AF	None	29	85.3%	1.000
	Present	1	100.0%	
Meningitis/ Encephalitis	None	29	85.3%	1.000
	Present	1	100.0%	
Kidney failure	None	27	84.4%	1.000
	Present	3	100.0%	
Arrhythmia	None	30	88.2%	0.143
	Present	0	0.0%	
Panic attack	None	30	88.2%	0.143
	Present	0	0.0%	

DM: diabetes mellitus, Ca: cancer, CAD: chronic artery disease, CHF: chronic heart failure, BPH: benign prostate hyperplasia, HL: hyperlipidemia, AF: atrial fibrillation.

in this population. In our study, no statistically significant difference was found in the drug interaction rates resulting from the patients having comorbidity. No statistically significant change was found in the parameters reflecting organ functions (EGFR, AST-ALT, SPO_2, ECG) from the first day to the last day of hospitalization, depending on the treatment we applied in the intensive care unit of our hospital.[5]

In New York city, arrhythmia was reported in 18.5% of 130 patients who needed invasive mechanical ventilation, and 95.8% of these patients developed atrial arrhythmia. In an Italian cohort of 99 patients hospitalized with COVID-19, atrial fibrillation occurred in 19% of all cases and 36% of those patients with underlying cardiovascular disease. The most common cause of drug-related life-threatening ventricular arrhythmias was reported to be antiarrhythmic drug-drug interactions, and 74% of these cases were associated with QT prolongation.[18] In our study, no statistically significant difference was found between drug interaction rates and the occurrence of complications in those patients with complications.

In the study of Hosseinpoor et al.[19], which included 200 COVID-19 patients hospitalized in an intensive care unit, QT prolongation and related drug-drug interactions were evaluated. QT prolongation

Table 8. Complication occurrence rates in patients with and without serious-use alternative interaction

	Serious-use alternative interaction				p-value
	None		Present		
	n	%	n	%	
ARDS	5	100.0	25	83.3	1.000
Sepsis	3	60.0	5	16.7	0.067
Septic shock	1	20.0	2	6.7	0.380
Cardiac arrest	0	0.0	1	4.8	1.000
Hepatotoxicity	0	0.0	1	4.8	1.000
Intubation	4	80.0	20	66.7	1.000
	Monitor closely interaction				**p-value**
	None		**Present**		
	n	**%**	**n**	**%**	
ARDS	13	92.9	17	81.0	0.627
Sepsis	3	21.4	5	23.8	1.000
Septic shock	2	14.3	1	4.8	0.551
Cardiac arrest	1	4.3	0	0.0	1.000
Hepatotoxicity	16	69.6	8	66.7	1.000
Intubation	8	57.1	16	76.2	0.283
	Minor interaction				**p-value**
	None		**Present**		
	n	**%**	**n**	**%**	
ARDS	19	82.6	11	91.7	0.640
Sepsis	4	17.4	4	33.3	0.402
Septic shock	1	4.3	2	16.7	0.266
Cardiac arrest	0	0.0	1	3.3	1.000
Hepatotoxicity	0	0.0	1	3.3	1.000
Intubation	16	69.6	8	66.7	1.000

ARDS: acute respiratory distress syndrome, n: number.

occurred in 10.7% of patients. In a cohort of 138 COVID-19 patients in Wuhan, China, 44% of patients in the intensive care unit and 17% of all patients developed cardiac arrhythmias. Sudden cardiac arrests both in and out of the hospital have also been reported in patients with COVID-19. In a cohort study of 90 patients with COVID-19, those who received a combination of hydroxychloroquine and azithromycin had more QT interval prolongation than those who received hydroxychloroquine alone. Frequent electrocardiographic evaluation should be strongly considered in those patients with COVID-19 treated with hydroxychloroquine and/or azithromycin.[20] In our study, as a result of the simultaneous use of hydroxychloroquine and azithromycin, QT Prolongation was found to be the most common (32.7%) intervention to be followed. ECGs of all our patients were monitored and it was observed that QT prolongation did not occur in any of them.

In the study conducted by Surmelioglu and Demirkan[21] making suggestions about the drugs used on COVID-19 patients in intensive care units in Turkey, it was argued that polypharmacy and comorbidities increase the risk of occurrence of drug interactions. Additionally, organ dysfunctions associated with COVID-19 may affect the severity of drug interactions. Some of their suggestions include: dose adjustment, alternative drug use or drug monitoring in cases where lopinavir and ritonavir are used together; follow-up of the patient by electrocardiography and discontinuation when the clinical situation requires in cases when lopinavir, ritonavir, hydroxychloroquine and azithromycin are used in combination or with other drugs that prolong the QT interval; and dose adjustment due to the risk of increased concentrations of these drugs in the simultaneous use of hydroxychloroquine and amiodarone, dabigatran, edoxaban and immunosuppressants. Therapeutic level follow-up of drugs is among the fundamental suggestions based on the concerns that azithromycin may increase the concentrations of some drugs when used with certain narrow therapeutic index drugs such as digoxin, theophylline and warfarin despite its low drug interaction potential. The drug interaction potential of favipiravir has been found, albeit low, with the simultaneous use of theophylline and paracetamol.[21]

In the study by Brandariz-Nuñez et al.[22], which included 361 COVID-19 patients, a total of 369 potential interactions were recorded with 52 different drugs. 20.92% of these interactions are drug combinations that should be avoided. Among the results found were that 20.92% of interactions are combinations of drugs that should be avoided, 63.32% should consider treatment changes, and the remaining 15.76% require follow-up. In our study, the combination of drugs that should be avoided and alternative drugs that can be preferred was determined to be the most common for the combination of azithromycin and enoxaparin (37.14%).

Similarly to the study of Jyotsna and Hemalatha[23], in our study, serious-use alternative interaction was found in 85.7% of our patients, monitor closely interaction in 60% and minor interaction in 34.3%. Serious-use alternative interactions which recorded the highest rates of occurrence were hydroxychloroquine and azithromycin with 48.57%; enoxaparin and azithromycin with 37.14%; Paracetamol and favipiravir with 25.71%; metoprolol and hydroxychloroquine with 17.14%; Insulin and hydroxychloroquine with 14.29%; Rocuronium and hydroxychloroquine with 14.29%; Amlodipine and azithromycin with 11.43%, amlodipine and hydroxychloroquine with 11.43%; and furosemide and hydroxychloroquine with 11.43%.[23]

Limitations of the Study

Our study has several limitations. It is a single-center study with a relatively low number of patients. The patients were not randomized for treatment but were categorized according to severity when allocated to different therapeutic regimens.

CONCLUSION

Polypharmacy, which is inevitable when the treatment for COVID-19 is added to the treatment of chronic disease conditions in patients diagnosed with COVID-19, is the most important factor that causes drug-drug interactions. Our knowledge on potential drug-drug interactions that may be caused by other drugs used in the management of COVID-19, especially antiviral drugs, is limited. It is assumed that drug-drug interactions and the problems they cause are associated with poor clinical outcomes. In order to manage these risks, interventions such as drug dosage adjustment, drug change and the monitoring of parameters that may indicate drug side effects in the patient may be necessary. Therefore, awareness of drug-drug interactions is vital.

MAIN POINTS

- ARDS and sepsis, which are the most common complications in COVID-19 patients, are associated with longer intubation times.
- Serious-use alternative interaction was detected in the majority of COVID-19 patients in their treatment applied in the ICU.
- Drug-drug interactions caused by polypharmacy and complications in patients are associated with poor clinical response.
- Awareness of drug-drug interactions is vital in COVID-19 patients.

ETHICS

Ethics Committee Approval: The study was approved by the research Ethics Committee of the İstanbul Medipol University (10840098-604.01.01-E.17838).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: N.T., B.Ş., D.K., C.E., Design: N.T., B.Ş., D.K., C.E., Supervision: D.K., C.E., Data Collection and/or Processing: N.T., B.Ş., D.K., C.E., Analysis and/or Interpretation: N.T., B.Ş., D.K., C.E., Literature Search: N.T., B.Ş., D.K., C.E., Writing: N.T., B.Ş., D.K., C.E., Critical Review: N.T., B.Ş., D.K., C.E.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

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