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Drug-Drug Interactions and Prescription Appropriateness in COVID-19 ICU Patients in a Tertiary Care Hospital, Karnataka, India

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Abstract

Severe Coronavirus disease 2019 (COVID-19) management has been challenging due to varying treatment protocol. Additionally, co-morbidities and older age group receiving polypharmacy increases the risk for drug-drug interactions (DDIs).With limited DDI research studies in Indian setup, we aimed to assess the frequency and severity of potential DDIs in COVID-19 ICU patients. This was a retrospective, observational study conducted in a tertiary care hospital, Karnataka, India. Case record of all patients aged ≥18 years with COVID-19 disease admitted to the COVID-19 ICU during March 2021 to July 2021 and treated with two drugs at least were included. A total of one hundred ninety one medical records of COVID-19 patients confirmed by RTPCR were reviewed from medical record department. DDIs were assessed by validated INTERCheck® web system and prescription appropriateness by Beers criteria. Among 191 COVID-19 treated patients, a total of 1049 pDDIs were recorded. Thirty nine percent of the total interactions were classified as potentially severe (class C + class D). Severe pDDIs increased significantly (140 to 274; $p < 0.001$) during hospitalization. Consistently, a significant increase in drug interactions trend was observed during hospitalization (432 to 617; $p < 0.001$). Hence, this study concludes that the severe pDDIs increased significantly during hospitalization and consistent increase in overall (Class A, B, C D) drug interactions trend was observed during hospitalization largely because of the drugs managed to treat comorbidities. Therefore, web based system with multidisciplinary team of expertise may be adopted in hospitals for regulating the dosage of interacting drugs and selecting substitute for overall optimizing the therapy.

Keywords: COVID-19, Drug-drug interaction, Intensive care unit, Prescription appropriateness.

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Introduction

As of 6 February 2022, India reported more than 1,225,011 active cases and over 501,979 deaths related to COVID-19 infection1. Although risk factors associated with coronavirus 2019 disease (COVID-19) have been recognized, co-morbidities and aging are well-recognized self-determining drivers of the development of drug-drug interactions (DDIs)[2-4].

Age-related and age-unrelated co-morbidities usually require polypharmacy for its optimum control, thus aggregating the threat of potential drug-drug interactions (pDDIs), potentially inappropriate medications (PIMs) and drug-specific adverse events[5-7]. However, pDDIs may be intensified in patients with COVID-19 as the polypharmacy burden is increased by the addition of specific treatments along with the medications used for the management of underlying medical comorbidities8. In addition to these, a number of drugs like hydroxychloroquine, methylprednisolone, dexamethasone, prophylactic dose of LMWH (enoxaparin) and investigational therapies like remdesivir and tocilizumab have been recommended for the treatment of moderate to severe COVID-19 disease[9].

Taken together, this puts an extremely high risk of pDDIs, inappropriate medication prescriptions and adverse clinical outcomes, independent of the severity of COVID-19 infection. Therefore an optimized and safer prescription practice in multiple co-morbid conditions and older individuals is often a difficult task. However, to address these issues, various computerized prescription support systems have been developed and one such is INTERCheck® Web System, which stores information on pDDIs, PIMs, dose adjustment in renal impairment cases and modality for drug withdrawal[10,11]. With limited data in the Indian context which addresses the burden of pDDIs and PIMs in COVID-19 ICU patients, we intended to assess the frequency and severity of pDDIs in COVID-19 ICU patients and to evaluate PIMs in a subgroup of patients aged more than 65 years.

Methods

This was a retrospective, observational, single centered study conducted in a tertiary care hospital, in Karnataka, India.

Patients Characteristics

After the ethical approval from the Institutional Ethics Committee and registration in CTRI (No: CTRI/2022/09/045611); case records of all patients aged ≥18 years with COVID-19 disease admitted to the COVID-19 ICU from March 2021 to July 2021 and treated with two drugs at least were included. Patients transferred to other wards from the ICU or discharged/died within 24 hours of admission were excluded. A total of one hundred ninety-one (n = 191) medical records of COVID-19 patients confirmed by RTPCR were reviewed by the Medical Record Department to record the demographic details, co-morbidity conditions, ICU stay and the number and nature of drugs prescribed were collected upon admission and during hospitalization on a pre-designed case report form. The following parameters were evaluated.

Drug-Drug Interactions

It was assessed using a validated INTERCheck® Web System developed by the Istituto Di Ricerche Farmacologiche Mario Negri IRCCS which is updated weekly[12]. According to their clinical relevance; pDDIs are classified as: minor (A, interaction not clinically relevant); moderate (B, interaction associated with an uncertain or variable event); major [C, interaction associated with a serious event, but which can be managed (e.g. by adjusting the dose)]; contraindicated or very serious (D, interaction associated with

a serious event for which co-administration should be avoided or carefully monitored).

Prescription Appropriateness

Appropriateness of drug prescription was evaluated upon admission and during hospitalization by using an American Geriatrics Society 2019 Updated AGS Beers Criteria®[6]. The results were analyzed by using statistical SPSS software version 17.0. Descriptive statistics were used for the categorical variables, which were reported as frequencies and percentages. Mean with standard deviation was expressed for continuous variables. Qualitative variables were analyzed using the Chi-square test and Fischer's exact test. A p-value of ≤ 0.05 was considered statistically significant.

Results and Discussion

Patients Characteristics

One hundred ninety-one medical records of patients with confirmed COVID-19 were evaluated. Table 1 shows the patient's demographic and clinical characteristics. Of the total study population, male sex predominated (55.50%), and the mean age was 51.27 ± 15.66 years (range 18-87). The majority of the study population was in the age group 41-60 years attributing to 40.31%. The median number of medications administered during admission and upon hospitalization was 8 (IQR, 6-9) and 13 (IQR, 11-16) respectively. ARDS (20.42%) was the most common comorbidity, followed by diabetes with hypertension (16.23%) and hypertension (14.66%). Table 2 describes the drugs of different therapeutic classes. Two hundred forty-five prescriptions were antibiotics at the time of admission. Other frequently prescribed were PPIs (n = 158), antiviral drugs (n = 108) and systemic steroids (n = 98). During hospitalization, there was a significant increase in the use of anti-asthmatic drugs (20 to 77, $p < 0.001$), antiviral drugs [(108 to 142, $p < 0.03$; remdesivir (11 to 105; $p < 0.001$)], inhalational steroids (3 to 32, $p < 0.001$), LMWHs (68 to 106, $p < 0.003$) and systemic steroids (98 to142, $p < 0.00451$).

Drug-Drug Interactions

Among the 191 COVID-19 treated patients, a total of 1049 pDDIs were recorded. Thirty-nine percent of the total interactions were classified as potentially severe (class C + class D) with a twofold increase in class D DDIs (Table 3). Severe pDDIs increased significantly (140 to 274; $p < 0.001$) during hospitalization. Consistently, a significant increase in drug interactions trend was observed during hospitalization (432 to 617; $p < 0.001$).

Details of potentially severe DDIs and class B DDIs at admission and during hospitalization are described in Tables 4 & 5. The majority of the potentially severe DDIs observed at admission and during hospitalization increased the risk of QT prolongation attributing to 92.84% and 78.82% respectively. The main drivers for QT prolongation were ceftriaxone plus pantoprazole, ondansetron plus piperacillin, azithromycin plus piperacillin and azithromycin plus ondansetron. According to the credible Meds website, ondansetron, azithromycin, and levofloxacin are classified as 'known risk', piperacillin, pantoprazole, and metronidazole as 'conditional risk' for QT prolongation. DDIs observed due to different steroid administration increased the risk of tendon rupture (1.82%) in levofloxacin recipients, decreased the hypoglycaemic activity of antidiabetic agents (2.97%) and antagonized the action of antihypertensive drugs (1.47%). Table 6 describes the association between variables gender, age, ICU stay and pDDIs. A statistical significant association was found between ICU stay and pDDIs ($p < 0.003$).

Prescription Appropriateness

Of the 191 patients with COVID-19, 41 were aged more than 65 years (21.5%). Among them, 4 patients received only one PIM (9.8%), 9 received two PIMs (21.9%), 6 received three PIMs (14.6%), and 3 received four or more PIMs (7.3%). Among the varied of medications prescribed in study participants, 16 patients (39%) received medications that were categorized as medications potentially clinically important drug-drug interactions to be avoided, 11 patients (26.8%) received medications to be avoided in geriatrics regardless of medical conditions, and 6 patients (14.6%) received medications to be used with caution. The therapeutic classes of PIMs were corticosteroids (39%), non-steroidal anti-inflammatory drugs (39%), insulin (14.6%), diuretics (9.8%), antiplatelet medications (7.3%), anti-cholinergic medications (4.9%), and oral antidiabetes medications (2.4%).

The present study considered March-July 2021 as the study duration, as the larger number of COVID-19 patients required admission. The key finding of this study is that severe pDDIs increased significantly during hospitalization and consistent increase in overall (Class A, B, C D) drug interactions trend was observed during hospitalization largely because of the drugs managed to treat comorbidities and the secondary infection developed during the course of hospitalization.

Higher prevalence of poly-pharmacy (6-9 drugs) is notable in our study population. While concurrent use of five or more drugs is deemed polypharmacy in previous studies[13,14]; extensive polypharmacy is considered to be the use of 10 or more in adults[15].

Varied classes of drugs were used upon admission and during hospitalization (Table 2). An increasing trend in the use of some drugs like remdesivir because of antiviral property[16], systemic steroids because of anti-inflammatory properties and LMWHs due to their prophylactic role and curtailing viral persistence in COVID-19 patients[17] were proposed for treatment of SARS-C0V-2 infection. However, the increase in antibiotic consumption at admission in our study can partly be clarified by usage of azithromycin because of its immunomodulatory property[18] and hence suggesting its role in SARS-CoV-2 infection. We found that 39% of total interactions were potentially severe in nature with a twofold increase in potentially severe DDIs during hospitalization relating to combinations of drugs that should be evaded theoretically or managed by adjusting the dose or by monitoring carefully.

Considering varied of drug combinations which led to different adverse event (Table 4, 5); the most common was cardiac toxicity attributing to almost 80% of the pDDIs during hospitalization. This could due to increased risk of cardiovascular diseases in COVID-19 patients with reported decrease in potassium level leading to electrocardiographic changes[19-22]. Although, DDIs is a challenging task to recognize and to diagnose especially in clinical conditions with multiple comorbidities to clinicians, administration of non-specific drugs for COVID-19 such as azithromycin, pantoprazole, ondansetron, piperacillin with different inherent risk of prolonging QT interval prolongation could be attributable to increased trend in pDDIs during hospitalization as part of COVID-19 management[23]. Therefore, a high level of DDIs in our study could be attributable to several factors such as comorbidities, presence of extensive polypharmacy (median number of drugs prescribed during hospitalization 13; IQR 11-16), and longer hospital stay (median 11; IQR 7-17 days), and many others[24,25].

Although a significant use of remdesivir was observed in our study, it is noteworthy that no clinically important DDIs were noted; which encourages its use in terms of safety which corroborated with study conducted by Cattaneo D et al[12]. Another interesting finding was that the majority of the severe DDIs were determined by PPIs which could be attributable to its theoretical risk of electrolyte disturbances following its prolonged use. Yet the use of PPIs for causing clinically important DDIs is still undervalued[26-28].

Severe COVID-19 infection is linked with excessive inflammatory response which ensues endothelial and haemostatic activation leading to arterial and venous thrombotic state[29]. Therefore DDIs of oral anticoagulants must be anticipated while handling these clinical conditions. However, rivaroxaban and dabigatran were commonly ordered in our study. Among the direct oral anticoagulants (DOACs), rivaroxaban is a substrate for both CYP3A4 and P-glycoprotein (P-gp) transporter and in contrast dabigatran is a substrate only for P-glycoprotein transporter. Hence, co-administration with inhibitors of P-gp transporter and CYP3A4 (e.g., clarithromycin, fluconazole, verapamil) should be evaded due to raised serum concentration of rivaroxaban and dabigatran and hence tendency of bleeding[30]. Additionally COVID-19 patients with underlying cardiovascular diseases may use antiplatelets prophylactically and NSAIDs for symptomatic relief of fever and myalgia and therefore its administration with anticoagulants may escalate the threat of bleeding[31].

Analysis of variables like age, sex, and ICU stay with pDDIs revealed that the occurrence of DDIs is significantly associated with ICU stay which could be explained by the complicated conditions in critically ill patients and polypharmacy which corroborated with the study conducted by Amir Ali Mahboobipour and Shadi Baniasadi[32]. Nearing one-fourth of COVID-19 patients inducted in our study were aged more than 65 years, the threshold age for assessing PIMs. Among the varied PIMs of different therapeutic classes, the majority were corticosteroids and non-steroidal anti-inflammatory drugs. The majority of the patients received medications that were categorized as medications potentially clinically important drug-drug interactions to be avoided, followed by medications to be avoided in geriatrics regardless of medical conditions. This could be possibly explained by the fact that considering the severity of the COVID-19 patients, the treating physicians accepted the risk of DDIs but were not fully aware of the updated Beers criteria for optimizing drug prescriptions.

The strength of the study is that DDI studies among COVID-19 ICU patients are limited. Therefore, data provided by our research can encourage physicians to cautiously prescribe certain medications especially in older elderly and hence to optimize prescription in these set of patients. However, our study has certain limitations. First, the adverse event related to actual DDI was not evident in the patients' records and also the impact of DDIs on clinical outcomes could not be verified due to nature of study design. Second, although we found certain risk factors of DDIs in COVID-19 patients; causal inferences may not be ascertained considering the study design. Finally, it is important that as the new data emerge and constantly changing treatment protocols, physicians need to stay abreast with current trends and be vigilant while administering drugs.

Conclusion

Nearing forty percent of DDIs were severe in nature. Consequently, COVID-19 patients treated with medications with inherent

property of prolonging QT interval and cardiovascular comorbidity are at increased risks of cardiotoxicity. Therefore, web based system with multidisciplinary team may be adopted in hospitals for regulating the dosage of interacting drugs and selecting substitute for over all optimizing the therapy.

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Conflict of Interest
None declared.

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Table 1. Demographic and clinical characteristics of COVID-19 patients [N= 191]

Characteristics	Number (n)	(%)
Age (years)		
< 40	60	31.4
41-60	77	40.3
>61	54	28.3
Sex		
Male	106	55.5
Female	85	44.5
Comorbidities		
Acute Respiratory Distress Syndrome	39	20.4
Diabetes with Hypertension	31	16.2
Hypertension	28	14.7
Diabetes	27	14.1
Chronic Obstructive Pulmonary Disease	4	2.1
Asthma	3	1.6
Cerebrovascular Accidents	3	1.6
Chronic Kidney Disease	2	1.04
Deep Vein Thrombosis	2	1.04
Parkinson Disease	2	1.04
Hypothyroidism	1	0.5
Characteristics	**median (IQR)**	
Length of stay (in days)	11 (7-17)	
No of drugs prescribed,		
On admission	8 (6-9)	
During hospitalisation	13 (11-16)	

IQR:inter-quartile range

Table 2. Distribution of drug classes at admission and during hospitalization [N= 191]

Therapeutic class (examples of often-prescribed drugs	At admission n (%)**	During hospitalization n (%)**	p-value (Chi square/Fisher's exact test)
ACEI/ARBs (enalapril, telmisartan)	07 (3.6)	13 (6.8)	0.18
Antiasthmatic drugs (acebrophylline, formeterol, salmeterol and combinations withother antiasthmatic drugs)	20 (10.5)	77 (40.3)	<0.001*
Antibiotics (azithromycin, ceftriaxone, piperacillin+tazobactum)	245	160	<0.001*
Antiemetic drugs (ondansetron)	67 (35.1)	38 (19.9)	0.004*
Antiviral drugs (oseltamivir, remdesivir)	108 (56.5)	142 (74.3)	0.03*
CCBs	11 (5.8)	28 (14.7)	<0.001*
Inhalational steroids (budesonide, fluticasone)	03 (1.6)	32 (16.8)	<0.001*
LMWHs (enoxaparin, dalteparin)	68 (35.6)	106 (55.5)	<0.001*
PPIs (pantoprazole)	158 (82.7)	140 (73.3)	0.29
NSAIDs (paracetamol)	63 (32.9)	29 (15.2)	<0.001*
Systemic steroids (methylprednisolone, dexamethasone)	98 (51.3)	142 (74.3)	0.004*

*denotes p-value as statistically significant. ** Percentage may not add up to 100% because of multiple medications prescribed.

Direct Oral Anticoagulants (DOACs) and insulin was used only during the hospitalization i.e. in 26 and 13 patients respectively. Thus they were excluded from the analysis.
ARBs: angiotensin receptor blockers; ACEi:angiotensin converting enzyme inhibitors; CCBs:calcium channel blockers; LMWHs:low molecular weight heparin; PPIs:proton pump inhibitors; NSAIDs:non-steroidal anti-inflammatory drugs

Table 3. Distribution of pDDIs at admission and during hospitalization

Class	At admission	During hospitalization	p - value (Chi square/Fisher's exact test)
Class A	2	4	0.41
Class B	290	339	0.050*
Class C	50	78	0.013*
Class D	90	196	< 0.001*

*denotes p-value as statistically significant. pDDIs: potential drug-drug interactions

Table 4. Prevalence of the first 10 potentially severe drug-drug interactions (DDIs) at hospital admission and during hospitalization

Drug combination	Potential adverse events	Patients (n (%)) At admission	During hospitalization
Ceftriaxone + pantoprazole	Increased risk of cardiotoxicity i.e. QT interval prolongation, cardiac arrest, torsade de pointes,)	50 (35.7)	57 (20.8)
Ondansetron + piperacillin		23 (16.4)	42 (15.3)
Azithromycin + piperacillin		22 (15.7)	44 (16.1)
Azithromycin + ondansetron		28 (20.0)	37 (13.5)
Azithromycin + levofloxacin		03 (2.1)	08 (2.9)
Piperacillin + levofloxacin		03 (2.1)	08 (2.9)
Ondansetron + levofloxacin		01 (0.7)	09 (3.2)
Piperacillin + metronidazole		0	06 (2.2)
Metronidazole + ondansetron		0	05 (1.8)
Prednisolone + levofloxacin	Increased risk of tendon ruptures	0	05 (1.8)

Table 5. Prevalence of first 10 Class B DDIs at hospital admission and during hospitalization

Drug combination	Potential adverse event	Patients (n (%)) At admission	During hospitalization
Pantoprazole + ondansetron	Increased risk of cardiotoxicity i.eQT interval prolongation, torsade de pointes, cardiac arrest	64 (22.01)	88 (25.9)
Pantoprazole + piperacillin +		58 (20.0)	91 (26.8)
Azithromycin + pantoprazole		55 (18.9)	63 (18.6)
Pantoprazole + metronidazole		02 (0.7)	15 (4.4)
Pantoprazole + levofloxacin		04 (1.4)	11 (3.2)
Metformin + Prednisolone	Concomitant intake may decrease the hypoglycaemic activity of antidiabetic agents	0	05 (1.5)
Dexamethasone + Metformin		0	05 (1.5)
Dexamethasone + Telmisartan	Corticosteroids antagonize the action of antihypertensive drugs	0	05 (1.5)
Pantoprazole + dabigatran	Reduction of the absorption and bioavailability of dabigatran	0	04 (1.2)
Atorvastatin + clopidogrel	Possible reduction of the metabolic activation of clopidogrel and its therapeutic efficacy	0	02 (0.6)

Table 6. Association between variables gender, age, ICU stay and pDDIs [N= 191]

Variables	Interaction (n=166)	No interaction (n=25)	Odds ratio 95% CI	p-value (Chi square/Fisher's exact test)
Gender				
Male	93	13	0.85 (0.36-1.97)	0.71
Female	73	12		
Age				
< 60	103	16	1.08 (0.45- 2.6)	0.84
≥ 60	63	9		
ICU stay, days				
< 11	68	18	3.7 (1.46-9.35)	0.003*
≥ 11	98	7		

*denotes p-value as statistically significant.
ICU: intensive care unit; pDDIs: potential drug-drug interactions; CI: confidence interval