Analysis of pharmacological interventions among hospitalised patients with COVID-19: A focus on severe cases

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Abstract. Existing recommendations regarding pharmaceutical interventions for patients with coronavirus disease 2019 (COVID-19) focus on outpatient, inpatient and post-discharge care. However, there are no studies examining the actual activities of pharmacists in relation to hospitalised patients. The present study aimed to identify pharmacists' roles by analysing cases of pharmaceutical interventions, particularly for patients admitted to high-care units. Pharmacological interventions were provided to patients with severe COVID-19 or patients at high risk of severe disease in 2021. These pharmaceutical interventions were analysed and evaluated. Pharmacists also developed a COVID-19 drug compatibility chart for use by care team members. In the present study, 54 patients were included, of which 33 were severe cases. A total of 28 patients (52%) received pharmacological interventions and 25 of them were severe cases. Out of 68 pharmacological interventions, interventions for antimicrobial agents were the most common (28 interventions), followed by nutrition and anti-COVID-19 drug-related interventions. In addition, the need for interventions relating to drug compatibility was reduced by ~43% after the drug compatibility chart was implemented. In conclusion, pharmacists have a responsibility to improve the quality of pharmacotherapy for patients with COVID-19. They should focus on creating specific pharmacotherapy tools for patients with COVID-19 and supporting appropriate antimicrobial use for secondary bacterial infections.

Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease that continues to have a major worldwide impact. Governments have been imposing strong infection control measures to minimise the negative impacts of COVID-19, such as maintaining physical distancing and wearing masks (1). It is important to provide prompt and high-quality medical care for patients with COVID-19 who require medical interventions. Thus, pharmacists, as members of the healthcare team, have an important responsibility to improve the quality of drug therapy.

While numerous efforts have been made by healthcare providers to improve the quality of care for patients with COVID-19, the role of the pharmacist in this process has remained to be clarified (2,3). The pharmacist's role has been proposed to include medication counselling, management of long-term prescriptions to reduce the frequency of hospital visits and drug delivery (4,5). These activities are generally related to supporting outpatient care for patients with comorbidities who require long-term management, although there are several consistent recommendations regarding the tasks expected of pharmacists for patients hospitalised with COVID-19 (6,3). Simply put, pharmacists should support pharmaceutical care services by participating in making evidence-based decisions for medication, monitoring and evaluating medication safety and efficacy, providing enhanced care for special populations and patients with combined underlying diseases, monitoring and management of convalescent plasma therapy, providing emotional counselling and psychological support, and providing scientific information about COVID-19 vaccines. However, there have been few studies on pharmacists' actual approaches to inpatient pharmacotherapy in the context of COVID-19 (7).

At the same time, there is abundant evidence for the role of pharmacists in managing hospitalised patients without COVID-19. The Society of Critical Care Medicine has proposed 82 types of roles for pharmacists, including patient care and improving the quality of medical care. Above all, ensuring the safety and effectiveness of drug therapy is an essential task for pharmacists (8). Patients with severe COVID-19 require endotracheal intubation and must receive multidisciplinary treatment. Among these, drug therapy occupies an important place, with antiviral therapy centered on remdecivir, immunomodulatory therapy with steroids and tocilizumab, and anticoagulation therapy. Numerous other drugs are also in use, including antimicrobial therapy for complicated infections and analgesics and sedatives for pain during endotracheal intubation. Therefore, pharmacists, as experts in pharmacology, need to contribute to safe and effective drug therapy.

Against this background, the present study retrospectively examined pharmacist interventions among hospitalised

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patients with COVID-19, particularly severe cases. By doing so, the present study aimed to clarify the pharmacist's role in COVID-19 inpatient admissions and to identify standardised tasks to be performed by pharmacists.

Patients and methods

Selection of cases. Patients with COVID-19 admitted to the emergency center of Ogaki Municipal Hospital (Ogaki, Japan) between the 1st of January and 31st of December 2021 were included in the present study. Enrolment in this study was done retrospectively. This hospital had been designated as a COVID-19 priority medical institution in the Gifu Prefecture of Japan; nine beds in the emergency center were reserved for patients with severe COVID-19 or those at high risk of severe disease. This study included all patients who used these beds. An overview of the present study is provided in Fig. 1.

Intervention by pharmacists. During the study period, the clinical pharmacist in charge of ward pharmacy services at the high-care units provided pharmacological management for patients with COVID-19. The high-care unit is a ward that is commonly used in Japan to care for critically ill patients, similar to the intensive care unit. A clinical pharmacist collected patient information from electronic medical records to perform pharmacy management, and in addition, information was collected from physicians, nurses and other healthcare professionals as necessary. For severe cases of COVID-19, the pharmacist participated in weekday conferences with physicians, nurses, physical therapists and clinical engineering technicians to share information. The pharmacist addressed pharmacological management issues and interventions to improve the quality of patient care.

In addition, to aid comprehension of drug compatibility for injectable drugs, a drug compatibility chart was created exclusively for patients with COVID-19, which had been put into operation on the 1st of August 2021. The drug compatibility chart was limited to those drugs that were frequently used by physicians dealing with severe cases. The chart was also designed concisely so that it could be easily referred to, even during busy working hours while wearing personal protective equipment. In addition, it depicted examples of intravenous injection route combinations of the commonly used drugs. This table was prepared with reference to those that have been reported to be useful in the past (9,10). The chart is presented in Table I.

Evaluation methods. Interventions by pharmacists were classified according to their content. Two methods were used for classification. First, the interventions were classified according to the reason for the use of the drug that was the subject of the intervention and its pathophysiology. For instance, a case in which the pharmacist proposed steroid administration considering the stage of COVID-19 or discontinuation of remdesivir was classified as an 'intervention for COVID-19 drugs'. Second, referring to previous research (6,3), the interventions were categorised according to their purpose: i) Evidence-based decisions for medication; ii) medication safety; iii) medication efficacy; iv) drug interaction and management; v) pharmaceutical care for special populations; and vi) pharmaceutical care for patients with combined underlying diseases. Each item was counted for interventions relating to multiple items. For instance, designing antimicrobial dosing for haemodialysis patients fulfilled items ii), iii) and v). Pharmacist interventions that were continuous over a long period, such as drug blood level monitoring, were counted as a single intervention.

In the present study, patients were classified by respiratory physicians upon admission according to the severity classification widely used in Japan (11): Mild disease (no pneumonia), moderate disease I (no respiratory failure), moderate disease II (pneumonia but no ventilatory management) or severe disease (mechanical ventilation required).

Statistical analysis. The usefulness of the injectable drug compatibility chart was evaluated using Fisher's exact test for the proportion of intervention cases prior to and after the start of its operation. EZRver2.3 (The R Foundation for Statistical Computing) was used for all statistical analyses. $P<0.05$ was considered to indicate statistical significance.

Results

Patient characteristics. A total of 54 patients were included in the present study, with 33 cases of severe disease and 16 cases of moderate disease II. There were also 2 mild and 3 moderate I cases who were considered to be at high risk for severe disease. Details on the patients' backgrounds are presented in Table II. Of these patients, 28 (52%) were subjected to pharmacist interventions, 25 of which were severe cases. There were 68 pharmacist interventions in total.

Classification of pharmacist interventions for patients with COVID-19. The classification of pharmacist interventions is indicated in Table III. In terms of target drugs or conditions, antimicrobial interventions were the most common, accounting for 28 cases (41.2%). This was followed by interventions related to nutrition and infusion (10.3%), as well as COVID-19 drugs (8.8%). In addition, according to the abovementioned classification, based on previous studies (6,3), interventions related to the safe use of medicines were the most common, followed by interventions focused on achieving high efficacy.

Table IV provides examples of pharmacist interventions for the patient population of the present study. The most common intervention was the recommendation to change to an appropriate antimicrobial agent due to the detection of drug-resistant bacteria. The most common intervention was to suggest appropriate antimicrobials for drug-resistant organisms. Another common intervention was therapeutic drug monitoring to maximize efficacy and contribute to safety.

Outcomes from the use of the specific COVID-19 treatment drug compatibility chart. Before to the use of the drug compatibility chart, pharmacist interventions for drug compatibility were provided to 9 of 34 patients (26.5%). After its use, 3 of 20 patients (15.0%) received interventions. There was no statistically significant difference between the two groups (P=0.5). With regard to severe cases, interventions were performed in 9 of 21 (42.9%) cases before the chart's use and 3 of 12 (25%) cases after its use. There was no significant difference between the two groups (P=0.5). Obstruction of the

Table I. Drug compatibility chart for severe COVID-19 cases: Combination of continuous injections that should not be mixed.

Drugs	Amino acid	Dobutamine	Nicardipine	Nor-adrenaline	hANP	Insulin	Furosemide	Heparin
Amino acid			x		x			
Dobutamine					x			x
Nicardipine	x					x		
Nor-adrenaline						x		
hANP	x	x				x	x	x
Insulin			x	x	x			
Furosemide					x			
Heparin		x			x			

Examples of frequently used infusions: i) Fluid 3 + insulin + fentanyl; ii) lactated ringer + hANP + (nicardipine or nor-adrenaline); iii) DEX + (nicardipine or nor-adrenaline) + dobutamine. Drugs that are injected intravenously as a single dose, such as antibiotics, are administered through i). COVID-19 injection route: Fluid 3, fentanyl, DEX, nitroglycerin and propofol may be injected from anywhere. Lactated ringer and nicardipine (>5 ml/h) should be used with caution (the position of lactated ringer should be changed). Fluid 3, maintenance fluid in Japan; DEX, dexmedetomidine; hANP, human atrial natriuretic peptide; COVID-19, coronavirus disease 2019.

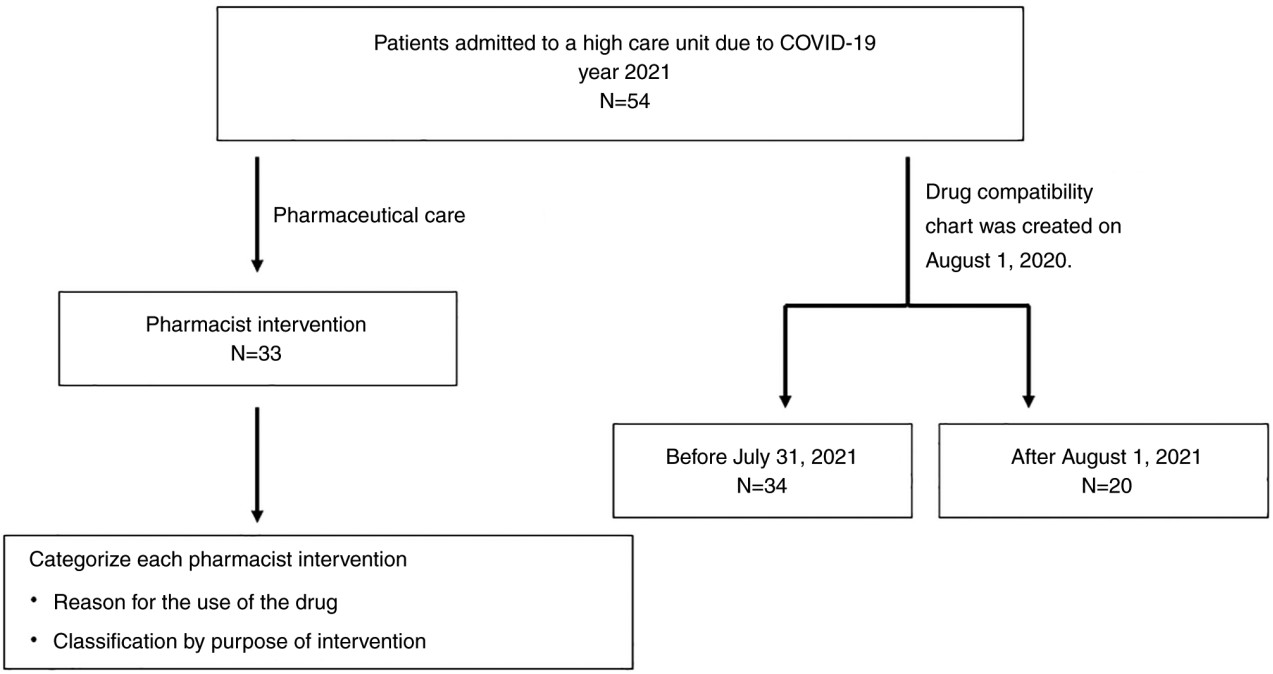

Figure 1. Schematic diagram for the present study.

intravenous administration route occurred once before and once after the use of the drug compatibility chart.

Discussion

The present study provides information on the role of pharmacists in team care for patients with COVID-19 admitted to an intensive care unit. The study demonstrates that several pharmacist interventions are used, particularly for severely ill patients with COVID-19. In other words, pharmacists may improve the quality of drug treatments for patients with COVID-19 through a variety of interventions. The study also suggests that providing information about antimicrobials and combination changes to patients with COVID-19 is an important task for pharmacists.

Klopotowska *et al* (12) reported that antimicrobial-related interventions accounted for 23.4% of all prescribing interventions by resident pharmacists in intensive care units. In the present study, antimicrobial-related interventions accounted for the largest proportion of pharmacist interventions, i.e. ~40%. The reason for the higher rate of antimicrobial interventions than in previous studies may be that secondary bacterial infections frequently occur in patients with COVID-19. Infections caused by drug-resistant organisms such as methicillin-resistant *Staphylococcus aureus* are particularly problematic in severe cases (13). In general, the treatment of drug-resistant organisms frequently involves a difficult choice of antimicrobial agents; drugs that require therapeutic drug monitoring, such as vancomycin, are often necessary. In addition, severe COVID-19 cases

Table II. Patient characteristics (n=54).

Parameter	Value
Age, years	64 (50-73)
Male sex	37 (68.5)
Body mass index, kg/m^2	25.9 (22.3-31.5)
Body weight, kg	69.5 (57.3-86)
Hemodialysis treatment	2 (3.7)
Underlying diseases	
Diabetes	17 (31.4)
Hypertension	11 (20.3)
Stroke	8 (14.8)
Pulmonary diseases[a]	7 (13.0)
Tumor	3 (5.6)
Severity[b]	
Mild	2 (3.7)
Moderate I	3 (5.6)
Moderate II	16 (29.6)
Severe	33 (61.1)
Medical intervention	
Mechanical ventilation	32 (59.3)
Extracorporeal membrane oxygenation	2 (3.7)
Remdesivir	47 (87.0)
Steroid	50 (92.6)
Antithrombotic drugs	18 (33.3)
Antibiotics	36 (66.7)
Intubation or until tracheostomy, days	14 (11-20)
Length of stay, days	24 (15-38)
Length of stay in high care unit, days	13 (5-19)
Clinical outcome	
Home discharge	35 (64.8)
Transfer or institutional discharge	7 (13.0)
Death	13 (24.1)

Values are expressed as n (%) or median (interquartile range). [a]Chronic obstructive pulmonary disease and asthma; [b]Patients were classified by respiratory physicians upon admission according to the severity classification widely used in Japan: Mild disease (no pneumonia), moderate disease I (no respiratory failure), moderate disease II (pneumonia but no ventilatory management) or severe disease (mechanical ventilation required).

Table III. Classification of pharmacological interventions.

A, Classification by target drug or condition of intervention (n=68)

Pharmacological intervention	N
Antimicrobial agent	28
Nutritional supplements and infusions	7
Anti-COVID-19 drugs	6
Antithrombotic drugs	5
Medication for underlying diseases	4
Sedation and delirium medications	2
Diuretics	2
Others	1
Compatibility management	13

B, Classification based on previous studies (n=68 cases) (3,7)

Pharmacological intervention	N
Evidence-based decision-making for medication	6
Monitoring and evaluation of medication safety	37
Monitoring and evaluation of medication efficacy	28
Drug interaction management	14
Pharmaceutical care for special populations	17
Pharmaceutical care for patients with combined underlying diseases	5
Others	2

COVID-19, coronavirus disease 2019.

frequently occur among elderly patients with impaired organ function and obese patients, for whom drug doses must be carefully adjusted (14,15). Furthermore, while intravenous antimicrobials are used in >80% of patients with severe COVID-19 (16), complications from bacterial infection are thought to occur in ~8% of cases (17). Thus, the inappropriate use of antimicrobial agents may be an issue; therefore, such treatments must be optimised. Accordingly, pharmacists with expertise in antimicrobial chemotherapy are expected to have a significant role in the care of critically ill patients with COVID-19.

Providing information on drug compatibility accounted for 19% of the pharmacist interventions. In the present study, pharmacists were unable to perform bedside intravenous drip route checks from an infection control perspective. Therefore, interventions were required to be based on prescription details and information about the intravenous route from care team members, considering the risk of drug compatibility. Consequently, the route of administration was required to be discussed for most cases over time, which required significant effort among care team members. Pharmacists attempted to simplify this process by creating a drug compatibility chart.

In the present study, the usefulness of the chart could not be statistically confirmed. However, after the creation of the drug compatibility chart, the number of situations in which pharmacist interventions were necessary decreased by ~43%, which may have reduced the burden on the medical team and on the patients. There have been several studies on drug compatibility charts and their usefulness (9,10). However, no studies have focused on the creation of a chart tailored to the characteristics of COVID-19. In caring for patients with COVID-19, the creation of individualised tools that focus only on drugs suitable for these patients and are easily visible even when personal protective equipment is required. Creating effective tools to minimise drug-related problems is an important responsibility for pharmacists.

The present study has several limitations. First, the study reported from a single center and thus did not consider the impact of facility conditions and care team skills. Another

Table IV. Examples of pharmaceutical interventions.

Summary of pharmaceutical intervention	Intervention target drugs	Expected benefits	Number of cases with similar interventions within the present study
Therapeutic drug monitoring of vancomycin in patients with severe obesity or renal failure	Antibiotics	Maximisation of effectiveness and minimisation of side effects	7
Recommendation to change to an appropriate antimicrobial due to the detection of drug-resistant bacteria	Antibiotics	Maximisation of effectiveness	8
Recommendations for antimicrobial dosing according to renal function and other factors	Antibiotics	Maximisation of effectiveness and minimisation of side effects	4
Recommendation to end unnecessary zinc supplementation	Nutritional supplements	Minimisation of side effects; cost reduction	2
Recommendation to change from oligomeric formula enteral nutrition to polymeric formula enteral nutrition for patients without gastrointestinal tract function problems	Nutritional supplements	Increase of physiological nutrient supply	2
Recommendation to discontinue remdesivir in palliative treatment patients	Anti-COVID-19 drugs	Minimisation of side effects; cost reduction	1
Recommendation to discontinue remdesivir dosing beyond 10 days	Anti-COVID-19 drugs	Evidence-based treatment practices; cost reduction	1
Recommendations for anticoagulant use or activated partial thromboplastin time monitoring in patients experiencing atrial fibrillation	Antithrombotic drugs	Evidence-based treatment practices	4
Recommendations not to interrupt antiplatelet medications in patients with a history of myocardial infarction	Medication for underlying diseases	Evidence-based treatment practices	2
Recommendation to discontinue diuretics in anuric patients dependent on hemodialysis	Diuretics	Minimisation of side effects; cost reduction	1

COVID-19, coronavirus disease 2019.

limitation is the small sample size. The sample size and intervention rate of the present study yielded a statistical power of 0.09; this value is low and the results should thus be interpreted with caution. However, the 43% reduction in the requirement of pharmacist intervention for drug compatibility is clinically important. Furthermore, the present study analysed the content of pharmacist interventions; however, there is limited information on whether these interventions led to improved clinical outcomes. In addition, as pharmacy management was conducted without any direct patient observation in terms of infection control, information related to efficacy and side effects was only obtained at the case review by the care team, which may have led to a decrease in the quality and number of interventions. It is esteemed that future studies will address these issues.

COVID-19 is a new infectious disease with a short history and its pharmacological treatment is still evolving. In the present study, interventions were applied that led to the appropriate use of remdesivir. In other words, pharmacists are required to organise information about COVID-19 drugs and provide interventions that promote their proper use. In addition, diabetes mellitus and cerebral infarction have been reported as risk factors regarding the severity of COVID-19 and a large proportion of patients with underlying diseases are at risk (18). In other words, numerous patients with COVID-19 are taking certain medications prior to admission and supporting seamless pharmacy management for patients with severe disease is a key task for pharmacists.

In summary, the present study indicated that pharmacists have a responsibility to improve the quality of pharmacotherapy for patients with COVID-19, with a focus on creating specific medication-related tools and supporting the appropriate use of antimicrobials for secondary bacterial infections.

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Availability of data and materials

The datasets generated and analyzed in this study are available from the corresponding author upon reasonable request.

Authors' contributions

YS conceived and designed the study, acquired and interpreted the data and wrote the manuscript. KO, TM and TY contributed to the interpretation of the data. All authors have read and approved the final manuscript. YS, KO, TM and TY reviewed manuscript and confirm the authenticity of all the raw data.

Ethics approval and consent to participate

In accordance with the ethical code of our hospital, opt-out consent was obtained for all patients. This study was conducted in accordance with the Ethical Guidelines in Japan with approval from the Clinical Research Review Committee at Ogaki Municipal Hospital (Ogaki, Japan) and with considerations for the protection of personal information (approval no. 20220428-14).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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