J Young Pharm, 2022; 14(3) : 322-326
A multifaceted peer reviewed journal in the field of Pharmacy
www.jyoungpharm.org | www.phcog.net

Original Article

The Association of Medication Complexity with COVID-19 Severity and its Impact on Pharmacotherapy Evaluation

Yogendra Shrestha*, Rajesh Venkataraman, Jeet Bahadur Moktan, Sonakshi Mallikarjuna, Sindhu Shree Narayan, Manisha Hemmige Madappa, Priyanka Anekere Satya
Department of Pharmacy Practice, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, BG Nagara, Nagamangala, Karnataka, INDIA.

ABSTRACT

Background: Off-level medicines do not provide adequate health outcomes since there is insufficient efficacy and/or toxicity evidence. Off-level medicines are more vulnerable to adverse drug reactions (ADRs), which are a prominent cause of morbidity and mortality. Objective of the study is to determine the relationship between the medication complexity and severity of COVID-19 and its impact on pharmacotherapy evaluation. **Materials and Methods:** A prospective, cross-sectional study was conducted in the COVID ward where medication complexity was assessed for all prescriptions on admission using the Medical Regimen Complexity Index's guidelines and subjected to pharmacotherapy evaluation. **Results:** Overall, the patients spent an average of 7.55 ± 3.60 days in the hospital. Each prescription contained an average of 6.54 ± 2.51 drugs. Polypharmacy was found in 82.70% (263) of the prescriptions, while medication duplication was found in 17.29% (55), severe drug interactions accounted for 83.01% (264), and drug dosage adjustment was performed in 10.06% (32). The mean medication complexity was 26.86 ± 7. 58. When comparing medication complexity concerning the severity of COVID-19, we found that the average medication complexity score for mild was 24.62 ± 6.04, moderate was 31.65 ± 8.39, severe was 35.19 ± 6.81, and critical was 28.59 ± 8.60. we found a statistically significant positive correlation between the medical complexity and the hospital stay (P-value, 0.000), and there was an association between the medication complexity and the Covid-19 severity (p <0.001). **Conclusion:** The assessment of the medication complexity in routine pharmacotherapy evaluations could be beneficial in alerting potential risks, suggesting additional focus wherever required, and decreasing the financial burden by reducing hospital stay. It demonstrated an association between medication complexity and the severity of COVID-19.

Keywords: Pharmacotherapy Evaluation, Medication Complexity, Drug Interaction, Polypharmacy, Medication Duplication, Dosage Adjustment.

Correspondence

Dr. Yogendra Shrestha,

Department of Pharmacy Practice, Sri Adichunchanagiri College of Pharmacy, Adichunchanagiri University, BG Nagara-571448, Nagamangala, Karnataka, INDIA.

Email id: dryogendrastha@gmail.com

DOI: 10.5530/jyp.2022.14.63

INTRODUCTION

Although scientific efforts to develop focused medicine are ongoing, the symptomatic approach to treatment and prevention remains the best option for COVID-19 treatment. A wide range of medications is being used off-label as symptomatic treatments in combinations that may not provide adequate health outcomes due to a lack of efficacy and/or toxicity evidence.[1-3] This increases the number of medications on prescription as well as their complexity. The medication complexity can be determined by the number of medicines (polypharmacy) prescribed, the frequency per day, the route of administration, and the administration instructions.[4-6]

Complicated medication regimens are more susceptible to adverse drug reactions (ADRs), the risk of developing a drug-drug interaction (DDI), and errors, which are a leading cause of morbidity and mortality and a significant financial burden.[4-7]

In their study, Ji Sun *et al*. reported 37.8 percent of ADRs with COVID-19 treatment, with 96.8 percent occurring within 14 days of admission.[8] ADR risk increases by 3% every year, as shown by Jia Yin Lee *et al*.[9] The increase in cardiac ADRs was observed by Alexandre G *et al*. as a raw incidence of serious cardiac ADRs in the range of 0.8 to 2.5%.[10] All of these possible adverse drug effects can be minimized by using medication rationally and evaluating pharmacotherapy daily. The objectives of the study is to study the implications of medication complexity assessment for pharmacotherapy evaluation and to determine the relationship between medication complexity at the time of admission and the severity of the coronavirus infection.

MATERIALS AND METHODS

Study site

The data was collected at Adichunchanagiri Hospital and Research Centre's (AH & RC) COVID ward, which is one of the largest tertiary care teaching hospitals in the Mandaya district, with 1090 beds, and is affiliated with Adichunchanagiri University. Until they were discharged, all admitted patients were checked regularly for drug-related complications. The study was approved by the Intuitional Ethics Committee of Adichunchanagiri Hospital and Research Centre (Approved No. IEC/AH&RC/AC/004/2021). Informed consent was obtained from all individuals included in this study.

Participants

Irrespective of gender, all patients over the age of 18 years who have been diagnosed with COVID-19 with reverse transcription-polymerase chain reaction (RT-PCR) and admitted to the COVID ward of AH&RC between July 8th, 2021, and October 21st, 2021, and discharged under the Ministry of Health and Family Welfare's standardized updated discharge policy for COVID-19 were included in the study.[11] The study excluded patients who were under the age of 18 years old, discharged against medical advice, or did not meet the study's inclusion criteria.

Study Procedure

On each new admission, the hospital administration was requested to inform the study team. The required data (*demographic details, symptoms of the disease, investigation carried out during hospitalization, prescription*)

were collected from the patient case sheet in a patient data collection form, which was then subjected to a prescription audit where medication complexity [*using Medical Regimen Complexity Index (MRCI)*], potential drug interactions (*using Medscape*), medication duplication, and polypharmacy were checked. Based on the clinical presentation of the disease, the patients were divided into mild, moderate, severe, and critical categories as per the World Health Organization (WHO) mentioned in the Therapeutic and COVID-19 guidelines.[12]

A team of two experts was selected from the list of authors to evaluate medication and calculate the MCRI score, and they were supervised by an experienced clinical pharmacist. In the event of a higher MRCI score, medicine duplication, incorrect dosage, or drug interaction, the immediate assessment of the prescription was shared with the treating clinician.

Polypharmacy

Polypharmacy is most often described as the prescription of five or more drugs at the same time.[13] It frequently results in unpleasant to dangerous, life-threatening consequences for patients and the community, including possible DI, drug-disease interactions, ADRs, non-compliance, drug-associated complications, adversative clinical consequences, lower quality of life, and increased healthcare costs for individuals and society.[14-15] Except for a vitamin supplement, we considered all of the medicines for polypharmacy.

The severity of COVID-19 disease

The severity of the disease is classified as mild (if there is no radiographic indication of pneumonia) or moderate (*if pneumonia with fever and respiratory tract symptoms is detected*), severe (*if respiratory rate ≥ 30 breaths per minute, oxygen saturation ≤93% when breathing ambient air or PaO2/FiO2 ≤300mm Hg*), or critical (*if respiratory failure requiring mechanical ventilation or organ failure requiring intensive care*) based on the signs and symptoms.[12,16]

Medication Complexity

The medication complexity was measured using MRCI. The MRCI has three sections providing information on the dosage form (Section A), dosing frequencies (Section B), and additional instructions (Section C).[17] The sum of the sub-scores for the three sections measures the total MRCI score.[18-19] Each enrolled patient's MRCI score on the first day of admission was calculated. A combination of drugs is recommended since the treatment is focused on symptomatic management. As the number of drugs in a prescription increases, so does the MRCI score. In a pilot study of 40 samples, we analyzed the maximum and minimum scores according to the national COVID-19 treatment guidelines[20] and divided them into three groups: less than 15, 15–30, and greater than 30.

Medication Duplication

Medication duplication is defined as the prescription of two drugs from the same class prescribed at the same time to the same patient.[21] Patient characteristics, such as increasing age, various medical conditions, therapy expectations, and self-treatment decisions; physician characteristics, such as unnecessary prescribing and multiple provider systems; and the lack of a coordinating provider are all factors that contribute to this issue.[22-23]

Data Analysis

For the statistical analysis, SPSS version 26 software was used for the statistical analysis, whereby categorical variables such as demographic data, drugs in prescription, the severity of disease, polypharmacy, and medication duplication were assessed for frequency and percentage, while numerical variables such as medication complexity (MRCI score), number of drugs in prescription, and duration of hospital stay were assessed using mean, median, and standard deviation (SD). The association of medication complexity with the severity of COVID-19 disease was determined by the Chi-Square test, and an independent sample median test was used to compare the median medication complexity in the severity of diseases, considering 0.05 as a significant level.

RESULTS

During the study, 333 COVID-19 patients were admitted, 15 of whom did not meet the study's inclusion criteria. There were 318 patients in this study, with 55% (175) men and 45% (143) women, and 16.67% (53) geriatrics (over 65 years old). Overall, the patients spent an average of 7.55 ± 3.60 days in the hospital, with an interquartile range of 5 [Q3(10)

Table 1: Patient's characteristics, the severity of disease, broad class of drugs, polypharmacy, medication duplication, dosage adjustment, and drug interaction.

Patient's characteristic		Total number	Percentage (*n*=318)
Gender	Male	175	55%
	Female	143	45%
Geriatric patient		53	16.67%
Age Group	Under 20 years	14	4.4%
	20-29 years	57	17.9%
	30-39 years	61	19.2%
	40-49 years	52	16.4%
	50-59 years	60	18.9%
	60-69 years	36	11.3%
	70 years and Older	38	11.9%
Severity	Mild	223	70.1%
	Moderate	53	16.7%
	Severe	26	8.2%
	Critical	16	5%
Antiviral prescription		244	76.72%
Antibiotic prescription		298	93.71%
Antiprotozoal prescription		252	79.23%
Monoclonal antibody		5	1.57%
Polypharmacy		263	82.70%
Therapeutic Duplication	Total	55	17.29%
	Drugs from the same class	13(23.64%)	4.09%
	Drugs for the same indication	10(18.18%)	3.14%
	The same drug in different dosage form	7(12.73%)	2.20%
	During switching the route of administration	25(45.45%)	7.86%
Drug interaction	Total (Serious + Monitor closely)	274	86.16%
	Serious drug-drug interaction	264 (96.35%)	83.01%
	Drug-drug interaction required close Monitoring	10 (3.65%)	3.14%
Drug dosage adjustment	Total	32	10.06%
	Inj. Piperacillin/tazobactam	08 (25%)	2.52%
	Inj. Potassium chloride	06 (18.75%)	1.89%
	Inj. Magnesium Sulphate	05 (15.63%)	1.57%
	Tab. Moxifloxacin	04 (12.5%)	1.26%
	Inj.Amphotericin B (emulsion)	04 (12.5%)	1.26%
	Inj. Colistin	02 (6.25%)	0.63%
	Inj. Amikacin	02 (6.25%)	0.63%
	Inj. Diclofenac	01 (3.12%)	0.31%

Table 2: Descriptive analysis of prescribed drugs, medication complexity, and hospital stay.

		Total Case (N)	Minimum	Maximum	IQR (Q_3, Q_1)	Mean	SD
Drug Prescribed		318	3	20	3 (10, 7)	9.22	2.69
Drug Excluding Vitamin supplements		318	1	18	3 (8, 5)	6.54	2.5
Medication Complexity	**Under 15**	20				12.75	2.06
	15-30	199				24.01	3.94
	Above 30	99				35.44	4.71
	Total	318	9	57.5	9.5 (31.5, 22)	26.86	7.58
Hospital Stay		318	1	22	5(10, 5)	7.55	3.60

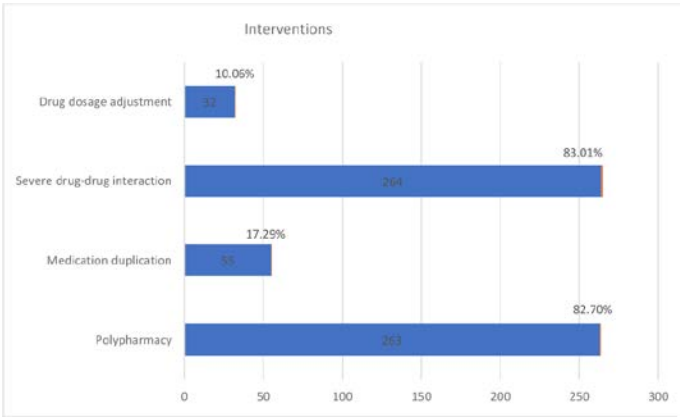

Figure 1: Intervention found during study periods.

and Q1(5)]. COVID-19 cost the lives of 5.7% (18) of those people (Table 1 and 2).

In the study, each prescription contained an average of 9.22 ± 2.69 drugs, with an interquartile range of 3 [Q3(10) and Q1 (7)]. After removing vitamin supplements, each prescription had an average of 6.54 ± 2.51 drugs. Polypharmacy was identified in 82.70% (263) of the prescriptions, whereas medication duplication was identified in 17.29% (55) and drug dosage adjustment was done in 10.06% (32) of the prescriptions (Table 1 and Figure 1). The most medication duplication was identified when switching the route of administration 45.45% (25), followed by being treated with drugs from the same class (23.64%, 13), being treated with drugs for the same indication (18.18%, 10), and being treated with the same drug in a different dosage form 12.73% (07). Out of all the dosage adjustments, most of the adjustments were made to piperacillin/tazobactam 25% (08), followed by injectable potassium chloride 18.75% (06), injectable magnesium sulphate 15.63% (05), Moxifloxacin 12.5% (04), amphotericin B emulsion 12.5% (04), colistin 6.25% (02), amikacin 6.25% (02) and injectable diclofenac 3.12% (1). Antiviral drugs were prescribed in 76.72% (244) of the prescriptions, antibiotics in 93.71% (298), and antiprotozoal drugs in 79.23% (252) of the prescriptions. 86.16% (274) of the prescriptions had a moderate to severe drug-drug interaction, with severe drug interactions accounting for 83.01% (264) of the total (Table 2). Serious drug interactions were observed when hydroxychloroquine and azithromycin, ondansetron, and ofloxacin were combined, followed by remdesivir and hydroxychloroquine, and enoxaparin and piperacillin/tazobactam.

In the study we found, 26.86 ± 7.58 as an average medication complexity in an interquartile range of 9.5 [Q3(31.5) and Q1 (22)]. When we evaluated medication complexity by the severity of disease, we found out that the average medication complexity for mild was 24.62 ± 6.04,

Table 3: Distribution of medication complexity as per the disease severity.

Severity	Medication Complexity				Mean	Std. Deviation
	Under 15	15-30	Above 30	Total		
Mild	17	165	41	223	24.62	6.04
Moderate	1	22	30	53	31.65	8.39
Severe	0	5	21	26	35.19	6.82
Critical	2	7	7	16	28.59	8.60
Total	20	199	99	318	26.86	7.58

Table 4: Chi-square test performed in medication complexity and the severity of disease, and Pearson correlation of medication complexity and hospital stay.

Medication complexity Vs	Test	Test Statistic	Significance
Severity of Disease	Chi-Square	64.78	<0.001
Hospital stays	Correlation	0.296	0.000
The significance level is 0.050.			

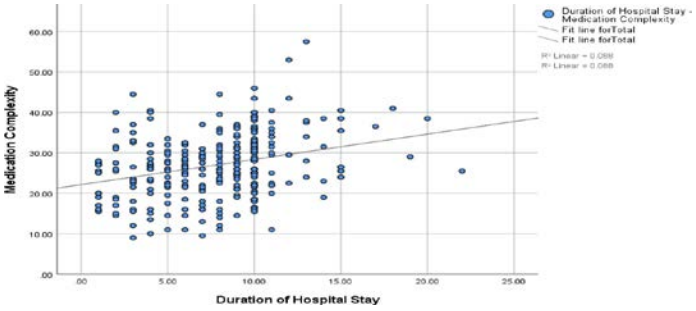

Figure 2: Correlation between medication complexity and the hospital stay.

moderate was 31.65±8.39, severe was 35.19±6.81, and critical was 28.59±8.60 (Table 2 and 3).

The Pearson Chi-Square test was used to find out the association between the severity of disease and the medication complexity, considering the 0.05 level of significance (*the null hypothesis was that there was no association between the medication complexity and the severity of disease*), and a $p< 0.001$ was obtained, making it significant in terms of statistics. As a result, they have an association. The medication complexity and hospital stay have a statistically significant positive correlation (P value 0.000), with a 0.296 as a correlation value (Table 4 and Figure 2).

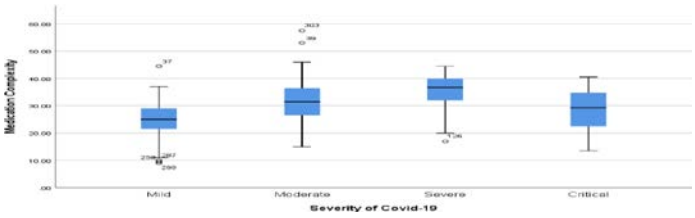

Figure 3: Distribution of Medication Complexity as per the severity of the disease.

DISCUSSION

With a total of 318 patients, the study found a greater rate of coronavirus infection in men than in women, similar to Alsofayan YM *et al*.,[24] and 40.1% of the individuals were over 50 years old. The goal of this study was to determine if there was an association between the medication complexity at admission and the severity of the coronavirus infection, as well as what this meant for pharmacotherapy evaluation. The study demonstrated an association between the severity of disease and the medication complexity at admission (Table 4). Although there is an association, the mean medication complexity is not constant across severity categories and does not increase as severity increases (Figure 3). National guidelines for treating COVID-19[20] could have an impact on this, as they are based on the severity of the condition and increase the amount of medicine and life-supporting measures as the severity worsens.

The quantity, frequency, and route of administration of the medicine have the largest impact on the medication complexity, which arises as a consequence of polypharmacy. In the study, we found 82.70% polypharmacy (Table 1). A rise in polypharmacy may be the outcome of the symptomatic approach to curing COVID-19. This could result in drug interactions, therapeutic duplication, and dosage selection errors. The majority of therapeutic duplication occurred when the route of administration was switched, and the previous drug appeared to be continued together with the new medication where anti-gastritis and nonsteroidal anti-inflammatory drugs (NSAIDs) are more common. Antibiotics, steroids, and NSAIDs have all been attributed to therapeutic duplication caused by drugs from the same class, with piperacillin/tazobactam and amoxicillin/clavulanic acid, hydrocortisone and dexamethasone, and diclofenac and aceclofenac being the most frequently detected. Therapeutic duplication induced by drugs for the same indication is frequently encountered in antiemetic and pain-relieving drugs. Similarly, therapeutic duplication produced by the same drug in different dosage forms is more often seen with salbutamol and acebrophylline. Therapeutic duplication has been exacerbated by the availability of numerous brands of the same drug with fixed-dose combinations. It can be reduced by prescribing a drug's generic name rather than its brand name, using a single drug rather than a combination drug, and educating the healthcare professional about the risks of therapeutic duplication. Significant dosage modifications were made to injectable antibiotics and an electrolyte replenisher. At the start of the study, piperacillin/tazobactam, amphotericin B emulsion, and moxifloxacin were frequently suggested for dosage adjustments, and that was significantly reduced later. Potassium and magnesium, whose dosages are quite often adjusted in an electrolyte replenisher, are very vulnerable to administrative errors and can be life-threatening. We also noticed that electrolyte replenishment continued after the serum electrolyte levels were normalized. More care should be exercised during administration, and regular electrolyte monitoring is essential. Diclofenac is an NSAID that has had its dosage changed. The problem stems from a lack of understanding of dose frequency, as well as the significant burden imposed by the rising doctor-to-patient ratio. Cardiac toxicity with QTc prolongation was observed with the combinations of hydroxychloroquine and azithromycin, ondansetron, and ofloxacin, followed by a reduction in antiviral properties with the combination of remdesivir and hydroxychloroquine, and an increase in anticoagulant action or risk of bleeding with the combination of enoxaparin and piperacillin/tazobactam. *Beyzarov et al*.,[25] reported that hydroxychloroquine and azithromycin caused high drug interactions, which is similar to our findings. Regular prescription inspections and suggestions for alternatives in cases of high health risk due to drug interactions would help to reduce drug interactions and improve treatment quality.

Antibiotics were prescribed in almost all cases (93.71%), which is similar to the findings of Zhou F *et al*.,[26] while the number of antivirals prescribed increased. More than 92% of mild and moderate cases were prescribed antibiotics, which is in contrast to the revised guidelines against the use of empirical antibiotics in COVID-19.[27] Despite being aware of the revised guidelines, we were unable to restrict the inappropriate use of antibiotics. One possible reason is that the current pandemic's focus is on reducing the immediate impact on individuals, and another could be that clinical pharmacists in Indian hospital settings are underutilized. This has hidden the longer-term hazard of AMR, which Rawson *et al*.,[28] emphasized in their article.

In comparison to the systematic review conducted by Rees EM *et al*.,[29] we observed a reduction in the overall hospital stay in the study. It could be the result of clinicians being able to prioritize patients after recognizing vulnerable patients by the assessment of the medication complexity during therapy. As a result, the patient's financial burden was indirectly reduced.

The adoption of the medication complexity assessment as a routine admission protocol may suggest that the prescription be double-checked and the patient be observed more frequently. It will help to improve the significance of pharmacotherapy evaluation by detecting drug-related concerns relatively quickly. Which can detect and correct any medication errors made during therapy, as well as reduce antimicrobial agent resistance, patient financial burden, and improve patient safety. The clinical pharmacist can take the lack of adequate medicine in the treatment of COVID-19 as an opportunity to emphasize the necessity of pharmacotherapy evaluation.

Study limitation

This study was conducted in a single location; however, if it had been conducted in multiple locations with an equal number of patients in each illness severity category, a better interpretation would have been possible, which was not the case in our study.

CONCLUSION

There is an association between medication complexity and the severity of the disease. The median medication complexity, on the other hand, does not remain consistent throughout severity categories and does not increase linearly as severity increases. More research, including a multi-center study, is necessary to corroborate the study findings.

The assessment of medication complexity on admission in the routine protocol for pharmacotherapy evaluation may indicate which prescriptions need to be double-checked and monitored more regularly. It has the potential to reduce potential drug-related complications, unnecessary load on healthcare providers, and economic burden, while also increasing treatment quality and improving overall patient safety.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

1. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic treatments for coronavirus disease 2019 (COVID-19): A review. JAMA. 2020;323(18):1824-36. doi: 10.1001/jama.2020.6019, PMID 32282022.
2. Li L, Wang X, Wang R, Hu Y, Jiang S, Lu X. Antiviral agent therapy optimization in special populations of COVID-19 patients. Drug Des Dev Ther. 2020;14:3001-13. doi: 10.2147/DDDT.S259058, PMID 32801640.
3. Takahashi T, Luzum JA, Nicol MR, Jacobson PA. Pharmacogenomics of COVID-19 therapies. npj Genom Med. 2020;5(1):35. doi: 10.1038/s41525-020-00143-y, PMID 32864162.
4. Lindquist LA, Lindquist LM, Zickuhr L, Friesema E, Wolf MS. Unnecessary complexity of home medication regimens among seniors. Patient Educ Couns. patient ed. 2014;96(1):93-7. doi: 10.1016/j.pec.2014.03.022, PMID 24793007.
5. Schmidt SJ, Wurmbach VS, Lampert A, Bernard S; HIOPP-6 Consortium, Haefeli WE, Seidling HM, Thürmann PA. Individual factors increasing complexity of drug treatment-a narrative review. Eur J Clin Pharmacol. 2020 ;76(6):745-54. doi: 10.1007/s00228-019-02818-7.
6. Muir AJ, Sanders LL, Wilkinson WE, Schmader K. Reducing medication regimen complexity: A controlled trial. J Gen Intern Med. 2001;16(2):77-82. doi: 10.1046/j.1525-1497.2001.016002077.x, PMID 11251757.
7. Alayed N, Alkhalifah B, Alharbi M, Alwohaibi N, Farooqui M. Adverse drug reaction (ADR) as a cause of hospitalization at a government hospital in Saudi Arabia: A prospective observational study. Curr Drug Saf. 2019 Nov 1;14(3):192-8. doi: 10.2174/1574886314666190520105330, PMID 31109277.
8. Sun J, Deng X, Chen X, Huang J, Huang S, Li Y, *et al*. Incidence of adverse drug reactions in COVID-19 patients in China: An active monitoring study by hospital pharmacovigilance system. Clin Pharmacol Ther. 2020 Oct;108(4):791-7. Doi: 10.1002/cpt.1866, PMID 32324898.
9. Lee JY, Ang ASY, Mohd Ali N, Ang LM, Omar A. Incidence of adverse reaction of drugs used in COVID-19 management: A retrospective, observational study. J Pharm Policy Pract. 2021 Dec;14(1):84. Doi: 10.1186/s40545-021-00370-3, PMID 34696800.
10. Gérard A, Romani S, Fresse A, Viard D, Parassol N, Granvuillemin A, *et al*. 'Off-label' use of hydroxychloroquine, azithromycin, lopinavir-ritonavir and chloroquine in COVID-19: A survey of cardiac adverse drug reactions by the French Network of Pharmacovigilance Centers. Therapie. 2020 Jul 1;75(4):371-9. doi: 10.1016/j.therap.2020.05.002, PMID 32418730.
11. Government of India Ministry of Health and Family Welfare. Revised discharge policy for COVID-19. Available from: https://www.mohfw.gov.in/pdf/RevisedDischargePolicyforCOVID19updatedon9thJanuary2022.pdf [cited 29/6/2022].
12. WHO. Therapeutic and COVID-19: living guideline. Available from: https://www.mhcluster.org/WHO-2019-nCoV-therapeutics-2021.2-eng.pdf [cited 29/6/2022].
13. Iloanusi S, Mgbere O, Essien EJ. Polypharmacy among COVID-19 patients: A systematic review. J Am Pharm Assoc (2003). 2021;61(5):e14-25. doi: 10.1016/j.japh.2021.05.006, PMID 34120855.
14. Rahman S, Singh K, Dhingra S, Charan J, Sharma P, Islam S, *et al*. The double burden of the COVID-19 pandemic and polypharmacy on geriatric population – public health implications. Ther Clin Risk Manag. 2020;16:1007-22. Doi: 10.2147/TCRM.S272908, PMID 33116550.
15. Saljoughian M. Polypharmacy and drug adherence in elderly patients. US Pharm. 2019;44(7):33-6.
16. Yeoh YK, Zuo T, Lui GC, Zhang F, Liu Q, Li AY, *et al*. Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. Gut. 2021;70(4):698-706. Doi: 10.1136/gutjnl-2020-323020, PMID 33431578.
17. George J, Phun YT, Bailey MJ, Kong DC, Stewart K. Development and validation of the medication regimen complexity index. Ann Pharmacother. 2004 Sep;38(9):1369-76. Doi: 10.1345/aph.1D479, PMID 15266038.
18. McDonald MV, Peng TR, Sridharan S, Foust JB, Kogan P, Pezzin LE, *et al*. Automating the medication regimen complexity index. J Am Med Inform Assoc. 2013;20(3):499-505. doi: 10.1136/amiajnl-2012-001272, PMID 23268486.
19. Hirsch JD, Metz KR, Hosokawa PW, Libby AM. Validation of a patient-level medication regimen complexity index as a possible tool to identify patients for medication therapy management intervention. Pharmacotherapy. 2014;34(8):826-35. doi: 10.1002/phar.1452, PMID 24947636.
20. Government of India Ministry of Health and Family Welfare. Clinical guidance for management of adult COVID-19 patients. Available from: https://www.mohfw.gov.in/pdf/UpdatedDetailedClinicalManagementProtocolforCOVID19adultsdated24052021.pdf [cited 29/6/2022].
21. Rahmanzade R, Cabrera Diaz F, Zaugg C, Schuetz P, Salili AR. Therapeutic duplication of anticoagulants: A retrospective study of frequency and consequences in a tertiary referral hospital. Thromb J. 2020;18(1):14. doi: 10.1186/s12959-020-00227-w, PMID 32774174.
22. Huynh I, Rajendran T. Therapeutic duplication on the general surgical wards. BMJ Open Qual. 2021 Sep 1;10(3):001363, doi: 10.1136/bmjoq-2021-001363, PMID 34475037.
23. Kan WC, Kuo SC, Chien TW, Lin JJ, Yeh YT, Chou W, *et al*. Therapeutic duplication in Taiwan hospitals for patients with high blood pressure, sugar, and lipids: Evaluation with a mobile health mapping tool. JMIR Med Inform. 2020;8(7):e11627. doi: 10.2196/11627, PMID 32716306.
24. Alsofayan YM, Althunayyan SM, Khan AA, Hakawi AM, Assiri AM. Clinical characteristics of COVID-19 in Saudi Arabia: A national retrospective study. J Infect Public Health. 2020;13(7):920-5. doi: 10.1016/j.jiph.2020.05.026, PMID 32534945.
25. Beyzarov E, Chen Y, Julg R, Naim K, Shah J, Gregory WW, *et al*. Global safety database summary of COVID-19-related drug utilization-safety surveillance: A sponsor's perspective. Drug Saf. 2021;44(1):95-105. doi: 10.1007/s40264-020-01035-x, PMID 33354753.
26. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: A retrospective cohort study. Lancet. 2020;395(10229):1054-62. doi: 10.1016/S0140-6736(20)30566-3, PMID 32171076.
27. World Health Organization. Clinical management of COVID-19: Interim guidance; May 27 2020. Available from: https://apps.who.int/iris/handle/10665/332196 [cited 29/6/2022].
28. Rawson TM, Moore LSP, Castro-Sanchez E, Charani E, Davies F, Satta G, *et al*. COVID-19 and the potential long-term impact on antimicrobial resistance. J Antimicrob Chemother. 2020 Jul 1;75(7):1681-4. Doi: 10.1093/jac/dkaa194, PMID 32433765.
29. Browne AJ, Kashef Hamadani BH, Kumaran EAP, Rao P, Longbottom J, Harriss E, *et al*. Drug-resistant enteric fever worldwide, 1990 to 2018: A systematic review and meta-analysis. BMC Med. 2020;18(1):1. doi: 10.1186/s12916-019-1443-1. PMID 31898501.

Article History: Received: 05-01-2022; Revised: 16-04-2022; Accepted: 06-06-2022.
Cite this article: Shrestha Y, Venkataraman R, Moktan JB, Mallikarjuna S, Narayan SS, Madappa MH, Satya PA. The Association of Medication Complexity with COVID-19 Severity and its Impact on Pharmacotherapy Evaluation. J Young Pharm. 2022;14(3):322-6.