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FARMACOVID: Retrospective cohort study of the profile and management of drug interactions in critically ill patients with COVID-19 in a tertiary care hospital in Colombia

Junior Lopez-Cardenas[1], Blanco Jhosep[1], Rosa-Helena Bustos[1], Andres Cruz[2], Sharon Lechtig-Wasserman[1], Nicolas Díaz-Pinilla[1], Jennifer-Andrea Pinedo[2], Maria-Jose Ortega[2]; Nicolas Bastidas1; Hans Liebisch-Rey[1], Yuli V. Fuentes[1]*

[1] Department of Clinical Pharmacology, Evidence-Based Therapeutics Group, Faculty of Medicine, Universidad de La Sabana and Clínica Universidad de La Sabana, Campus del Puente del Común, Km. 7, Autopista Norte de Bogotá. Chía, Cundinamarca, Colombia 140013. rigoberto.lopez@unisabana.edu.co (J.L.-C.), josepblme@unisabana.edu.co (J.B.), rosa.bustos@unisabana.edu.co (R.-H.B.), andrescrgo@unisabana.edu.co (A.C.), sharonlele@unisabana.edu.co (S.L.-W.), nicolasdipi@unisabana.edu.co (N.D.-P.), jenniferpiag@unisabana.edu.co (J.-A.P.), mariaortgo@unisabana.edu.co (M.-J.O), nicolasbagu@unisabana.edu.co (N.B.) hanslire@unisabana.edu.co (H.L.-R.),

[2] Faculty of Medicine, Universidad de La Sabana, Chía 140013, Colombia

*Corresponding author: Yuli Viviana Fuentes Barreiro, MD, MSc; Universidad de La Sabana, Campus del Puente del Común, Km. 7, Autopista Norte de Bogotá. Chía, Cundinamarca, Colombia 140013. Phone: +57-1608615555; E-mail: yulifuba@unisabana.edu.co (Y.-V. F.)

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Abstract: Critically ill patients with COVID-19 have important risk factors for the occurrence of drug-drug interactions. The aim of this study was to characterize and describe the profile and management of drug-drug interactions in critically ill patients affected by COVID-19 in a tertiary care hospital in Colombia. A descriptive retrospective cohort with an exploratory analytical component was performed. The medical records of 191 patients were reviewed from August 2020 to February 2021. An initial descriptive analysis was performed, and a bivariate approach was developed to include variables of significance in a multivariate analysis. In our cohort of critically ill patients the following factors were associated with a higher risk of major outcome development: a higher age, Charlson comorbidity index (CCI), Sequential Organ Failure Assessment (SOFA) score, a greater number of prescribed drugs, number of interactions, and the presence of type D interactions.

Keywords: Drug-interactions, Covid-19, Critically ill patients

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has represented a challenge for global public health. The rapid spread, mutation, lack of information and efficient therapies generated a high mortality worldwide. To thrive in this situation, new drug indications, dosages, combinations, and developments were approved by different international organizations and regulatory entities despite the low evidence. This

scenario increased the possibility of prescribing errors and drug-drug interactions due to polypharmacy and prolonged therapies in the ICU [1].

Drug-drug interactions (DDI) are an important and underestimated cause of medication errors. The prevalence of adverse drug interactions ranges between 2.2 to 30% and 9.2 and 70.3% in hospitalized patients and outpatients, respectively [2]. In the Harvard Medical Practice Study of Adverse Events, 20% of acute in-hospital events were drug-related; of these, 8% were secondary to drug-drug interactions [3]. Although the overall incidence of adverse drug-drug interactions is probably quite low (<1%), this is a persistent and considerable problem because of the overall number of patients at risk and its potential relationship with morbidity and mortality [2]. The occurrence of DDI can be related to intrinsic factors (age, organ dysfunction, genetic variations, etc.) or extrinsic (polypharmacy, multiple prescribers, self-medication, drug abuse, poor adherence, etc.) [2,4,5].

The local data in DDI is sparse, especially in critically ill patients. The largest study of its kind in Colombia was published in 2018. It found a proportion of patients with at least one interaction of 84%, with a median of six interactions per patient, demonstrating a high rate of drug interactions in hospital settings and in intensive care at the local level and highlighting the relevance of pharmacovigilance and risk management in the clinical setting to prevent, reduce, anticipate, and control medication related adverse effects [6,7].

To achieve the previously proposed objectives in clinical practice, multiple electronic tools have been created to calculate the frequency of drug-drug interactions, the risks they poise and their severity, as well as recommendations on ways to avoid them. Among the best known are Micromedex®, Lexicomp ®, Medscape, Clinical Pharmacology Drug Interaction Report, Stockley's Drug Interactions (10th edition), Drug Interactions Analysis & Management: Facts and Comparisons 2014 (9th edition, 2014), Drugs.com and the drug interaction appendix of the British National Formulary-76 [8]. These softwares were evaluated by Patel et al. concluding that both Lexicomp and Micromedex are highly accurate and sensitive [9].

This study evaluated the profile and management of drug-drug interactions and adverse drug reactions in critically ill patients with COVID-19, this allows a characterization of the main interactions and the generation of better treatments, while having an impact on morbidity, mortality, and healthcare costs.

2. Materials and Methods

2.1. Type of study and patient selection

The study was a retrospective descriptive cohort study with an exploratory analytical component. The medical records of a cohort of patients from August 2020 to February 2021 were reviewed, and a database was created with the variables of interest. Once the information was collected, statistical analyses of the data was performed. The study population were the critically ill patients affected by COVID-19 in a third level hospital in Colombia. The inclusion criteria were adults over 18 years of age, having been hospitalized in the ICU for >24 hours, and a positive RT-PCR test for SARS-CoV-2. Subjects with incomplete medical records were excluded. The following were considered as major outcomes: in-hospital mortality, cardiac arrest, arrhythmia, deterioration of liver function, initiation of renal replacement therapy, increased length of hospital stay. Only variables with a P less than 0.2 in the bivariate analysis were included in the model.
The study followed the ICH practice guidelines [10], the Declaration of Helsinki [11], Colombian legislation and the principles of contemporary bioethics. Data protection was

achieved by assigning an identification number to each patient, collecting sociodemographic and clinical variables of interest, and by deleting medical records. The study was approved by the ethics committee of the Universidad de La Sabana clinic (code 20211106, 8th November, 2021).

The Materials and Methods should be described with sufficient details to allow others to replicate and build on the published results. Please note that the publication of your manuscript implicates that you must make all materials, data, computer code, and protocols associated with the publication available to readers. Please disclose at the submission stage any restrictions on the availability of materials or information. New methods and protocols should be described in detail while well-established methods can be briefly described and appropriately cited.

Research manuscripts reporting large datasets that are deposited in a publicly available database should specify where the data have been deposited and provide the relevant accession numbers. If the accession numbers have not yet been obtained at the time of submission, please state that they will be provided during review. They must be provided prior to publication.

Interventionary studies involving animals or humans, and other studies that require ethical approval, must list the authority that provided approval and the corresponding ethical approval code.

2.2. Detection and characterization of drug interactions

We used the Lexicomp™ drug-drug interaction software, version 2022, developed by the Wolters Kluwer Group, which is available through the UpToDate, Inc. computer system [12]. In the Lexicomp™ system, drug-drug interactions are classified according to the degree of documentation, as excellent, good, bad, or unknown; according to severity, as mild, moderate, important or contraindicated (Table 1); according to the time of occurrence, as early (<24 hours) or late (>24 hours); and according to their type, as pharmacokinetic, pharmacodynamic or mixed [12].

Table 1. Classification of interactions according to the Lexicomp™ software

Severity category	Definition	Communication level
X	Contraindicated	Excellent: proven with high quality clinical studies
D	Major: may cause damage or require handling	Good: well documented, and well known. Not validated by clinical studies
C	Moderate – may exacerbate clinical conditions or require modifications in treatment.	Moderate: there are suggestive data. Good documentation for a similar drug
B	Minor: May have minimal clinical effects and requires no modifications to therapy.	Poor: very limited data, but theoretically possible
A	There is no known risk	There is no known risk

The time of appearance of the first interaction and exposure time in days were recorded. Data on age, sex, Charlson comorbidity index (CCI) (19 items), chronic diseases, smoking, BMI, number of drugs prescribed, length of hospital stay, arrhythmia, cardiac

arrest, initiation of renal replacement therapy, liver failure, mortality, and a combined result of the above 5 variables were collected in the Microsoft Excel™ document format for analysis. The database contained information from electronic medical records, which were filled in by medical personnel.

2.3. Data analysis

A descriptive analysis of the information was performed, with absolute frequencies and percentages for the categorical variables and continuous variables in medians and interquartile ranges, given that they did not have a normal distribution, followed by a bivariate analysis between the covariables (clinical and sociodemographic variables). The Mann-Whitney test was used for quantitative variables and the chi-squared test (◎2) for categorical variables.

Multivariate analyses were performed using a logistic regression model for dichotomous variables such as the presence of a major outcome or segregated outcomes such as mortality, arrhythmia, cardiac arrest, and renal replacement therapy onset. For length of stay, a Poisson model was developed. Variables included in the model were those with a p-value less than 0.2 in the bivariate analysis. All the models were fitted to find the best explanatory capacity with the outcome variable. A significance level of 0.05 and a 95% confidence interval (95% CI) were chosen. We used the software package R version 3.6.1 for statistical analyses.

3. Results

3.1 Sociodemographic information

Of the 191 patients' clinical records analyzed, 82 patients had a major outcome, and 109 patients had a minor outcome. The median age (IQR) of the patients analyzed was 65 years (53 – 73 years), where the majority were men (72.3%). Regarding clinical characteristics, 66% had previous comorbidities; likewise, 75.6% had a major outcome. Other relevant factors were a smoking history (28.3%), and an elevated body mass index (24.9 – 31 kg/m2). The median CCI score (IQR) was 3 pts (1-4 pts) and the median Sequential Organ Failure Assessment (SOFA) score was 5 pts (3-7 pts). The median maximum number of medications was 10 drugs (8 – 13). The proportion of type X drug interactions was 17.8% and of type D drug interactions was 62.3%. In addition, patients who had a major outcome had more drug interactions (median: 10; IQR: 5-17) compared to patients who did not have a major outcome (median: 4; IQR: 1-8). The pharmacologic management of drug interactions was drug discontinuation (7.9%), drug switching (7.9%), and clinical or laboratory test follow-up (32.5%) (Table 2.)

Table 2. Baseline characteristics of critically ill patients with COVID-19.

Characteristic	All cohort (n=191)	Major outcome (n=82)	No major outcome (n=109)
Sociodemographic characteristics			
Age (years), median (IQR)	65 (53-73)	68 (57-74)	60 (50-72)
Male, n (%)	138 (72.3)	62 (75.6)	76 (69.7)
Clinical characteristics			
Morbid conditions, n (%)	126 (66)	62 (75.6)	64 (58.7)
Smoking, n (%)	54 (28.3)	27 (32.9)	27 (24.8)
Body Mass Index (BMI) (kg/m^2), median (IQR)	27.8 (24.9-31)	27.6 (25.4-30.3)	27.8 (24.7-31.5)
Charlson Comorbidity Index (CCI) (points), median (IQR)	3 (1-4)	3 (2-5)	2 (1-3)
Sequential Organ Failure Assessment (SOFA) Score	5 (3-7)	6 (4-8)	4 (3-6)
D Interactions			
Fentanyl - Lorazepam	15 (7.9)	11 (13.4)	4 (3.7)
Fentanyl - Ketamine	13 (6.8)	10 (12.2)	3 (2.8)
Fentanyl - Clonidine	8 (4.2)	7 (8.5)	1 (0.9)
Atorvastatin - Clarithromycin	7 (3.7)	6 (7.3)	1 (0.9)
Pharmacological profile			
Maximum number of drugs, median (IQR)	10 (8-13)	12 (9-16)	9 (7-12)
Drug interactions, median (IQR)	6.5 (3-12)	10 (5-17)	4 (1-8)
Patients with type X drug interactions, n (%)	34 (17.8)	19 (23.2)	15 (13.8)
Patients with type D drug interactions, n (%)	119 (62.3)	69 (84.2)	50 (45.9)
Exposure time to type X or D drug interactions (days), median (IQR)	4 (2-8)	4 (2-8)	3 (1-8)
Pharmacological management, n (%)	92 (48.2)	50 (61)	42 (38.5)
Suspension of any drug, n (%)	15 (7.9)	10 (12.2)	5 (4.6)
Change of any drug, n (%)	15 (7.9)	10 (12.2)	5 (4.6)
Clinical or paraclinical monitoring, n (%)	62 (32.5)	30 (36.6)	32 (29.4)

X= 47, D=414 (interactions), Others: 1198, Without interactions: 16. Total=1675

3.2. Drug interactions frequency

A total of 47 drug interactions of type X were presented, where the majority (42%) caused by interactions between quetiapine and other drugs such as methadone (19%), metoclopramide (15%), ipratropium (6%) and potassium chloride (2%); other important drug interactions were caused by interactions between potassium chloride and other drugs (19%). Drugs that are frequently prescribed to patients with severe COVID-19 infection, such as clopidogrel and clarithromycin, also caused non-negligible drug interactions (9% and 8%, respectively) (Table 3.). As for type D drug interactions, a total of 414 interactions were reported. Interactions between midazolam and fentanyl were the most frequent (9%). Likewise, other pharmacological interactions which occurred frequently involved dexamethasone and cisatracurium (8%), fentanyl and clarithromycin (6%), midazolam and clarithromycin (5%) and enoxaparin and dipyrone (4%) (Table S1). Considering the above, the results showed that the most frequent drug related interactions involved fentanyl (n=183), clarithromycin (n=74), midazolam (n=74), dexamethasone (n=53) and methadone (n=50) (Figure 1).

Table 3. Drug interactions frequency

Drug Interaction	n	%
Quetiapine - methadone	9	19%
Quetiapine - metoclopramide	7	15%
Potassium Chloride – ipratropium	5	11%
Clopidogrel – omeprazole	4	9%
Haloperidol- ipratropium	3	6%
Quetiapine – ipratropium	3	6%
Clarithromycin - methadone	2	4%
Loratadine -ipratropium	2	4%
Salbutamol – carvedilol	2	4%
Cefuroxime – omeprazole	1	2%
Clarithromycin- amiodarone	1	2%
Potassium Chloride - hydroxyzine	1	2%
Potassium Chloride - loratadine	1	2%
Potassium Chloride - atropine	1	2%
Potassium Chloride – quetiapine	1	2%
Diphenhydramine - ipratropium	1	2%
Hydroxyzine - ipratropium	1	2%
Methimazole - dipyrone	1	2%
Salmeterol/Fluticasone - clarithromycin	1	2%
Total	**47**	**100%**

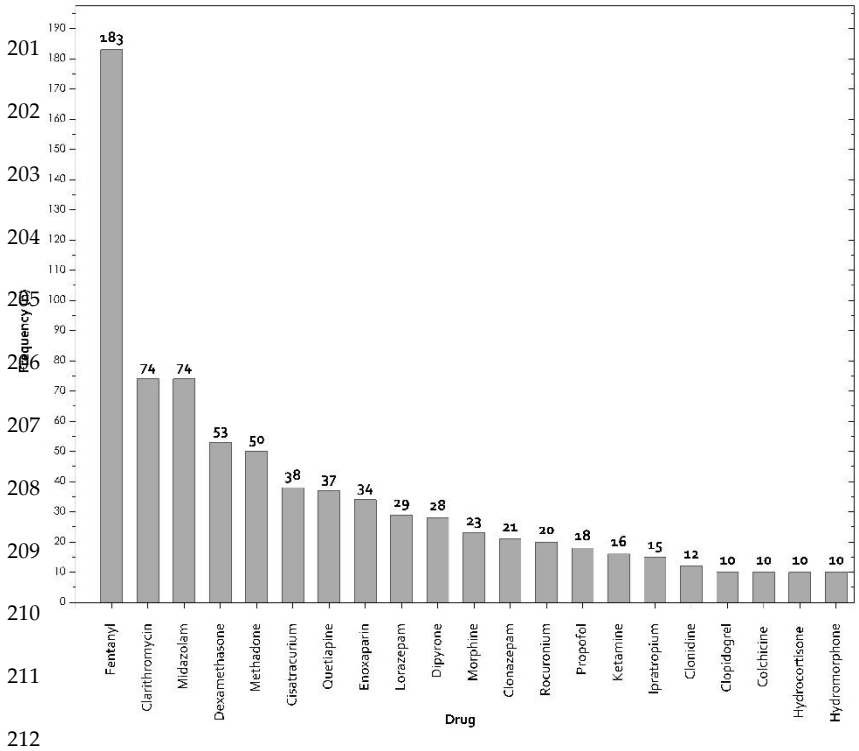

Figure 1. Frequencies of drugs involved in pharmacological interactions

3.3. Clinical Outcomes

Patients admitted to the intensive care unit for COVID-19 present a high risk of drug interactions, partly due to the emerging treatments for this disease. Among the main results of our study, considering drug interactions of particular clinical relevance- were that in the entire cohort there were 82 (42.9%) subjects who presented a major outcome (in-hospital mortality, cardiac arrest, arrhythmia, deterioration of liver function, initiation of renal replacement therapy, length of hospital stays [days]. Patients with type X pharmacological interactions had a higher risk of clinical complications regardless of the outcome 19 (55.9%) of the subjects who had type X interactions were found to have a major outcome. As for type D interactions, 69 subjects, corresponding to 58% also presented a major outcome, 46.2% presented in-hospital mortality, 43.7% presented cardiorespiratory arrest, 23.5% presented a type of arrhythmia, 2.5% presented deterioration of hepatic function, 23.5% initiated renal replacement therapy, and 17% had an increased length of hospital stay. On the other hand, only 2 patients, representing 12.5% of the study subjects who had any major outcome, had no type D or X interactions. As a secondary outcome, days of hospital stay were measured and showed that patients without type D or X drug interactions had fewer days of hospital stay (9 days) than patients with type D or X interactions (13 vs 25 days respectively) (Table 4).

Table 4. Clinical Outcomes frequency

Outcome	Entire cohort (n=191)	X drug interaction (n=34)	D drug interaction (n=119)	No drug interactions (n=16)
Major outcome, n (%)	82 (42.9)	19 (55.9)	69 (58)	2 (12.5)
In-hospital mortality, n (%)	64 (33.5)	11 (32.4)	55 (46.2)	1 (6.3)
Cardiac arrest, n (%)	61 (31.9)	14 (41.2)	52 (43.7)	1 (6.3)
Arrhythmia, n (%)	39 (20.4)	9 (26.5)	28 (23.5)	2 (12.5)
Impaired liver function, n (%)	3 (1.6)	0	3 (2.5)	0
Renal replacement therapy onset, n (%)	33 (17.3)	9 (26.5)	28 (23.5)	1 (6.3)
Length of hospital stay (days), median (IQR)	13 (9-21)	25 (12-40)	17 (10-28)	9 (6.5-12)

3.4. Bivariate Analysis

Regarding bivariate analysis, variables such as age, CCI and SOFA score may be predictors of worse outcomes with statistically significant results for the main outcome (p=0.037, p=0.001 and p=0.001 respectively). Our results further suggest that the number of D-type drug interactions is associated with the worst outcomes (p<0.001) (Table 5.). Another surprising result was that D-type drug interaction between fentanyl and ketamine were related to higher in-hospital mortality (p<0.01) (Table 5).

The most important variables related to cardiorespiratory arrest were a greater number of type D drug interactions (p<0.001), interactions between dexamethasone and rocuronium (p=0.017) (Table 6). Patients who presented a significant clinical arrhythmia, had a higher number of prescribed drugs and drug interactions (p=0.004 and p=0.01) (Table 6). For the initiation of renal replacement therapy, the most related variables were a greater number of type D drug interactions, a greater number of prescribed drugs and a higher number of drug interactions (p=0.006, p=0.022 and p=0.022, respectively) (Table 6).

Table 5. Bivariate and multivariate analysis by major outcome and in-hospital mortality 248

Variable	Major Outcome				In-hospital mortality			
	Bivariate Analysis		**Multivariate Analysis**		**Bivariate Analysis**		**Multivariate Analysis**	
	***p* value**	**OR (CI 95%)**	***p* value**	**OR (CI 95%)**	***p* value**	**OR (CI 95%)**	***p* value**	**OR (CI 95%)**
Sociodemographic characteristics								
Age (years)	**0.037**	1.02 (1.00 to 1.04)			**<0.001**	1.07 (1.04 to 1.10)	<0.001	1.07 (1.03 to 1.10)
Male	0.369	1.34 (0.70 to 2.57)			0.79	1.09 (0.55 to 2.14)		
Clinical characteristics								
Morbid conditions	**0.016**	2.17 (1.15 to 4.10)			**0.013**	2.39 (1.20 to 4.78)		
Smoking	0.217	1.49 (0.79 to 2.80)			0.51	1.24 (0.64 to 2.40)		
BMI (kg/m^2)	0.84	0.99 (0.94 to 1.05)			0.94	1.00 (0.94 to 1.06)		
CCI	**<0.001**	1.33 (1.14 to 1.56)	0.001	1.31 (1.11 to 1.57)	**<0.001**	1.58 (1.32 to 1.89)		
SOFA	**0.001**	1.21 (1.08 to 1.36)			**<0.001**	1.28 (1.13 to 1.45)	0.008	1.20 (1.05 to 1.38)
D Interactions								
Fentanyl - Lorazepam	**0.020**	4.06 (1.24 to 13.28)						
Fentanyl - Ketamine	**0.019**	4.90 (1.30 to 18.45)			**0.009**	5.03 (1.48 to 17.04)		
Fentanyl - Clonidine	**0.032**	10.08 (1.21 to 83.63)						
Atorvastatin - Clarithromycin	**0.049**	8.52 (1.00 to 72.26)						
Pharmacological profile								
Maximum number of drugs	**<0.001**	1.15 (1.08 to 1.24)	0.024	1.08 (1.01 to 1.17)	**0.004**	1.09 (1.02 to 1.15)		
Drug interactions	**<0.001**	1.09 (1.05 to 1.14)			**0.002**	1.06 (1.02 to 1.10)		
Patients with type X drug interactions	**0.09**	1.88 (0.89 to 3.99)			0.87	0.93 (0.42 to 2.06)		
Patients with type D drug interactions	**<0.001**	6.26 (3.10 to 12.64)	0.001	3.78 (1.71 to 8.69)	**<0.001**	6.01 (2.74 to 13.20)	<0.001	5.58 (2.47 to 13.78)
Exposure time to type X or D drug interactions (days)	0.97	0.99 (0.95 to 1.04)			0.84	0.99 (0.94 to 1.04)		
Pharmacological management	**0.002**	2.49 (1.38 to 4.48)			**0.013**	2.17 (1.17 to 4.02)		
Suspension of any drug	**0.062**	2.88 (0.94 to 8.80)			0.98	0.99 (0.32 to 3.03)		
Change of any drug	**0.062**	2.88 (0.94 to 8.80)			**0.09**	2.44 (0.84 to 7.08)		
Clinical or laboratory monitoring	0.29	1.38 (0.75 to 2.55)			**0.08**	1.72 (0.92 to 3.24)		

CCI: Charlson Comorbidity Index (points), SOFA: Sequential Organ Failure Assessment (SOFA) Score, BMI: Body Mass Index

3.5. Multivariate Analysis

Variables significatively associated with the major outcome were the CCI [p=0.001; OR 1.31 (95% CI: 1.11 – 1.57)], maximum number of medications [p=0.024; OR 1.08 (95% CI: 1.01 – 1.17)] and type D drug interactions [p= 0.001; OR 3.78 (95% CI: 1.71 – 8.69)] (Table 5.). For in-hospital mortality, age [p<0.001; OR 1.07 (95% CI: 1.03 – 1.10)] and type D drug interactions [p<0.001; OR 5.58 (95% CI: 2.47 – 13.78)] were the most relevant variables (Table 5). Likewise, the most significant variables associated with cardiorespiratory arrest where age [p<0.001; OR 1.05 (95% CI: 1.02 – 1.08)], the frequency of drug interactions [p=0.013; OR 1.06 (95% CI: 1.01 – 1.11)] and the number of type D drug interactions [p= 0.032; OR 2.76 (95% CI: 1.10 – 7.32)] (Table 6.). The SOFA score p= 0.015; OR 1.18 (95% CI: 1.03 – 1.35) and maximum number of medications [p=0.021; OR 1.08 (95% CI: 1.01 – 1.16)] were associated with a higher risk of cardiac arrhythmia (Table 6.).

The CCI and SOFA score were also associated with an increased risk of initiating renal replacement therapy. Additionally, methadone and lorazepam interactions had a significant association with this outcome [p=0.003: OR 11.58 (95% CI: 2.20 – 69.04)] (Table 6.). There were only 3 instances of liver function impairment, thus bivariate and multivariate analyses were not performed for this outcome.

Table 6. Bivariate and multivariate analysis by cardiac arrest, arrhythmia, and renal replacement therapy onset

Cardiac arrest					Arrhythmia					Renal replacement therapy onset				
Variable	Bivariate Analysis		Multivariate Analysis		Variable	Bivariate Analysis		Multivariate Analysis		Variable	Bivariate Analysis		Multivariate Analysis	
	p value	OR (CI 95%)	*p* value	OR (CI 95%)		*p* value	OR (CI 95%)	*p* value	OR (CI 95%)		*p* value	OR (CI 95%)	*p* value	OR (CI 95%)
Sociodemographic characteristics														
Age (years)	**<0.001**	1.05 (1.02 to 1.08)	<0.001	1.05 (1.02 to 1.08)		**0.049**	1.02 (1.01 to 1.05)				0.62	0.99 (0.96 to 1.02)		
Male	0.98	0.99 (0.50 to 1.95)				0.46	1.35 (0.59 to 3.09)				0.35	1.52 (0.61 to 3.76)		
Clinical characteristics														
Morbid conditions	**0.005**	2.81 (1.36 to 5.78)				**0.11**	1.94 (0.86 to 4.39)				**0.016**	3.42 (1.25 to 9.36)		
Smoking	**0.1**	1.72 (0.89 to 3.33)				**0.05**	2.08 (0.99 to 4.35)				0.77	1.12 (0.49 to 2.55)		
BMI (kg/m^2)	0.44	1.02 (0.96 to 1.08)				0.5	0.98 (0.91 to 1.05)				0.74	1.01 (0.94 to 1.09)		
CCI	**<0.001**	1.37 (1.16 to 1.61)				**0.046**	1.19 (1.01 to 1.41)				**0.001**	1.40 (1.15 to 1.69)	0.001	1.40 (1.14 to 1.73)
SOFA	**0.001**	1.23 (1.09 to 1.38)	0.033	1.15 (1.01 to 1.32)		**0.006**	1.20 (1.05 to 1.36)	0.015	1.18 (1.03 to 1.35)		**0.003**	1.23 (1.07 to 1.40)	0.014	1.19 (1.03 to 1.38)
D Interactions														
Dexamethasone – Rocuronium	**0.017**	3.44 (1.24 to 9.55)			Dexamethasone - cisatracurium	**0.015**	2.77 (1.21 to 6.30)			Fentanyl - Methadone	**0.033**	3.28 (1.10 to 9.80)		
Fentanyl - Lorazepam	**0.021**	3.57 (1.21 to 10.55)			Fentanyl - Clarithromycin	**0.043**	2.55 (1.02 to 6.31)			Fentanyl - Clonidine	**0.023**	5.31 (1.25 to 22.44)		
Fentanyl - Ketamine	**0.002**	8.30 (2.19 to 31.40)			Dexamethasone – Rocuronium	**0.033**	3.11 (1.09 to 8.78)			Methadone - Lorazepam	**0.013**	7.12 (1.51 to 33.52)	0.003	11.58 (2.20 to 69.04)
					Fentanyl -	**0.049**	4.22 (1.00 to 17.74)							
Pharmacological profile														
Maximum number of drugs	**<0.001**	1.13 (1.06 to 1.21)				**0.004**	1.10 (1.03 to 1.17)	0.021	1.08 (1.01 to 1.16)		**0.022**	1.08 (1.01 to 1.16)		
Drug interactions	**<0.001**	1.08 (1.04 to 1.13)	0.013	1.06 (1.01 to 1.11)		**0.01**	1.05 (1.01 to 1.09)				**0.022**	1.05 (1.01 to 1.09)		
Patients with type X drug interactions	**0.2**	1.63 (0.76 to 3.51)				0.33	1.52 (0.64 to 3.59)				**0.12**	1.99 (0.82 to 4.79)		
Patients with type D drug interactions	**<0.001**	5.43 (2.47 to 11.93)	0.032	2.76 (1.10 to 7.32)		**0.17**	1.70 (0.79 to 3.68)				**0.006**	4.12 (1.51 to 11.23)		
Exposure time to type X or D drug interactions (days)	0.37	0.97 (0.92 to 1.03)				**0.17**	0.94 (0.87 to 1.02)				0.27	1.02 (0.97 to 1.08)		
Pharmacological management	**0.008**	2.32 (1.24 to 4.34)				**0.064**	1.97 (0.96 to 4.06)				**0.11**	1.83 (0.85 to 3.94)		
Suspension of any drug	0.9	1.07 (0.34 to 3.28)				**0.013**	3.93 (1.33 to 11.64)	0.025	3.63 (1.14 to 11.42)		**0.022**	3.67 (1.21 to 11.17)		
Change of any drug	**0.07**	2.65 (0.91 to 7.68)				**0.2**	2.08 (0.66 to 6.50)				0.77	1.21 (0.32 to 4.57)		
Clinical or laboratory monitoring	**0.08**	1.74 (0.92 to 3.29)				0.8	0.90 (0.42 to 1.93)				0.9	1.04 (0.47 to 2.32)		

CCI: Charlson Comorbidity Index (points), SOFA: Sequential Organ Failure Assessment (SOFA) Score, BMI: Body Mass Index

3.6. In-hospital stay

When observing the statistically significant results related to the hospital length of stay, it can be inferred that the maximum number of drugs ($p<0.001$) and pharmacological interactions, regardless of their type ($p<0.001$), are closely related to the prolongation of hospital length of stay. Another point to worth noting is that, when performing a multivariate analysis, the statistical significance of these factors is not affected in its value, again reinforcing this significant relationship (Appendix 2.). In the Poisson model, the variables collected were not dispensable for determining hospital stay. Due to the above, no measures of association were calculated since this model does not explain the objective result.

4. Discussion

In our study there was a statistically significant risk between the D-type methadone-lorazepam interaction and initiation of renal replacement therapy, this may be due to methadone's direct and indirect effects in the kidney. These effects include rhabdomyolysis (leading to acute kidney injury), volumetric changes, renal lipidosis and amyloidosis, kidney growth during pregnancy, and kidney transplant rejection.

The low statistical significance related to major outcomes and type X interactions could be explained by the low number of type X interactions. This finding could be related to the pharmacological risk management performed by the treating physicians in the intensive care unit. The strong association between type D interactions and the major outcome could be explained by the fact that in intensive care units the risk/benefit analysis of administering a therapy is performed frequently in ICU, with type D interactions being managed by monitoring of therapy. Of note, we were able to describe a possible association between type D interactions as a risk factor for mortality in our study. Additionally, no correlation was found between the variables measured and length of hospital stay. Although there was a statistically significant relationship between the presence of X or D interactions and length of stay in the ICU, the Poisson model did not fully explain the results as there are likely other unmeasured variables that may better explain the length of hospital stay. Older age, a worse SOFA score, a greater number of comorbidities according to the CCI and a greater number of interactions were associated with worse outcomes, which could be explained by a more deteriorated clinical condition at admission.

In an ICU setting, drug-drug interactions are a frequent concern that physicians face in their daily practice. Critically ill patients are administered a greater number of medications and as they are more likely to develop poor outcomes considering their comorbid conditions. A recent multicenter retrospective observational multicenter study indicated that 53.8% of ICU patients were exposed to a possible drug-drug interaction and 38.2% to a possible clinically relevant drug-drug interaction [13]. The increasing admissions in ICU during the COVID-19 pandemic and the lack of evidence to establish an adequate treatment, it was noted that a great variety of drugs were used to treat COVID-19 infection, such as antivirals, corticosteroids, antibiotics, antiparasitic agents, and drugs that inhibit the biological activity of IL-1 and its end product, IL-6. These drugs may have a potential effect when used simultaneously. It is importat to keep in mind that some of these patients have comorbid conditions and the coadministration of these drugs, may influence COVID-19 treatment with possible interaction effects [14].

Regarding the nature of interactions, they may be both physicochemical or pharmacological, the latter being further divided into pharmacodynamic (synergism or

antagonism-) or pharmacokinetic interactions [15]. The main type D interaction detected was the association of midazolam (benzodiazepine) with fentanyl (opioid analgesic), an interaction classified as pharmacodynamic. The sedative effects of both drugs achieve a synergistic pharmacological effect. This interaction is intentionally used and sought in the routine of intensive care units, aiming to improve the comfort and anxiety of patients under mechanical ventilation and to optimize oxygenation. Currently this interaction is classified in the pharmacokinetic category, because fentanyl is a cytochrome P450 3A4 inhibitor and midazolam is metabolized by the same enzymatic system. Despite the fact that this association is common, its risk/benefit should always be assessed individually, with adequate follow-up and once the withdrawal of analgesia is considered. A progressive decrease and rotation to methadone or buprenorphine should be made in order to avoid withdrawal syndrome, which occurs in 50% of patients hospitalized in the intensive care unit. This may reduce morbidity and mortality, as well as the associated costs of the patient hospitalized in the ICU [16,17] .

Our results have shown that most of the type D drug interactions were due to cisatracurium and dexamethasone (8 %). A study published in 2021 that explains pharmacological treatments for acute respiratory distress syndrome (ARDS), it was found that cisatracurium, compared to vecuronium, is associated with fewer ICU days and need for assisted ventilation in patients with ARDS, which explains why its use is more common nowadays. It also indicates that, based on multiple investigations, the administration of dexamethasone has several advantages and improves the results in this type of patients. Dexamethasone reduced mortality at day 28 in those on supplemental oxygen with or without invasive mechanical ventilation; furthermore, it has demonstrated to decrease in the length of hospital stay by 1 day compared to placebo. Moreover, the study concluded that to date, no other medication has demonstrated a clear benefit in COVID-19-related ARDS [18].

Even though both cisatracurium and dexamethasone are the preferred options for COVID-19 treatment, it is important to highlight that the combination of these agents may lead to further increased risk of prolonged muscle weakness, as well as neuropathy, myopathy, and/or paralysis. This has been observed mainly in the ICU setting, particularly in patients presenting with sepsis or severe asthma requiring high-dose intravenous steroids and mechanical ventilation. Recovery from these effects may take weeks to months [19,20]. Although concomitant neuromuscular blockade and corticosteroid therapy may be therapeutically necessary, critical care guidelines recommend to use neuromuscular blocking drug only when necessary, employing the lowest doses possible and limiting the duration of either agent to limit the risk of developing myopathy or neuropathy. Close monitoring for new onset or worsening muscle weakness, reduction, or loss of deep tendon reflexes and/or peripheral sensory decrements should be performed [21].

In our study, 17.8% of patients had type X drug interactions. The most frequent involved quetiapine and methadone (19%), followed by quetiapine and metoclopramide, and in third place potassium chloride and ipratropium. Methadone is being used for pain management in the ICU in patients who require high doses and prolonged duration of analgesia and sedation, however when used with quetiapine, it has additive side effects. This means that as methadone itself may increase the probability to present delayed respiratory depression, QT prolongation and serotonin syndrome, simultaneous administration with quetiapine should be avoided [22]. Likewise, when quetiapine is administered in conjunction with metoclopramide, it could increase antidopaminergic effects, including extrapyramidal symptoms and neuroleptic malignant syndrome [23].

Within the group of drugs used for COVID-19 treatment, clarithromycin was the most common drug related with type X drug interactions, when administered with methadone and amiodarone, with a frequency of 4% and 2% respectively. Among the effects caused by these interactions, it is important to highlight that administration of methadone and macrolides, particularly clarithromycin, increases the risk of withdrawal syndrome [24]. In March 2022, a study that assessed the role of different drugs used in COVID-19 and their arrhythmogenic risk, it was found that both clarithromycin and amiodarone, are potentially QT-prolonging drugs. Due to this possible effect, the authors propose that all patients treated with any QT-prolonging drugs should be evaluated with a Tisdale score at baseline [25]. Critically ill patients are at an increased risk to develop drug–drug interactions (DDIs). DDIs that increase the risk of QT prolongation, and ultimately torsades de pointes, can result in a medical emergency. As a risk minimization strategy before prescribing a patient a drug that could prolong the QT interval it is important to evaluate and mitigate risks [17,26].

The main strength of our study is that it allows a description between drug interaction profiles and the presence of adverse clinical outcomes. It explores the association between sociodemographic and clinical variables with the presence of interactions of clinical importance (type X and type D). It also describes a possible statistically significant association between type D interactions and a major outcome such as mortality. Additionally, this study identified the main drug-drug interactions present in critically ill patients with COVID-19and proposes possible risk minimization plans.

The limitations of our study are that since it is mainly a retrospective-descriptive study with an analytical exploratory component, it does not allow causal associations to be made. Another limitation of this study is that critically ill patients may have other unmeasured variables that impact clinical outcomes, such as the CCI (19 items), impaired baseline renal or hepatic function. Although there was a statistically significant relationship between the presence of X or D interactions and length of ICU stay, the Poisson model does not fully explain the results, as there are likely other unmeasured variables that may better explain the length of hospital stay.

5. Conclusions

In conclusion, our study was able to demonstrate that subjects with an older age, a higher CCI, a higher SOFA score, a higher number of interactions and a higher number of prescribed drugs had a statistically significant higher risk of outcome. Patients who present type D interactions have a higher risk of mortality. This can be explained because the management of type D interactions is conservative in most cases, based on a risk minimization plan. This descriptive study may serve as a starting point for further studies, which may clarify whether X-type interactions are also correlated with mortality, as well as to determine why X or D interactions may increase the length of hospital stay.

Supplementary Materials: The following supporting information can be downloaded at: www.mdpi.com/xxx/s1, Table S1: Frequencies of drugs involved in pharmacological interactions; Table S2: Bivariate and multivariate analysis by length of stay (LOS)

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