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Polypharmacy and Drug Interactions in the COVID-19 Pandemic

Ricardo Enrique Barcia[1,2], Guillermo Alberto Keller[3], Natalia Bello[4], Francisco Azzato[1], Roberto Alejandro Diez[3], Guido Giunti[5,6]

[1]6° Cátedra de Medicina Interna, Hospital de Clínicas "José de San Martín", Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina;
[2]DrApp, Empresa de Desarrollos Informáticos para Medicina, Buenos Aires, Argentina;
[3]Centro de Vigilancia y Seguridad de Medicamentos, Departamento de Toxicología y Farmacología, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina;
[4]División Infectología, Hospital de Clínicas "José de San Martín", Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina;
[5]University of Oulu, Oulu, Finland;
[6]School of Medicine, Trinity College Dublin, Dublin, Ireland

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Abstract: The COVID-19 pandemic generated a great impact on health systems. We compared evolution, polypharmacy, and potential drug-drug interactions (P-DDIs) in COVID-19 and non-COVID-19 hospitalizations during first wave of pandemic. Prescriptions for hospitalized patients ≥ 18 years (COVID-19 and non-COVID-19 rooms) between April and September 2020 were included. The computerized medical decision support system SIMDA and the physician order entry system Hdc.DrApp.la were used. Patients in COVID-19 rooms were divided into detectable and non-detectable, according to real-time reverse transcription polymerase chain reaction (RT-PCR). Number of drugs, prescribed on day 1, after day 1, and total; polypharmacy, excessive polypharmacy, and P-DDIs were compared. 1,623 admissions were evaluated: 881 COVID-19, 538 detectable and 343 non-detectable, and 742 non-COVID-19. Mortality was 15% in COVID-19 and 13% in non-COVID-19 (RR [non-COVID-19 vs. COVID-19]:

Mailing Address: Dr. Ricardo E. Barcia, Av. Córdoba 2351, piso 10, 6° Cátedra de Medicina Interna (C1120AAR) Ciudad Autónoma de Buenos Aires, Argentina; e-mail: ricardoebarcia@hotmail.com

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0.84 [95% CI] [0.66–1.07]). In COVID-19, mortality was 19% in detectable and 9% in non-detectable (RR: 2.07 [1.42–3.00]). Average number of drugs was 4.54/patient (SD ± 3.06) in COVID-19 and 5.92/patient (±3.24) in non-COVID-19 ($p<0.001$) on day 1 and 5.57/patient (±3.93) in COVID-19 and 9.17/patient (±5.27) in non-COVID-19 ($p<0.001$) throughout the hospitalization. 45% received polypharmacy in COVID-19 and 62% in non-COVID-19 (RR: 1.38 [1.25–1.51]) and excessive polypharmacy 7% in COVID-19 and 14% in non-COVID-19 (RR: 2.09 [1.54–2.83]). The frequency of total P-DDIs was 0.31/patient (±0.67) in COVID-19 and 0.40/patient (±0.94) in non-COVID-19 ($p=0.022$). Hospitalizations in the COVID-19 setting are associated with less use of drugs, less polypharmacy and less P-DDIs. Detectable patients had higher mortality.

Introduction

On March 11, 2020, the World Health Organization (WHO) declared a new world pandemic (WHO, 2020), reaching our centre (Hospital de Clínicas "José de San Martín" – HCJSM) on March 15, 2020 (CDC COVID-19 Response Team, 2020; Ludueña et al., 2020). The COVID-19 pandemic had a significant impact on all health systems. In our hospital, special rooms were assigned to care for these patients, which functioned in parallel with hospitalization rooms for non-COVID-19 patients. Health personnel found themselves faced with caring for those affected by a pandemic while continuing to care for patients with the usual pathologies that are treated in the Department of Medicine. The drugs proposed for treatment in the first stage of the pandemic generated great doubts not only regarding their efficacy but also their potential adverse effects (Gandhi et al., 2020; Roden et al., 2020).

Polypharmacy and potential drug-drug interactions (P-DDIs) were under study in our hospital at that time, with a computerized medical decision support system (CMDSS) SIMDA in association with the physician order entry system (POES) Hdc.DrApp.la (Barcia et al., 2023). The emergence of the Pandemic gave us a unique opportunity to evaluate the impact of a new disease, new drugs and new P-DDIs.

The drugs that have been used in COVID-19 patients, include antiviral drugs (remdesivir, molnupiravir, favipiravir, ivermectin), steroids (dexamethasone), monoclonal antibodies (anti-spike protein including casirivimab and imdevimab or sotrovimab), immunomodulatory drugs (anti-interleukin-6 tocilizumab or the janus kinase inhibitor baricitinib), anticoagulants (heparin, enoxaparin) and antibiotics (including macrolides like azithromycin with potential antiviral and immunomodulatory effects, doxycycline, ceftriaxone). All these drugs have been the subject of academic discussion about their efficacy, safety, and in particular the risk of interactions and risk/benefit balance. Most of them have been associated with important adverse reactions such as arrhythmias, prolongation of the QT interval, or neurological toxicity, among others (Gandhi et al., 2020; Roden et al., 2020).

In this study, we compared the evolution, polypharmacy, and P-DDIs between hospitalizations in COVID-19 wards and hospitalizations in non-COVID-19 wards

in the Department of Internal Medicine of the HCJSM during the first wave of the COVID-19 pandemic in Buenos Aires, Argentina, between April 4, 2020 and September 3, 2020. This period was included in the implementation phase of our work: the CDMSS SIMDA was used in both groups (Barcia et al., 2023). We also analyzed the impact of the administration of convalescent plasma in patients with COVID-19.

Material and Methods

Setting

The Hospital de Clínicas "José de San Martín" is a teaching hospital dependent on the Facultad de Medicina of the Universidad de Buenos Aires, located in the Ciudad Autónoma de Buenos Aires. The HCJSM has more than 3,200 employees and receives more than 400,000 external consultations per year. The HCJSM does not have a unified electronic medical record system between the different departments and services, but there are customized developments in each area with occasional points of contact. The Department of Internal Medicine was in charge of its 8 usual rooms and 3 rooms were added due to the COVID-19 pandemic: 11 rooms in total. The rooms were divided into COVID-19 rooms and non-COVID-19 rooms in accordance with the requirements of each moment. The medical prescriptions were made by Internal Medicine resident physicians, with personalized access to the Hdc.DrApp.la POES after signing a consent with authorization for the use of information for the study. All the resident physicians voluntarily adhered to the use of the systems. Internal Medicine physicians supervised the prescriptions in the Hdc.DrApp.la POES.

Selection criteria

All prescriptions from all patients 18 years of age or older admitted to the wards of the Department of Internal Medicine of the HCJSM during the period detailed above were evaluated with respect to the following inclusion and exclusion criteria:

Inclusion criteria: prescriptions for patients 18 years of age or older who were hospitalized at the start of the study, or who required hospitalization during the phase of the study.

Exclusion criteria: prescriptions for patients who were hospitalized more than 14 days before the start date of each phase.

Elimination criteria: prescriptions for patients who were hospitalized for readmission following identical and preestablished therapeutic schemes (example: chemotherapy), and without complications during hospitalization that would justify other treatments. In the case of readmission, only the first hospitalization was recorded. Patients who remained hospitalized beyond 60 days after the closing date and patients with discordant data between the different systems that could not be resolved were also eliminated.

Data collection

The study was conducted between April 4, 2020, and September 3, 2020. This period constitutes intervention phase of a phased study that compares before/after the implementation of the CMDSS SIMDA (Barcia et al., 2023). In this phase, the CMDSS SIMDA was available, which detects P-DDIs automatically and adjusts drug dosage according to renal function. To determine the P-DDIs, DrugBank was used (Wishart et al., 2018). Glomerular filtration rate was calculated using the CPK-Epi formula (Levey et al., 2009) and the adjusted doses were calculated based on standardized creatinine clearance formulas (Karsch-Völk et al., 2013).

Resident physicians were in charge of filling prescriptions: informed consent was obtained from all participants. The prescriptions were classified into those of the first day and prescriptions after the first day. P-DDIs were analyzed for the first-day prescriptions. The hospital record data was obtained from the "Camas" computer system, exclusive to the HCJSM. The data from POES Hdc.DrApp.la were compared with those from the Camas system. Drugs administered orally, parenterally, inhaled, transdermally, or intrathecally were included. Fluid and electrolyte infusions, topical application drugs, and oral, enteral, or parenteral nutrition schemes were excluded. Supplementary oxygen administration (yes/no) during hospitalization was included. The pharmacological treatments on day 1 were divided into 4 groups: usual medication, which is that which the patient received prior to admission and continues during hospitalization; current medication, which is the one that was added due to the problem that led to hospitalization; thromboprophylaxis and insulin therapy. The following combinations were registered as 1 single drug: trimethoprim-sulfamethoxazole (cotrimoxazole), ampicillin-sulbactam, amoxicillin-clavulanic acid, levodopa-carbidopa, piperacillin-tazobactam, and valsartan-sacubritil. The different insulin formulations were registered as a single drug. Fixed combinations of: antihypertensives (except valsartan-sacubritil), bronchodilators, drugs for benign prostatic disease, and drugs for digestive disorders were recorded as 2 or more drugs. Polypharmacy was defined as the prescription of 5 or more drugs; excessive polypharmacy such as the prescription of 10 or more drugs (Jyrkkä et al., 2009; Leelakanok et al., 2017; Masnoon et al., 2017).

In the COVID-19 wards, patients suspected of having this disease or diagnosed with this disease were admitted to isolation rooms with 1 or 2 beds, according to the medical and epidemiological condition of each patient. The diagnosis of COVID-19 infection was made by nasopharyngeal swab (NPS) with the determination of the viral genome through a real-time reverse-transcription polymerase chain reaction (RT-PCR), according to the protocol of Centers for Disease Control and Prevention (CDC, Atlanta, USA) (CDC, 2019). The results of the RT-PCR studies were compared with the data registered in the Sistema Integrado de Información Sanitaria Argentina (SISA). According to the result, each patient in the COVID-19 group was assigned to the detectable or non-detectable subgroup. The situation of

hospitalization and isolation were redefined according to this result, in accordance with the clinical and epidemiological conditions of each case.

The convalescent plasma transfusion was carried out in the context of a HCJSM protocol, designed to systematize the transfusion from June 1, 2020. Patients included were ≥ 18 years old, diagnosed with COVID-19 by RT-PCR (detectable) in NPS, who had to sign an informed consent, and with at least 1 of the following severity criteria: oxygen saturation < 93% with fraction of inspired oxygen (FiO_2) of 21%, arterial pressure of oxygen PaO_2/FiO_2 ratio < 300, progression of radiological infiltrates greater than 50% in the last 24–48 hours, septic shock or multiple organ dysfunction. Terminally ill patients (life expectancy < 6 months) were excluded. Treatment with convalescent plasma had to be established in the first 14 days from the onset of symptoms, in 2 transfusions of 200 to 300 ml, separated by 48 hours, according to the criteria of the treating medical team.

With the information generated by the HDC.DrApp POES and the confirmatory data of each hospitalization of the Camas system, an Excel spreadsheet was generated. For this form, the information of each patient and the consistency between the systems were verified. Once the Excel spreadsheet was completed, another blinded statistical analysis was performed, without the identity of the patients.

Variables

Age, length of hospitalization, mortality, referral to critical area, and mortality in patients who were transferred to critical areas were compared between groups. The number of drugs in all the modalities analyzed, the percentage of patients with polypharmacy and with excessive polypharmacy, and the number of P-DDIs in studied groups were also compared. The same variables were compared between patients 65 years or older in relation to patients younger than 65 years. In the COVID-19 group, the same comparisons were done between COVID-19 detectable and COVID-19 non-detectable. The evolution among those who received convalescent plasma transfusion was also analyzed.

Ethics

The study and its subsequent adjustments were approved by the Department of Internal Medicine, the Ethics Committee, the Department of Teaching and Research, and the Management of the HCJSM. The identity and confidentiality of the data of each patient were preserved. No animals were used in the study. All procedures with people were carried out in accordance with the ethical standards of the regulations for studies, both national and international, and with the Declaration of Helsinki revised in 2013.

This trial was registered with ClinicalTrial.gov (NCT03901820) and Registro Nacional de Investigaciones en Salud, RENIS (IS003175).

Statistical analysis

Normal variables were expressed as mean (±SD). Univariate differences between qualitative data were evaluated with the chi-square test, Yates' correction, or Fisher's exact test. The differences between the quantitative data were explored with ANOVA and post hoc tests. Statistica 6.0 and MedCalc 2009 programs were used.

Results

Patient demographics

1,675 hospitalizations were registered in the evaluated period. After applying the inclusion, exclusion, and elimination criteria, 1,623 hospitalizations of 1,491 patients entered the study, with 132 readmissions (Figure 1). Among the 1,623 hospitalizations, 38 were reassigned during hospitalization between to COVID-19 and non-COVID-19 wards. Patients who were in the COVID-19 and non-COVID-19 wards during the same hospitalization were included in the COVID-19 group.

The patients in the COVID-19 group were significantly younger ($p<0.001$), hospitalized for less time ($p<0.001$), referred to critical areas more frequently, and had higher mortality among those referred to critical areas than the non-COVID-19 group (Table 1). The higher mortality of the COVID-19 group did not reach statistical significance. Those over 65 years of age had significantly higher mortality in both groups. In the COVID-19 group, but not in the non-COVID-19 group, those ≥ 65 years also had significantly longer hospital stays, more referrals to critical areas, and higher mortality among those referred to critical areas.

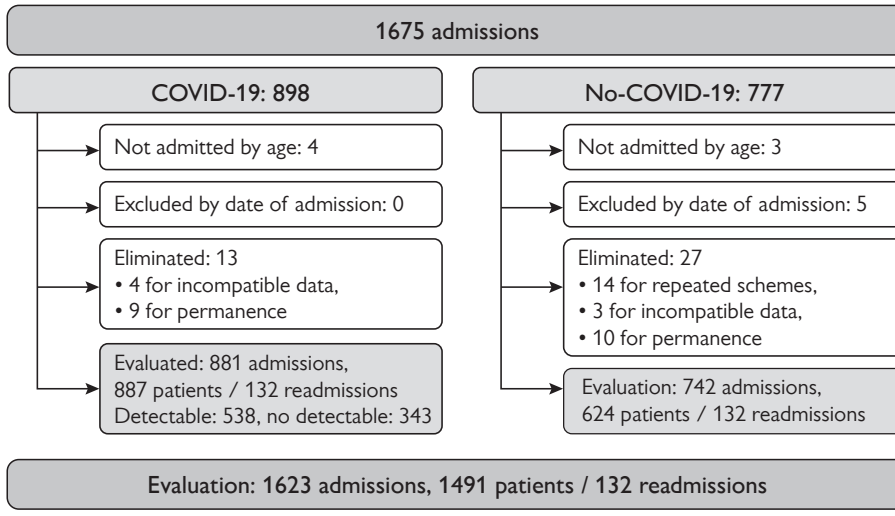

Figure 1 – Population evaluated.

Table 1 – Characteristics of the evaluated population and its evolution, according to mortality and referral to critical area, with comparison COVID-19 vs. non-COVID-19 and by age between <65 vs. ≥65 years

Variable	COVID-19				Non-COVID-19				Non-COVID-19 vs. COVID-19
	total	<65 years	≥65 years	statistics	total	<65 years	≥65 years	statistics	statistics
N=1,623 (%)	881 (54.28)	519 (58.91)	362 (41.09)		742 (45.72)	386 (52.02)	356 (47.98)		
Female N (%)	448 (50.85)	259 (49.90)	189 (52.21)		357 (48.11)	168 (43.52)	189 (53.09)		
Age media ± SD	57.57 ± 20.81	43.24 ± 12.83	78.86 ± 8.53	p<0.001	61.25 ± 19.42	46.23 ± 13.61	77.63 ± 8.48	p<0.001	p<0.001
Length of stay days ± SD	13.24 ± 16.86	10.53 ± 15.11	17.26 ± 18.47	p<0.001	15.90 ± 20.81	15.19 ± 16.95	16.68 ± 24.31	p=0.330	p=0.004
Mortality (%)	136 (15.44)	18 (3.47)	118 (32.60)	RR 7.62 (4.70–12.35)	96 (12.94)	25 (6.48)	71 (19.94)	RR 3.30 (2.12–5.13)	RR 0.84 (0.66–1.07)
Referral to critical area (%)	66 (7.49)	25 (4.82)	41 (11.33)	RR 1.91 (1.17–3.09)	28 (3.77)	14 (3.63)	14 (3.93)	RR 1.16 (0.56–2.42)	RR 0.50 (0.33–0.78)
Mortality in referral to critical area (%)	31 (46.97)	6 (24.00)	25 (60.98)	RR 4.84 (2.00–11.72)	8 (28.57)	4 (28.57)	4 (28.57)	RR 1.16 (0.29–4.63)	RR 0.31 (0.14–0.66)

SD – standard deviation; RR – relative risk

Prescription characteristics

COVID-19 patients had significantly fewer drugs on day 1, both total and usual, current ($p<0.001$), thromboprophylaxis, and insulin ($p=0.024$). They also had significantly less drugs added after day 1, fewer total drugs during hospitalization, less polypharmacy, less excessive polypharmacy, less total P-DDIs, and less severe P-DDIs. In the comparison by age of the patients, those ≥ 65 years old presented significantly more usual drugs on day 1 in both groups. In the COVID-19 group, but not in the non-COVID-19 group, patients ≥ 65 years also received more total drugs on day 1, with more thromboprophylaxis and more insulin on day 1. They also presented significantly higher values of drugs added after day 1, total drugs during hospitalization, polypharmacy, excessive polypharmacy, total P-DDIs, and moderate P-DDIs. Among patients in the non-COVID-19 group, those < 65 years received significantly more current drugs on day 1 than those ≥ 65 years. In COVID, in 11 hospitalizations (1.12%) there were no pharmacological indications on the first day and in 428 hospitalizations (48.58%) no new medication was added after the first day (Table 2).

Drugs characteristics and P-DDIs

Among the drugs used for COVID-19, the most frequent indications (% compared to the COVID-19 group) were: dexamethasone 274 (31.10%), ceftriaxone 267 (30.30%), clarithromycin 204 (23.15%), oseltamivir 71 (8.05%), azithromycin 45 (5.10%), amoxicillin-clavulanic 41 (4.65%), hydroxychloroquine 33 (3.74%), ritonavir-lopinavir 17 (1.92%) and darunavir 1 (0.11%). On the other hand, among COVID-19 patients, 639 (72.53%) received enoxaparin, 526 (59.70%) received paracetamol. Oxygen therapy in the COVID-19 population was significantly higher than in the non-COVID-19 population and in both groups it was higher among those patients aged 65 or over (Table 3).

The most frequent P-DDIs were analyzed, showing that clarithromycin stands out among the associated drugs in the potential P-DDIs in the COVID-19 group (Table 4).

COVID-group disaggregated analysis

In the COVID-19 group, the 881 patients were divided into 538 detectable and 343 non-detectable, according to the RT-PCR result. Of the 14 readmissions in the COVID-19 group, 6 were detectable in both, 3 non-detectable in both, and 5 detectable once and non-detectable once. COVID-detectable patients were older and had higher amounts of length of hospitalization, mortality, and referral to the critical area. Among the detectable patients hospitalized in the COVID-19 wards, those ≥ 65 years of age had significantly longer hospitalizations, and higher mortality, risk for critical area referral, and mortality (among those who were referred to critical areas). Among the patients admitted to the non-detectable COVID-19 wards, those ≥ 65 years old, the percentage of women was significantly higher, they had significantly longer hospitalizations, higher mortality, and a higher risk of being referred to the

Table 2 – Drugs per patient on day 1, divided into usual medication, current medication, thromboprophylaxis, and insulin; drugs added after day 1, total drugs during hospitalization, polypharmacy, excessive polypharmacy, P-DDIs on day 1, total and according to severity. In all these cases, COVID-19 and non-COVID-19 hospitalizations are compared and by age between <65 vs. ≥65 years

Parameter	COVID-19			
	total	<65 years	≥65 years	statistics
N=1,623 (%)	881 (54.28)	519 (58.91)	362 (41.09)	
Oxygen therapy (%)	206 (23.38)	86 (16.57)	120 (33.15)	p=0.025
Day 1 total drugs ± SD	4.54 ± 3.06	3.53 ± 2.57	6.03 ± 3.13	p<0.001
Day 1 usual drugs ± SD	1.78 ± 2.26	1.14 ± 1.80	2.72 ± 2.53	p<0.001
Day 1 current drugs ± SD	1.94 ± 1.51	1.71 ± 1.45	2.29 ± 1.55	p<0.001
Day 1 thromboprophylaxis (%)	600 (68.10)	294 (56.64)	306 (84.53)	p=0.027
Day 1 insulin (%)	117 (13.28)	53 (10.21)	64 (17.67)	p=0.021
Drugs added after day 1 ± SD	1.04 ± 2.29	0.88 ± 2.16	1.27 ± 2.45	p=0.012
Total drugs in hospitalization ± SD	5.57 ± 3.93	4.41 ± 3.54	7.30 ± 3.87	p<0.001
Polypharmacy (%)	397 (45.06)	161 (31.02)	236 (65.19)	RR 1.70 (1.44–2.01)
Excessive polypharmacy (%)	59 (6.70)	15 (2.89)	44 (12.15)	RR 3.41 (1.92–6.06)
P-DDIs/patient total SD	0.31 ± 0.67	0.19 ± 0.55	0.48 ± 0.79	p<0.001
P-DDIs/patient moderate ± SD	0.17 ± 0.51	0.07 ± 0.34	0.31 ± 0.67	p<0.001
P-DDIs/patient severe ± SD	0.06 ± 0.30	0.05 ± 0.30	0.08 ± 0.30	p=0.098
P-DDIs/patient mild ± SD	0.08 ± 0.30	0.07 ± 0.28	0.09 ± 0.32	p=0.326

P-DDIs – potential drug-drug interactions; SD – standard deviation; RR – relative risk

critical area, without significant differences in mortality among those who were referred to critical areas (Table 5).

Detectable patients had a significantly higher oxygen requirement, more thromboprophylaxis, more drugs added after day 1, and more total drugs during hospitalization, with no significant differences in the other variables analyzed (Table 6). Among detectable hospitalized patients in the COVID-19 wards, those 65 years and older received significantly more oxygen therapy, more total drugs on day 1, both current and usual, and thromboprophylaxis; more drugs added after day 1, more polypharmacy, more excessive polypharmacy, more total P-DDIs, and more moderate P-DDIs than those younger than 65 years. Insulin indication on day 1, severe P-DDIs, and mild P-DDIs were not significantly higher in those 65 years or older than in those younger than 65 years.

Non-COVID-19				Non-COVID-19 vs. COVID-19
total	**<65 years**	**≥65 years**	**statistics**	**statistics**
742 (45.72)	386 (52.02)	356 (47.98)		
35 (4.72)	8 (2.07)	27 (7.58)	p=0.018	p<0.001
5.92 ± 3.24	5.91 ± 3.32	5.92 ± 3.16	p=0.941	p<0.001
2.42 ± 2.31	2.12 ± 2.28	2.74 ± 2.30	p<0.001	p<0.001
2.51 ± 2.22	2.86 ± 2.30	2.13 ± 2.06	p<0.001	p<0.001
577 (77.76)	291 (75.58)	286 (80.11)	p=0.836	p=0.024
157 (21.15)	63 (16.36)	94 (26.33)	p=0.017	p=0.024
3.25 ± 4.10	3.49 ± 4.58	3.00 ± 3.49	p=0.102	p<0.001
9.17 ± 5.27	9.40 ± 5.73	8.92 ± 4.71	p=0.220	p<0.001
460 (61.99)	240 (62.18)	220 (61.80)	RR 1.07 (0.92–1.23)	RR 1.38 (1.25–1.51)
104 (14.02)	55 (14.25)	49 (13.76)	RR 1.04 (0.72–1.50)	RR 2.09 (1.54–2.84)
0.40 ± 0.94	0.36 ± 0.97	0.44 ± 0.91	p=0.243	p=0.022
0.18 ± 0.53	0.16 ± 0.50	0.21 ± 0.55	p=0.154	p=0.565
0.11 ± 0.41	0.12 ± 0.44	0.10 ± 0.37	p=0.604	p=0.006
0.11 ± 0.38	0.09 ± 0.36	0.13 ± 0.41	p=0.145	p=0.082

Among the non-detectable patients admitted to the COVID-19 wards, those 65 years of age or older received significantly more oxygen therapy, more total drugs on day 1, more usual drugs on day 1, more current drugs on day 1, more thromboprophylaxis on day 1, more insulin on day 1, more total drugs during hospitalization, more polypharmacy, more excessive polypharmacy, more total P-DDIs, and more moderate P-DDIs than in those under 65 years of age. There were no significant differences in drugs added after day 1, severe P-DDIs and mild P-DDIs were not significantly higher among those 65 years and older compared with those younger than 65 years (Table 6).

Among the 538 detectable patients admitted to COVID-19 wards, 114 received convalescent plasma transfusion. No differences in mortality could be observed between those who received convalescent plasma (23/114: 20.17%) compared to those who did not (81/424: 19.10%) (RR [relative risk]: 1.05, 95% CI [confidence

Table 3 – The 20 most used drugs in each group are presented

	COVID-19 (N=881)		Non-COVID-19 (N=742)	
	drugs	**N (%)**	**drugs**	**N (%)**
1	Enoxaparin	639 (72.53)	Enoxaparin	502 (67.65)
2	Paracetamol	526 (59.70)	Omeprazole	275 (37.06)
3	Ceftriaxone	263 (29.85)	Insulin	158 (21.29)
4	Dexamethasone	253 (28.71)	Atorvastatin	131 (17.65)
5	Clarithromycin	212 (24.06)	Paracetamol	131 (17.65)
6	Omeprazole	207 (23.49)	Enalapril	127 (17.11)
7	Insulin	150 (17.02)	ASA	120 (16.17)
8	Enalapril	132 (14.98)	Piperacillin TZB	92 (12.39)
9	Piperacillin TZB	115 (13.05)	Tramadol	92 (12.39)
10	Clonazepam	98 (11.12)	Meprednisone	83 (11.18)
11	ASA	97 (11.01)	Ceftriaxone	79 (10.64)
12	Quetiapine	85 (9.64)	Cotrimoxazole	76 (10.24)
13	Levothyroxine	84 (9.53)	Amlodipine	71 (9.56)
14	Morphine	72 (8.17)	Bisoprolol	71 (9.56)
15	Amlodipine	69 (7.83)	Dexamethasone	69 (9.29)
16	Tramadol	67 (7.60)	Levothyroxine	69 (9.29)
17	Lactulose	66 (7.49)	Metoclopramide	69 (9.29)
18	Bisoprolol	64 (7.26)	Allopurinol	61 (8.22)
19	Atorvastatin	60 (6.81)	Furosemide	61 (8.22)
20	Carvedilol	60 (6.81)	Ranitidine	52 (7.00)
20	Meprednisone	60 (6.81)		

ASA – acetylsalicylic acid; TZB – tazobactam

interval]: 0.69–1.59). In the subanalysis that compares the evolution according to the date convalescent plasma was administered in relation to the date of onset of symptoms, no significant differences were observed in mortality among those who received it within the first 3 days of the onset of symtoms (8/38: 21.05%), between the 4th and 7th day of the onset of symptoms (6/24: 25.00%) or after the 7th day of the onset of symptoms (9/52: 17.30%).

Discussion

This work shows important data on mortality, drug prescription pattern and interactions linked to the pandemic. Its design started in a previous period, and with originally different purposes (evaluating the effects of the implementation of an interaction detection software) makes it a unique material to be able to compare how the epidemiological situation modified the use of drugs, and to detect factors demographic factors associated with increased risk, such as belonging to age groups. The present work also shows higher mortality in patients with detectable virus.

In our study, younger patients diagnosed with COVID-19 were hospitalized for shorter periods (10.53 ± 15.11 vs. 17.26 ± 18.47, $p<0.001$; Table 1), were more

Table 4 – Potential drug-drug interactions (P-DDIs) more frequent in each group

COVID-19 (N=881)				Non-COVID-19 (N=742)			
Drugs	**P-DDIs**	**N**	**%**	**Drugs**	**P-DDIs**	**N**	**%**
Clarithromycin-Dexamethasone	altered metabolism by CYPs	71	8.06	Metoclopramide-Morphine	constipation	15	2.02
ASA-Enoxaparin	risk of bleeding	66	7.49	Amlodipine-Paracetamol	hypertension	14	1.89
Enalapril-Paracetamol	hypertension	32	3.63	Clonazepam-Paracetamol	less effective benzodiazepines	12	1.62
Clonazepam-Paracetamol	less effective benzodiazepines	31	3.52	Alprazolam-Paracetamol	less effective benzodiazepines	10	1.35
Clarithromycin-insulin	hypoglycemia	30	3.41	Atorvastatin-Paracetamol	altered metabolism by CYPs	9	1.21
Levothyroxine-Paracetamol	less effective Levothyroxine	26	2.95	Levothyroxine-Paracetamol	less effective Levothyroxine	8	1.08
ASA-insulin	hyperglycemia	24	2.72	Losartan-Paracetamol	hypertension	7	0.94
Losartan-Paracetamol	hypertension	21	2.38	Enalapril-Paracetamol	hypertension	7	0.94
Carvedilol-Paracetamol	altered metabolism by CYPs	20	2.27	Carvedilol-Paracetamol	altered metabolism by CYPs	7	0.94
Atorvastatin-Paracetamol	altered metabolism by CYPs	20	2.27	Amiodarone-Bisoprolol	bradycardia	7	0.94

ASA – acetylsalicylic acid; CYP – cytochrome p450; P-DDIs – potential drug-drug interactions

frequently referred to critical areas, and had higher mortality among those referred to critical areas than patients in non-COVID-19 wards. Since patients with confirmed COVID-19 and suspected COVID-19 patients were admitted to the COVID-19 wards, not all of them were detectable: detectable were those with the highest mortality: 19.33%. In relation to another study carried out at the same time in our country, organized by the Sociedad Argentina de Medicine, in 37 centers, with 4,776 patients admitted to Medical Clinic Services, ≥18 years old with confirmed COVID-19, our detectable COVID population was older (61 vs. 56.9 years, although the study did not adjust for other factors), was hospitalized for a longer time (15 days vs. 8 days), had greater referral to the critical area (19.7 vs. 14.8%)

Table 5 – Evolution of COVID-19 hospitalizations according to detectable and non-detectable, total and by age <65 o ≥65 years

Parameter	Detectable				Non-detectable				Detectable vs. non-detectable
	total	<65 years	≥65 years	statistics	total	<65 years	≥65 years	statistics	statistics
N=881 (%)	538 (61.06)	288 (53.53)	250 (46.46)		343 (38.94)	231 (67.34)	112 (32.65)		
Female N (%)	262 (48.70)	130 (44.98)	132 (53.01)	p=0.894	186 (54.23)	90 (39.13)	96 (84.96)	p=0.027	
Age media ± SD	60.79 ± 19.83	45.21 ± 12.30	78.87 ± 8.07		53.50 ± 21.39	41.02 ± 12.75	78.89 ± 9.69		p<0.001
Length of stay days	15.24 ± 15.21	12.57 ± 12.33	18.34 ± 17.50	p<0.001	10.18 ± 18.72	7.93 ± 17.63	14.72 ± 20.07	p<0.001	p<0.001
Mortality (%)	104 (19.33)	10 (3.46)	94 (37.75)	RR 10.91 (5.81–20.48)	32 (9.33)	7 (3.04)	25 (22.12)	RR 7.27 (3.24–16.30)	RR 2.07 (1.42–3.00)
Referral to critical area	51 (9.47)	19 (6.59)	32 (12.8)	RR 1.94 (1.12–3.33)	15 (4.37)	6 (2.59)	9 (8.03)	3.09 (1.12–8.47)	RR 2.16 (1.23–3.79)
Mortality in referral to critical area (%)	26 (50.99)	3 (15.78)	23 (71.87)	RR 4.55 (1.57–13.15)	5 (33.33)	3 (50.00)	2 (22.22)	RR 0.44 (0.10–1.91)	RR 1.52 (0.71–3.28)

SD – standard deviaton; RR – relative risk

and higher mortality (19.33 vs. 12.3%) (Boietti et al., 2021). In another study from a single center in Buenos Aires city with 417 patients, the average age was 43 years and mortality 3.8% (Melendi et al., 2020). The correlation between age and unfavorable evolution is consistent in studies and meta-analyses (Bonanad et al., 2020; Boietti et al., 2021). Our patients 65 years of age or older had higher mortality in both the COVID-19 and non-COVID-19 groups, reaching the highest percentage among detectable COVIDs: 37.75%.

Another important parameter was the drug use pattern during the COVID-19 pandemic such as lower drug use, less polypharmacy, and less P-DDIs in COVID-19 hospitalizations. These data were noticeable, taking into account the number of specific treatments for coronavirus proposed with dissimilar therapeutic evidence. At the beginning of the pandemic, there was no approved treatment for COVID-19 disease. In the absence of a specific antiviral treatment, the WHO prioritized drugs to be investigated in clinical trials based on *in vitro* efficacy. Recommendations were made to treat these infections with different antiviral drugs that had been tested on other coronaviruses. Lopinavir-ritonavir had demonstrated inhibitory activity *in vitro* during the severe acute respiratory syndrome coronavirus (SARS-CoV-1) outbreak. This combination was already available in our country and was approved by the Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT) for use in patients with HIV infection (Ministerio de Salud Argentina, 2020a). The treatment established in our hospital was adapted to the recommendations of the Ministerio de Salud de la Nación Argentina. These recommendations were updated, based on available evidence and ongoing clinical trials (Ministerio de Salud Argentina, 2020b, c, 2021). The treatment regimen proposed at the begining of our study was as follows: for mild infection without pneumonia: no treatment; for mild infection with pneumonia according to pneumonia severity score, CURB-65: 0–1 (Lim et al., 2003): consider lopinavir/ritonavir; for severe respiratory infection (CURB-65: >2 pts) in >60 years, with comorbidities (arterial hypertension, diabetes mellitus, heart disease, chronic obstructive pulmonary disease (COPD), chronic renal failure, immunocompromised): lopinavir/ritonavir or darunavir/ritonavir + hydroxychloroquine (Singh et al., 2020). In addition, antibiotic treatment with ampicillin-sulbactam or ceftriaxone + azithromycin + oseltamivir was recommended. These treatment guidelines were published on March 20, 2020, and remained current through May 30, 2020 (Ministerio de Salud Argentina, 2021). Due to the limited evidence of therapeutic efficacy on COVID-19, the epidemiological dynamics of SARS-CoV-2, and due to the little or no favorable clinical impact of treatments with lopinavir-ritonavir, darunavir/ritonavir, hydroxychloroquine and oseltamivir, added to poor tolerance and adverse effects, these drugs were no longer used (Ministerio de Salud Argentina, 2021): this can be observed in the low rate of prescriptions observed for these drugs in our population: oseltamivir 71 (8.05%), hydroxychloroquine 33 (3.74%), ritonavir-lopinavir 17 (1.92%) and darunavir 1 (0.11%). On the other hand, in the COVID-19

Table 6 – Oxygen therapy, drugs per patient on day 1, divided into usual medication, current medication, thromboprophylaxis, and insulin; drugs added after day 1, total drugs during hospitalization, polypharmacy, excessive polypharmacy, P-DDIs on day 1, total and according to severity in detectable and non-detectable patients, total and by age <65 o ≥65 years

Parameter	Detectable			
	total	<65 years	≥65 years	statistics
N=881 (%)	538 (61.06)	288 (53.53)	250 (46.46)	
Oxygen therapy (%)	172 (31.9)	72 (24.91)	100 (40.16)	p<0.001
Day 1 total drugs ± SD	4.68 ± 2.89	3.72 ± 2.40	5.80 ± 3.02	p<0.001
Day 1 usual drugs ± SD	1.83 ± 2.27	1.19 ± 1.84	2.57 ± 2.49	p<0.001
Day 1 current drugs ± SD	1.95 ± 1.43	1.74 ± 1.44	2.19 ± 1.38	p<0.001
Day 1 thromboprophylaxis (%)	407 (75.65)	192 (66.66)	215 (86.00)	p<0.001
Day 1 insulin (%)	79 (14.68)	35 (12.15)	44 (17.60)	p=0.391
Drugs added after day 1 ± SD	1.17 ± 2.30	0.91 ± 1.95	1.48 ± 2.62	p=0.003
Total drugs in hospitalization ± SD	6.19 ± 6.11	5.23 ± 5.21	7.31 ± 6.86	p<0.001
Polypharmacy (%)	257 (47.77)	100 (34.60)	157 (63.05)	RR 1.82 (1.51–2.19)
Excessive polypharmacy (%)	34 (6.32)	6 (2.08)	28 (11.24)	RR 5.42 (2.28–12.87)
P-DDIs/patient total ± SD	0.32 ± 0.68	0.21 ± 0.58	0.45 ± 0.76	p<0.001
P-DDIs/patient moderate ± SD	0.18 ± 0.53	0.09 ± 0.39	0.28 ± 0.64	p<0.001
P-DDIs/patient severe ± SD	0.06 ± 0.31	0.05 ± 0.34	0.08 ± 0.27	p=0.364
P-DDIs/patient mild ± SD	0.08 ± 0.29	0.07 ± 0.28	0.09 ± 0.31	p=0.453

P-DDIs – potential drug-drug interactions; SD – standard deviation; RR – relative risk

population the use of antibiotics ceftriaxone in 267 patients (30.30%), clarithromycin in 204 (23.15%), azithromycinin 45 (5.10%), amoxicillin-clavulanate in 41 (4.65%) was high, which were prescribed more than in the non-COVID-19 population. Treatment with these antibiotics was maintained in cases of suspected bacterial superinfection throughout the period evaluated. In the Boietti et al. (2021) study, 27.9% received antibiotics, while in another study from a single center in Buenos Aires city with 417 patients, 39.6% received oral antibiotics and 29.3% intravenous antibiotics (Melendi et al., 2020).

Beyond antiviral or antibacterial treatment, the use of oxygen therapy, thromboprophylaxis, treatment with corticosteroids and symptomatic treatment with paracetamol should be highlighted. In the Boietti et al. (2021) study, 36.7% received supplemental oxygen therapy. Of the patients with O_2 supplementation, 25.5% (n=448) required intensive care unit (ICU) admission, and of these, 170 (45.7%) received mechanical ventilatory assistance (Boietti et al., 2021). Our

Non-detectable				Detectable vs. non-detectable
total	**<65 years**	**≥65 years**	**statistics**	**statistics**
343 (38.94)	231 (67.34)	112 (32.65)		
35 (10.20)	15 (6.52)	20 (17.70)	p<0.001	p<0.001
4.29 ± 3.30	3.21 ± 2.69	6.50 ± 3.36	p<0.001	p=0.066
1.69 ± 2.25	1.06 ± 1.71	2.96 ± 2.65	p<0.001	p=0.345
1.93 ± 1.64	1.63 ± 1.44	2.54 ± 1.85	p<0.001	p=0.863
193 (56.26)	102 (44.15)	91 (81.25)	p<0.001	p<0.001
38 (11.07)	18 (7.79)	20 (17.85)	p=0.006	p=0.063
0.60 ± 1.99	0.61 ± 2.12	0.58 ± 1.73	p=0.915	p=0.001
4.85 ± 5.73	3.51 ± 5.15	7.35 ± 5.21	p=0.003	p<0.001
140 (40.82)	56 (24.35)	84 (74.34)	RR 3.05 (2.37–3.93)	p=0.637
25 (7.29)	8 (3.48)	17 (15.04)	RR 4.33 (1.92–9.72)	p=0.732
0.29 ± 0.66	0.16 ± 0.49	0.54 ± 0.86	p<0.001	p=0.463
0.15 ± 0.49	0.05 ± 0.28	0.35 ± 0.72	p<0.001	p=0.402
0.06 ± 0.29	0.04 ± 0.24	0.09 ± 0.37	p=0.178	p=0.815
0.08 ± 0.30	0.07 ± 0.25	0.11 ± 0.39	p=0.236	p=0.974

detectable population received oxygen therapy in 31.9% of all cases or only in detectable cases.

Thromboprophylaxis, especially with enoxaparin, was common in both groups: 72.53% in COVID-19 and 67.65% in non-COVID. In a systematic review and meta-analysis of 33 studies (31 observational, 2 randomized clinical trials compared), heparins, in addition to low molecular weight ones, showed efficacy in reducing mortality in hospitalized patients with COVID-19, both at doses of thromboprophylaxis (hazard ratio – HR: 0.63, 95% CI 0.57–0.69) and anticoagulant dose (HR: 0.56, 95% CI 0.47–0.66), although with higher risk of bleeding with anticoagulant dose (odds ratio – OR: 2.01, 95% CI 1.14–3.53) in comparison with doses of thromboprophylaxis (Giossi et al., 2021).

Among the corticosteroids, the most used in COVID-19 was dexamethasone: 253 (28.71%), while in non-COVID-19 9.29% received dexamethose. In the Boietti et al. (2021) study, 29.7% received corticosteroids. In another study with 417

patients, 20.6% received corticosteroids (Melendi et al., 2020). This strategy of using dexamethasone in COVID-19 was consolidated from the preliminary publication of the RECOVERY Collaborative Group et al. (2021) study, in which an improvement in the prognosis of patients requiring oxygen therapy was observed if dexamethasone was used, this benefit was extensive for other corticosteroids among patients requiring oxygen therapy (van Paassen et al., 2020; Pasin et al., 2021). Paracetamol was a drug widely used for symptomatic treatment in the COVID-19 population (59.7%) and much less used in the non-COVID-19 population (17.65%).

Even so, and despite the considerations mentioned about potentially antiviral therapies and other therapies linked to the pandemic, such as the use of oxygen therapy, anticoagulants, and corticosteroids, the use of drugs throughout the entire hospitalization was significantly lower in COVID-19 than in non-COVID: 5.57 drugs/patient vs. 9.17 drugs/patient. This is a consequence of fewer drugs on day 1, both regular and current, and fewer drugs added after day 1. These differences are probably justified by the fact that it is a younger population and with a single hospitalization clinical condition. We also observed significantly less polypharmacy in (COVID-19 45.06%) than in non-COVID-19 (61.99%) and also less excessive polypharmacy: 6.70 and 14.02% respectively. In a systematic review of articles on COVID-19 published between November 2019 and September 2020, 7 articles with 10,519 detectable COVID-19 patients were included: 4,818 of them had polypharmacy (Iloanusi et al., 2021). In 5 of these 7 articles, polypharmacy was associated with unfavorable outcome. The presence of polypharmacy was significantly associated with detectable COVID, death among reactive COVID-19 males, greater kidney damage, and a higher frequency of adverse drug effects. The use of antipsychotics was associated with increased morbidity and mortality, both in men and women (Iloanusi et al., 2021).

Although the original trial was oriented towards classical pharmacological therapy, some characteristics of the study (design, methodology, data recording) allowed an excellent opportunity to evaluate other therapeutic strategies used during the pandemic (first phase of pandemics), such as the case of convalescent plasma. COVID-19 convalescent plasma is plasma collected from donors recovered from acute COVID-19 infection, with high levels of neutralizing antibodies against the SARS-CoV-2 virus, conferring immunity through direct binding and inactivation of the SARS-CoV-2 virus by neutralizing anti-SARS-CoV-2 antibodies, antibody-dependent complement activation, cytotoxicity, and phagocytosis. In addition to improving clearance, antibodies may also decrease disease severity and facilitate recovery, by modulating the exaggerated immune response and cytokine storm associated with severe disease and multiorgan dysfunction (Rojas et al., 2020). The administration of convalescent plasma generated considerable expectations in the first wave of the COVID-19 pandemic, whose effectiveness had to be demonstrated (Mucha and Quraishy, 2020). In a Cochrane review of a total of 5,443 participants in 20 studies, it did not show conclusive evidence to support the

efficacy of convalescent plasma in reducing mortality, improving clinical symptoms, or shortening hospital stay (Singh and Gupta, 2021). Other systematic reviews reach conflicting conclusions (Barreira et al., 2021; Janiaud et al., 2021; Kloypan et al., 2021). In our study, we did not observe a benefit in reducing mortality in the 114 patients who received convalescent plasma. These results are consistent with those observed in a multicenter clinical trial conducted in our country with 333 patients with similar characteristics (Simonovich et al., 2021). Based on the information emerging from these observations, convalescent plasma treatment appears to be of greatest benefit if administered early in the course of the disease, with high neutralizing antibody titres, in patients without respiratory compromise, according to another multicenter clinical trial, with 160 patients also carried out in our country (Libster et al., 2021).

The antiviral drugs used in the COVID-19 context, together with dexamethasone, hydroxychloroquine and antibacterials, raised alarms due to the probability of severe P-DDIs (Kumar and Trivedi, 2021). We observed a relatively low P-DDIs rate, both in the COVID-19 and non-COVID-19 population: 0.31/patient and 0.40/patient, respectively. This may be due, in part, to the fact that the drugs that presented the most P-DDIs were used comparatively little, with the exception of clarithromycin and dexamethasone, and, on the other hand, to the fact that the prescriptions were made with the SCSDM SIMDA that detected P-DDIs. We did not find articles that explored the frequency of P-DDIs in this type of hospitalization.

Limitations

The present work presents limitations to be taken into account, such as: (1) it was carried out in a single healthcare center, linked to a relatively homogeneous population that may not represent population groups from other regions; (2) analyzes the therapeutics used in the institution, which may present differences with other health institutions, given that multiple recommendations were generated during the pandemic that changed very quickly and with great intercenter heterogeneity, (3) physicians could modify prescriptions or write new ones on the system-generated paper forms: if those prescriptions were not later added as regular medications, they were not entered into the study; (4) we did not analyze parenteral hydration plans or the addition of electrolytes to these plans: this led to, for example, evaluating potassium intakes by mouth but not those made intravenously.

Conclusion

Hospitalizations completed during the COVID-19 pandemic (first phase) were associated with a particular prescription pattern, characterized by a lower number of drug use, with the consequent lower prevalence of polypharmacy and therefore lower risk of interactions (P-DDIs). Even so, the separation of patients in specific rooms showed that the group assigned as COVID-19, and in particular those with detectable virus, presented a higher mortality.

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