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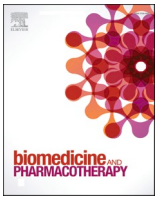

Assessing medication use patterns by clinical outcomes severity among inpatients with COVID-19: A retrospective drug utilization study

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A R T I C L E I N F O

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A B S T R A C T

Purpose: This study assessed medication patterns for inpatients at a central hospital in Portugal and explored their relationships with clinical outcomes in COVID-19 cases.
Methods: A retrospective study analyzed inpatient medication data, coded using the Anatomical Therapeutic Chemical classification system, from electronic patient records. It investigated the association between medications and clinical severity outcomes such as ICU admissions, respiratory/circulatory support needs, and hospital discharge status, including mortality (identified by ICD-10-CM/PCS codes). Multivariate analyses incorporating demographic data and comorbidities were used to adjust for potential confounders and understand the impact of medication patterns on disease progression and outcomes.
Results: The analysis of 2688 hospitalized COVID-19 patients (55.3% male, average age 62.8 years) revealed a significant correlation between medication types and intensity and disease severity. Cases requiring ICU admission or ECMO support often involved blood and blood-forming organ drugs. Increased use of nervous system and genitourinary hormones was observed in nonsurvivors. Corticosteroids, like dexamethasone, were common in critically ill patients, while tocilizumab was used in ECMO cases. Medications for the alimentary tract, metabolism, and cardiovascular system, although widely prescribed, were linked to more severe cases. Invasive mechanical ventilation correlated with higher usage of systemic anti-infectives and musculoskeletal medications. Trends in co-prescribing blood-forming drugs with those for acid-related disorders, analgesics, and antibacterials were associated with intensive interventions and worse outcomes.
Conclusions: The study highlights complex medication regimens in managing severe COVID-19, underscoring specific drug patterns associated with critical health outcomes. Further research is needed to explore these patterns.

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1. Introduction

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has emerged as a global health crisis, posing immense challenges to healthcare systems worldwide. Since its initial outbreak, the virus has relentlessly affected millions of individuals, with over 772 million confirmed cases, tragically resulting in over 6.9 million deaths, as reported by the World Health Organization (WHO) [1]. In Portugal, there have been 5.6 million confirmed cases of COVID-19, leading to 27,702 reported deaths as of 25 November 2023 [1].

COVID-19 presents a diverse range of symptoms, with fever, cough, dyspnoea/shortness of breath, fatigue, myalgia, and pharyngalgia being the most reported [2]. A set of therapeutic approaches with proven effectiveness and clinical safety is currently available for specific stages of the disease [3] For the majority of individuals infected with SARS-CoV-2, the infection is self-limited, as demonstrated by the EPIC-SR trial [4]. Each therapeutic option must prioritize those who stand to benefit most, considering individual characteristics such as age, immunity status, and underlying conditions that confer a higher risk of disease progression or death [5] As for now, the European Union has approved several treatments for COVID-19, including tixagevimab/cilgavimab, anakinra, nirmatrelvir/ritonavir, regdanvimab, tocilizumab, casirivimab/imdevimab, and remdesivir [6]. In parallel, recent developments have led to the withdrawal of the authorization request for molnupiravir as a COVID-19 treatment based on additional data from the phase 3 MOVe-OUT study [7]. This decision was made due to indications that the reduction in the risk of COVID-19 progression with hospitalization and/or death appeared to be lower. According to the Portuguese guidelines [8], remdesivir, dexamethasone, tocilizumab, and anakinra, are indicated for the management of COVID-19.

Concomitant medicines administered during hospitalization for COVID-19, play a complementary role to the primary treatment, addressing both pre-existing (including chronic diseases) and acute clinical conditions that may arise during hospitalization [9–11] To date, there is a global absence of published studies providing insights into the specific medication patterns employed for in-hospital drug use during COVID-19. Most studies have investigated repurposed and adjuvant drugs to treat COVID-19 patients, with a primary focus on assessing the impact of individual drugs on COVID-19 outcomes. Other studies show a statistically significant link between polypharmacy and more severe COVID-19 outcomes [12], including higher hospitalization and mortality rates [13,14], despite some exceptions suggesting protective effects for pre-existing conditions [15].

Initially, there were concerns surrounding ACE inhibitors (ACEI) and angiotensin receptor blockers (ARB) as experimental studies suggest they can increase ACE2 expression, the cellular entry point for SARS-CoV-2 [16,17] However, most published clinical studies to date indicate that their use does not lead to increased COVID-19 severity and may even offer potential benefits [18–22]. Another commonly used drug group, statins, has been studied for its antiviral and anti-inflammatory properties, showing promising effects in COVID-19 patients [23,24]. Managing the thrombotic risk associated with COVID-19 with anticoagulants is recommended for hospitalized and high-risk patients [25,26]. Hydroxychloroquine has also attracted attention for its potential anti-SARS-CoV-2 activity and reported benefits in COVID-19 outcomes [27]. Notably, during the early stages of the pandemic in Portugal, hydroxychloroquine was used off-label despite limited known evidence regarding its efficacy in treating this disease [28]. Although there is some investigation on some individual drugs, evidence from clinical practice regarding medication utilization patterns during COVID-19 hospitalizations in Portugal remains non-existent.

We performed a retrospective real-world drug utilization study aiming to assess medication patterns among inpatients with COVID-19 and their potential association with clinical outcomes. We hypothesize that specific medication patterns may be associated with significant modifications in patients' clinical outcomes during hospitalization. Additionally, we anticipate an increase in both the number and variety of medications used among patients with more severe COVID-19. Specifically, our aims were: to summarize baseline patients` characteristics; to describe medication use in specific patient subgroups; and to evaluate outcomes of clinical severity. Understanding medication usage patterns is crucial for optimizing treatment strategies and enhancing patient care during COVID-19 hospitalizations.

2. Methods

2.1. Study design and setting

This is a single-centre, population-based retrospective drug utilization study using real-world data from patients who have been hospitalized for treatment of COVID-19 at São João University Hospital Centre (*Centro Hospitalar Universitário São João*, CHUSJ), a prominent central hospital in northern Portugal. CHUSJ boasts an official capacity of 1105 beds across several medical and surgical specialties, along with 45 cribs, making it the third-largest hospital in Portugal and a key healthcare reference in the northern region. The hospital encompasses more than 50 medical and surgical specialties and offers a comprehensive range of ancillary diagnostic and therapeutic facilities [29].

The study protocol was approved by the hospital's Ethics Committee for Health (CES nr. 417/2020) and conducted in accordance with the principles outlined in the Declaration of Helsinki and the Oviedo Convention, ensuring the strict adherence to ethical standards and protection of personal data. Consent was not required since the data had been de-identified. No one received compensation or was offered any incentive for participating in this study.

2.2. Data sources

The data applied in this study were collected from healthcare records as part of patient care, utilizing routinely collected linked healthcare data, obtained from administrative and clinical secondary data. Specifically, the data were sourced from the "OpenDataCOVID-19" database, which contains medical records registered in CHUSJ's health informatics programs, including *SClínico*. To ensure the protection of patient privacy, the data provided underwent a series of pseudoanonymization steps with a risk minimization principle to prevent patient re-identification. The applied methodology for the defined dataset during the considered time period resulted in a risk of re-identification of users below 3% while maintaining data quality standards. However, it's important to note that the authors did not have access to patient identifiers. The analysis was conducted using a deidentified version of the database in a secure workspace. In addition to the open-access database, other variables of interest were considered, which were not initially included. These variables were extracted based on a research team-provided protocol accessed through the hospital's Data Intelligence Service. The dataset encompassed all COVID-19-coded episodes between March 2020 and January 2022, ensuring a comprehensive representation of electronic health records during this period for the study, in accordance with significant events, including the WHO pandemic declaration. Each patient in the study has a unique national health number, enabling the extraction of data from multiple sources of electronic patient records.

After the data extraction and consolidation, a pharmacist carefully reviewed the data, performing data cleaning that involved identifying potential outliers, inconsistencies, or duplicate cases.

2.3. Study population

The study population comprised patients diagnosed with COVID-19 who were hospitalized at the CHUSJ between March 2020 and January 2022. Patients were confirmed positive for COVID-19 through the detection of SARS-CoV-2 RNA nucleic acid amplification with probe

detection. The specific International Classification of Diseases, 10th edition, Clinical Modification (ICD-10-CM) code used for diagnosis was U07.1, indicating confirmed COVID-19 cases. Patients with negative or indeterminate results (unclear PCR results) were excluded since they were managed differently than those with laboratory-confirmed-covid-19 (U07.2 code).

The majority of patients are expected to be residents in the geographical area served by the hospital, given its scope of service. However, due to the dynamic nature of the public health emergency experienced during certain periods of those two years, there have been instances of admitting patients from other regions. This is often prompted by overcrowding in other hospitals or the need for specialized care offered at the CHUSJ as a central hospital (e.g., access to extra-corporeal membrane oxygenation, ECMO).

Patients were indiscriminately included in the study without any selection based on their therapeutic history or clinical progression during hospitalization, ensuring the absence of specific treatment influence on their inclusion.

Index date was established at the first inpatient admission after a COVID-19 diagnosis was documented in electronic health records. Index treatment was defined as the earliest medication received during the index admission date. Both were considered until the time of hospital discharge.

2.4. Drug use & covariates

The primary outcome of this study was the clinical severity outcomes. The assessment of clinical severity outcomes related to COVID-19 encompassed (i) the type of mechanical respiratory and circulatory support required (MRCS), (ii) the need for intensive care, and (iii) the outcome of hospital episode. The type of MRCS was classified using the ICD-10-Procedure Coding System (ICD-10-PCS) [30] and included ECMO, high-flow nasal cannula (HFNC), non-invasive ventilation (NIV), and invasive mechanical ventilation (IMV). The complete list of codes related to MRCS is available upon request from the corresponding author. Additionally, the outcome of the hospital episode addressed the type of hospital discharge and represented scenarios encompassing recovery (including transfers to nursing homes and private homes), death or transfers to other hospitals. For clinical purposes, patients were classified as “recovered” when they tested negative on two consecutive rRT-PCR tests, conducted at least 24 h apart, and performed no earlier than 14 days after the onset of symptoms.

We analysed treatment patterns within specific subgroups of patients sharing relevant clinical and sociodemographic characteristics over the study period. For this purpose, we extracted data on medications prescribed to these patients, including (i) pharmacological agents approved, under investigation, or reported to have potential effects against COVID-19 at the time of their utilization (e.g., remdesivir, azithromycin, and hydroxychloroquine); (ii) medications used for supportive care in COVID-19 patients (e.g., corticosteroids, antimicrobials/antibiotics, and anticoagulants); and (iii) miscellaneous medications that may be of interest to patients with COVID-19 (e.g., statins and omeprazole). Medications administered within the scope of clinical trials (i.e., not prescribed in the context of patients’ routine healthcare) were excluded from the analysis. No restrictions were made regarding the route of administration or dosage form. We coded all drugs according to the Anatomical Therapeutic Chemical (ATC) classification system and drugs were grouped into two levels based on the ATC classification system. The first level represents the main anatomical/pharmacological groups, and the second level represents the therapeutic subgroups. The medication variables were recorded as dichotomous variables indicating whether the patient received each medication at least once during their hospitalization. A comprehensive list of all referenced ATC codes can be found in the supplementary material (**Table S1**).

Patient characteristics, including age, gender, date of the first COVID-19 diagnostic test, and comorbidities, were summarized at baseline. Age was estimated based on patient birth year, as the birth date was removed from the dataset for de-identified data purposes. Comorbidities were defined as significant complications or conditions that could cause an increase in the length of hospital stay by at least one day for at least 75% of patients, as determined by the *All Patients Refined Diagnosis Related Groups (APR DRG) classification system* [31]. Moreover, comorbidities were coded according to the ICD-10-CM [32]. The following comorbidities were considered: cancer, cerebrovascular disease, diabetes mellitus (types 1 and 2), kidney disease, liver disease, chronic obstructive pulmonary disease (COPD), other respiratory diseases (primarily affecting the interstitium and other pulmonary diseases; excluding asthma and bronchiectasis), heart failure, transplant, obesity, history of smoking (tobacco use and/or nicotine dependence), neurological disorders, and others. The complete list of codes related to comorbidities is available upon request from the corresponding author.

The study follows the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [33] for reporting. A STROBE checklist can be found in the supplementary material (**Table S2**). Additionally, the study adheres to the methodological standards outlined in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [34].

2.5. Statistical analysis

Descriptive statistical analysis was performed to characterise sociodemographic and clinical variables. Categorical variables were summarised as absolute (n) and relative frequencies (%), and continuous variables such as age were represented by mean and standard deviation. Descriptive statistics were computed for each clinical severity indicator within 1st level ATC drug codes. Multivariable logistic regression models were employed to evaluate the relationship between independent variables, specifically drug groups categorized by 1st level ATC codes, and dependent variables related to clinical severity outcomes. These outcomes included ICU admission, type of hospital discharge, and the need for any MRCS. The models were utilized to estimate odds ratios (OR) and 95% confidence intervals (CI) for each clinical severity variable. Generally, a higher OR value indicates a greater likelihood of the occurrence of the event being studied, relative to the reference group, with adjustments made for confounders such as age, gender, and comorbidities.

For a comprehensive evaluation, descriptive analyses were executed for both general ATC drug groups and a subset of medications specifically considered clinically relevant to COVID-19. These analyses focused on their use patterns in relation to clinical severity outcomes. Also, radar charts were generated for clinically relevant variables, and heatmaps were used to assess the co-frequencies of drug groups at both the 1st and 2nd levels ATC drug codes.

The level of significance for all statistical tests was set at 5% ($p < 0.05$). All analyses were performed using SPSS Software (Statistical Package for the Social Sciences), version 29.0. The figures were generated using R software.

3. Results

3.1. Patient baseline characteristics

A total of 2688 COVID-19-diagnosed patients were admitted to CHUSJ during the study period. The sociodemographic and clinical characteristics of the study population are summarized in Table 1. The average age of the patients was 62.8 ± 19.9 (min-max: 0–95) years. Most patients were male (n = 1486; 55.3%), aged 65 years and older (n = 1595; 59.2%), with only a small residual percentage under 18 years of age (n = 103; 3.8%). Clinical outcomes revealed that 68.4% (n = 1828) of hospitalized patients successfully recovered, while 20.8% (n = 555)

died to various causes, and 10.8% (n = 290) were transferred to other hospitals.

The majority of inpatients had at least one comorbidity (n = 2240; 83.3%). Of the total number of patients, 31.3% (n = 840) had cancer, 29.3% (n = 788) had a diagnosis of diabetes mellitus, and 27.2% (n = 732) experienced neurological disorders. During their COVID-19 hospitalization, 22.9% (n = 616) of patients required MRCS, with 14.3% (n = 383) being placed under HFNC, 13.5% (n = 363) on IMV, 11.0% (n = 297) on NIV, and 2.9% (n = 79) necessitating ECMO.

Most patients tested positive for COVID-19 in two distinct moments, as shown in Fig. 1. The first peak was in March-April 2020, reflecting the early pandemic stage when testing expanded. The second peak occurred from November 2020 to February 2021, probably reflecting a resurgence or shifts in testing protocols. This temporal pattern highlights the pandemic's evolving nature and dynamic responses across its phases.

Among ICU-admitted patients, 88.6% (n = 760) were over 40 years old, with the 65–79 age group being most prevalent (40.6%), and a male predominance was observed (n = 552; 64.3%) Statistically significant differences in comorbidity profiles were noted among ICU and non-ICU patients: obesity, smoking history, other respiratory diseases and liver diseases were more frequent in ICU patients, while neurological disorders, heart failure, cerebrovascular disease were more frequent in non-ICU patients (Table 2).

Of the total patients with at least one comorbidity (n = 2240), hospital discharge varied with 65.2% (n = 1453) recovering, 23.2% (n = 517) dying, and 11.5% (n = 257) being transferred to other hospitals, with a male predominance in all three categories. 13 patients had no type of hospital discharge described. Most fatalities occurred among individuals over 79 years (n = 277; 49.9%), and no deaths were recorded under 18 years. For most comorbidities, statistically significant differences were found in the hospital discharge outcome of these patients, except for liver diseases and the group of other unspecified comorbidities. Considering the most common comorbidities in our population, such as cancer, diabetes mellitus, and neurological disorders, it was found that death was the most frequent outcome for all three (Table 3).

Among patients requiring MRCS, the 41–64 age group was most common for ECMO (62.0%, n = 49) and HFNC (41.1%, n = 158). In the case of NIV, the 41–64 age group (n = 118; 39.7%) and the 65–79 age group (n = 122; 41.1%) were both highly prevalent, representing the two most common age groups. Both 41–64 and 65–79 age groups showed equal prevalence in IMV procedure (41.3%, n = 150 each). Males were more common across all types of MRCS (Table 4).

Table 1
Sociodemographic and clinical characteristics of the study population (n = 2688).

Sociodemographics variables	
Mean age (sd) (in years)	62.8(± 19.9)
Age (in years), n (%)	
< 18y	103 (3.8)
18-40y	290 (10.8)
41-64y	703 (26.2)
65-79y	914 (34.0)
> 79	678 (25.2)
Gender, n (%)	
Female	1202 (44.7)
Male	1486 (55.3)
Clinical variables	
Intensive Care, n (%)[a]	858 (31.9)
Hospital discharge, n (%)	
Recovered	1828 (68.4)
Died	555 (20.8)
Other hospitals	290 (10.8)
Comorbidities, n (%)[a]	
Cancer	840 (31.3)
Diabetes Mellitus	788 (29.3)
Neurological disorders	732 (27.2)
Obesity	529 (19.7)
Heart failure	520 (19.3)
History of smoking	461 (17.2)
Kidney	419 (15.6)
Cerebrovascular	285 (10.6)
Other respiratory diseases	263 (9.8)
COPD	230 (8.6)
Liver	192 (7.1)
Transplanted	44 (1.6)
Other	342 (12.7)
MRCS, n (%)	
HFNC	384 (14.3)
IMV	363 (13.5)
NIV	297 (11.0)
ECMO	79 (2.9)

[a] The frequencies shown reflect the presence of the variable.

3.2. Medication use patterns

The results on medication use patterns are summarized in Table 5 and illustrated in Fig. 2.

Among ICU-admitted patients, the most commonly administered drug groups were B (99.7%; n = 855), followed by A (93.7%; n = 804) and N (83.6%; n = 717). Conversely, groups G and P were rarely used, representing just 0.5% (n = 4) and 1.2% (n = 10) of the ICU cohort. This pattern was also observed among non-ICU patients.

Among recovered patients, the most common drug groups were B (87.9%; n = 1607), followed by A (65.2%; n = 1191), and N (50.2%; n = 917). In deceased patients, N medications were used in 96.2% (n = 534) of cases, followed by B in 91.5% (n = 508), and A in 83.2% (n = 462). For patients transferred to other hospitals, group B drugs were used in 92.1% (n = 267) of cases, followed by A in 77.9% (n = 226), and P in 68.6% (n = 199). This pattern held true for all types of hospital discharges.

In patients requiring ECMO, universal usage (100%; n = 79) of drugs from groups A, B, and N were observed. HFNC patients received drugs from group B (100%; n = 384), along with A (96.4%; n = 370), and N (85.9%; n = 330). NIV patients had universal use of B (100%; n = 297), along with A (97.3%; n = 289), and N (89.2%; n = 265). In the IMV cohort, all patients received N (100%; n = 363), followed closely by B (99.7%; n = 360), A and C (99.2%; n = 360 each).

3.3. Multivariable logistic regression between 1st level ATC groups and clinical severity outcomes

Statistically significant differences were observed for almost all ATC groups, except for groups G and L (Table 6). Notably, strong associations were found between ICU admission and drugs from group B (OR=52.230 [95% CI: 16.323–167.128]). Among deceased inpatients, significant associations were observed with drugs from groups G (OR=20.874 [95% CI: 1.583–275.314]) and N (OR=29.939 [95% CI: 18.908–47.404]). Patients transferred to other hospitals also showed notable associations with the use of drugs from group G (OR=11.254 [95% CI: 1.790–70.740]). In patients requiring MRCS we observed a strong association between the need for ECMO and drugs from group G (OR=56.829 [95% CI: 2.349–1374.385]). For those requiring IMV, significant associations were observed across multiple drug groups, except for groups G, L, N, and R.

3.4. Patterns of use of drugs of interest

Significant associations were observed among patients receiving specific medications for COVID-19. These findings are presented in Table 7. Among patients treated with remdesivir, although the majority were admitted to the ICU (85.7%; n = 6), most recovered from COVID-19 (71.4%; n = 5). A similar pattern was observed for the other drugs, including dexamethasone, tocilizumab, and non-dexamethasone corticotherapy (including methylprednisolone and prednisolone).

Among patients receiving remdesivir treatment, the majority

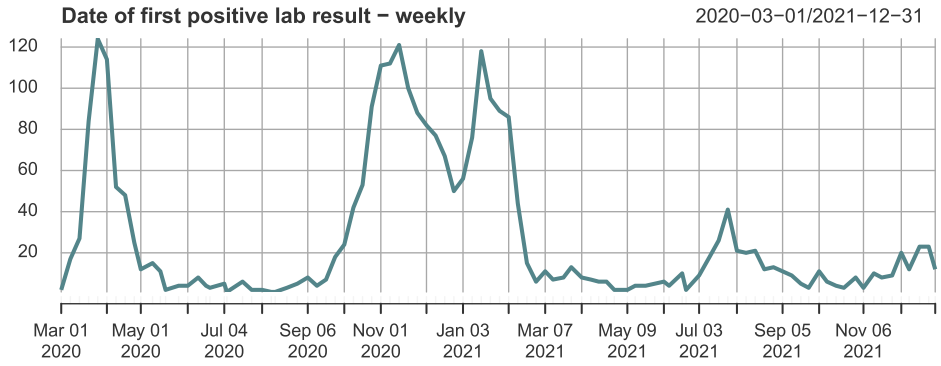

Fig. 1. Weekly temporal distribution of first positive COVID-19 lab results throughout the study period.

Table 2
Comparison of the variables age, gender, and comorbidities by need for intensive care.

Variables	Intensive Care		*p-value*[*]
	No	Yes	
Age (in years), n (%)			
<18y	88 (4.8)	15 (1.7)	
18-40y	207 (11.3)	83 (9.7)	
41-64y	390 (21.3)	313 (36.5)	**< 0.001**
65-79y	566 (30.9)	348 (40.6)	
>79y	579 (31.6)	99 (11.5)	
Gender, n (%)			
Female	896 (49.0)	306 (35.7)	**< 0.001**
Male	934 (51.0)	552 (64.3)	
Comorbidities, n (%)			
Cancer	573 (31.3)	267 (31.1)	0.920
Diabetes Mellitus	528 (28.9)	260 (30.3)	0.441
Neurological disorders	551 (30.1)	181 (21.1)	**< 0.001**
Obesity	280 (15.3)	249 (29.0)	**< 0.001**
Heart failure	374 (20.4)	146 (17.0)	**0.036**
History of smoking	266 (14.5)	195 (22.7)	**< 0.001**
Kidney	301 (16.4)	118 (13.8)	0.073
Cerebrovascular	218 (11.9)	67 (7.8)	**0.001**
Other respiratory diseases	95 (5.2)	168 (19.6)	**< 0.001**
COPD	153 (8.4)	77 (9.0)	0.596
Liver	111 (6.1)	81 (9.4)	**0.002**
Transplanted	25 (1.4)	19 (2.2)	0.106
Other	240 (13.1)	102 (11.9)	0.374

[*] Pearson's chi-squared test.

(71.4%; n = 5) required HFNC. Similarly, in the case of dexamethasone recipients, the majority (51.0%; n = 269) also underwent HFNC. As for patients undergoing tocilizumab treatment, most of them were supported by ECMO (66.7%; n = 6), HFNC (88.9%; n = 8), or NIV (77.8%; n = 7). Additionally, it's worth noting that the concomitance between remdesivir and non-dexamethasone corticotherapy was observed in only three patients (0.1%).

3.5. Co-frequencies of exposure by levels of ATC drug groups

Amongst the 1st level ATC drug groups, the dual administration of A+B emerged as the most prevalent combination (66.6% of patients), followed by B+N (55.6%), B+J (52.4%), and A+N (50.7%) (Fig. 3). For these frequently observed associations, heatmaps were constructed based on 2nd level ATC drug groups. The most common pairings were B01 +A02, N02 + A03, N02 + B01, and J01 +B01, respectively (Fig. 4).

Furthermore, we conducted a parallel analysis for 1st level ATC drug groups but within subgroups of patients who necessitated intensive care and those who did not survive. In the case of ICU-admitted patients, the prevailing dual association was A+B (n = 851; 93.4%), followed by B+N (n = 714; 83.2%), A+N (80.7%), and B+J (n = 692; 74.6%). Among individuals who died, the most robust association was observed for B+N (n = 494; 89.0%), followed by A+N (n = 449; 80.9%), A+B (n = 444; 80.0%), and B+J (n = 412; 74.2%) (Fig. 5).

Table 3
Comparison of the variables age, gender, and comorbidities by type of hospital discharge.

Hospital discharge				
Variables	**Recovered**	**Died**	**Other hospitals**	***p-value****
Age (in years), n (%)				
<18y	97 (5.3)	0 (0.0)	6 (2.1)	
18-40y	250 (13.7)	9 (1.6)	26 (9.0)	
41-64y	529 (28.9)	77 (13.9)	92 (31.7)	
65-79y	619 (33.9)	192 (34.6)	99 (34.1)	**< 0.001**
>79y	333 (18.2)	277 (49.9)	67 (23.1)	
Gender, n (%)				
Female	844 (46.2)	239 (43.1)	113 (39.0)	**0.048**
Male	984 (53.8)	316 (56.9)	177 (61.0)	
Comorbidities, n (%)				
Cancer	526 (28.8)	229 (41.3)	80 (27.6)	**< 0.001**
Diabetes Mellitus	527 (28.8)	188 (33.9)	71 (24.5)	**0.011**
Neurological disorders	425 (23.2)	219 (39.5)	86 (29.7)	**< 0.001**
Obesity	347 (19.0)	98 (17.7)	82 (28.3)	**< 0.001**
Heart failure	296 (16.2)	162 (29.2)	60 (20.7)	**< 0.001**
History of smoking	284 (15.5)	112 (20.2)	63 (21.7)	**0.004**
Kidney	247 (13.5)	130 (23.4)	42 (14.5)	**< 0.001**
Cerebrovascular	161 (8.8)	86 (15.5)	37 (12.8)	**< 0.001**
Other respiratory diseases	129 (7.1)	80 (14.4)	53 (18.3)	**< 0.001**
COPD	134 (7.3)	69 (12.4)	26 (9.0)	**< 0.001**
Liver	130 (7.1)	45 (8.1)	15 (5.2)	0.288
Transplanted	34 (1.9)	7 (1.9)	0 (0.0)	**0.048**
Other	236 (12.9)	60 (10.8)	40 (13.8)	0.341

*Pearson's chi-squared test.

4. Discussion

To our knowledge, this is the first paper to provide a comprehensive assessment of medication patterns among inpatients with COVID-19 in Portugal. Our analysis covers a wide spectrum of pharmacological agents, including those approved, under investigation, or reported to have potential favourable effects against COVID-19 at the time of their

Table 4
Comparison of the variables age, gender, and comorbidities by type of MRCS.

MCRS											
Variables	**ECMO**			**HFNC**			**NIV**			**IMV**		
	No	**Yes**	**p-value** *	**No**	**Yes**	**p-value** *	**No**	**Yes**	**p-value** *	**No**	**Yes**	**p-value** *
Age (in years), n (%)												
<18y	102 (3.9)	1 (1.3)		98 (4.3)	5 (1.3)		100 (4.2)	3 (1.0)		96 (4.1)	7 (1.9)	
18-40y	267 (10.2)	23 (29.1)		243 (10.5)	47 (12.2)		261 (10.9)	29 (9.8)		250 (10.8)	40 (11.0)	
41-64y	654 (25.1)	49 (62.0)	**< 0.001**	545 (23.7)	158 (41.1)	**< 0.001**	585 (24.5)	118 (39.7)	**< 0.001**	553 (23.8)	150 (41.3)	**< 0.001**
65-79y	908 (34.8)	6 (7.6)		768 (33.3)	146 (38.0)		792 (33.1)	122 (41.1)		764 (32.9)	150 (41.3)	
>79y	678 (26.0)	0 (0.0)		650 (28.2)	28 (7.3)		653 (27.3)	25 (8.4)		662 (28.5)	16 (4.4)	
Gender, n (%)												
Female	1177 (45.1)	25 (31.6)	**0.018**	1083 (47.0)	119 (31.0)	**< 0.001**	1108 (46.3)	94 (31.6)	**< 0.001**	1087 (46.8)	115 (31.7)	**< 0.001**
Male	1432 (54.9)	54 (68.4)		1221 (53.0)	265 (69.0)		1283 (53.7)	203 (68.4)		1238 (53.2)	248 (68.3)	
Comorbidities, n (%)												
Cancer	821 (31.5)	19 (24.1)	0.161	737 (32.0)	103 (26.8)	**0.043**	748 (31.3)	92 (31.0)	0.914	737 (31.7)	103 (28.4)	0.204
Diabetes Mellitus	773 (29.6)	15 (19.0)	**0.041**	668 (29.0)	120 (31.3)	0.368	692 (28.9)	96 (32.3)	0.227	680 (29.2)	108 (29.8)	0.844
Neurological disorders	721 (27.6)	11 (13.9)	**0.007**	666 (28.9)	66 (17.2)	**< 0.001**	663 (27.7)	69 (23.2)	0.101	650 (28.0)	82 (22.6)	**0.033**
Obesity	495 (19.0)	34 (43.0)	**< 0.001**	405 (17.6)	124 (32.3)	**< 0.001**	419 (17.5)	110 (37.0)	**< 0.001**	399 (17.2)	130 (35.8)	**< 0.001**
Heart failure	516 (19.6)	4 (5.1)	**0.001**	485 (21.1)	35 (9.1)	**< 0.001**	468 (19.6)	52 (17.5)	0.395	476 (20.5)	44 (12.1)	**< 0.001**
History of smoking	443 (17.0)	18 (22.8)	0.177	376 (16.3)	85 (22.1)	**0.005**	382 (16.0)	79 (26.6)	**< 0.001**	374 (16.1)	87 (24.0)	**< 0.001**
Kidney	415 (15.9)	4 (5.1)	**0.009**	386 (16.8)	33 (8.6)	**< 0.001**	377 (15.8)	42 (14.1)	0.466	385 (16.6)	34 (9.4)	**< 0.001**
Cerebrovascular	283 (10.8)	2 (2.5)	**0.018**	272 (11.8)	13 (3.4)	**< 0001**	275 (11.5)	10 (3.4)	**< 0.001**	260 (11.2)	25 (6.9)	**0.013**
Other respiratory diseases	212 (8.1)	51 (64.6)	**< 0.001**	180 (7.8)	83 (21.6)	**< 0.001**	197 (8.2)	66 (22.2)	**< 0.001**	156 (6.7)	107 (29.5)	**< 0.001**
COPD	228 (8.7)	2 (2.5)	0.052	202 (8.8)	28 (7.3)	0.339	197 (8.2)	33 (11.1)	0.095	207 (8.9)	23 (6.3)	0.104
Liver	186 (7.1)	6 (7.6)	0.874	153 (6.6)	39 (10.2)	**0.013**	160 (6.7)	32 (10.8)	**0.010**	160 (6.9)	32 (8.8)	0.183
Transplanted	44 (1.7)	0 (0.0)	0.244	32 (1.4)	12 (3.1)	**0.013**	36 (1.5)	8 (2.7)	0.128	37 (1.6)	7 (1.9)	0.638
Other	336 (12.9)	6 (7.6)	0.165	299 (13.0)	43 (11.2)	0.333	300 (12.5)	42 (14.1)	0.437	294 (12.6)	48 (13.2)	0.759

* Pearson's chi-squared test.

Table 5
Comparison of 1st level ATC codes by clinical severity outcomes.

ATC Codes	Intensive Care		Hospital discharge			MRCS			
	No (n = 1830)	**Yes (n = 858)**	**Recovered (n = 1828)**	**Died (n = 555)**	**Other hospitals (n = 290)**	**ECMO (n = 79)**	**HFNC (n = 384)**	**NIV (n = 297)**	**IMV (n = 363)**
A, n (%)	1088 (59.5)	804 (93.7)	1191 (65.2)	462 (83.2)	226 (77.9)	79 (100)	370 (96.4)	289 (97.3)	360 (99.2)
B, n (%)	1541 (84.2)	855 (99.7)	1607 (87.9)	508 (91.5)	267 (92.1)	79 (100.0)	384 (100.0)	297 (100.0)	360 (99.7)
C, n (%)	503 (27.5)	604 (70.4)	586 (32.1)	361 (65.0)	156 (53.8)	76 (96.2)	276 (71.9)	248 (83.5)	360 (99.2)
D, n (%)	58 (3.2)	67 (7.8)	82 (4.5)	25 (4.5)	17 (5.9)	7 (8.9)	36 (9.4)	28 (9.4)	40 (11.0)
G, n (%)	4 (0.2)	4 (0.5)	3 (0.2)	2 (0.4)	3 (1.0)	4 (5.1)	2 (0.5)	1 (0.3)	4 (1.1)
H, n (%)	257 (14.0)	515 (60.0)	375 (20.5)	279 (50.3)	114 (39.3)	66 (83.5)	302 (78.6)	221 (74.4)	282 (77.7)
J, n (%)	874 (47.8)	642 (74.8)	898 (49.1)	423 (76.2)	188 (64.8)	77 (97.5)	293 (76.3)	241 (81.1)	349 (96.1)
L, n (%)	31 (1.7)	33 (3.8)	42 (2.3)	15 (2.7)	6 (2.1)	8 (10.1)	19 (4.9)	17 (5.7)	16 (4.4)
M, n (%)	179 (9.8)	390 (45.5)	299 (16.4)	178 (32.1)	90 (31.0)	712 (89.9)	200 (52.1)	174 (58.6)	332 (91.5)
N, n (%)	941 (51.4)	717 (83.6)	917 (50.2)	534 (96.2)	199 (68.6)	79 (100.0)	330 (85.9)	265 (89.2)	363 (100.0)
P, n (%)	5 (0.3)	10 (1.2)	11 (0.6)	2 (0.4)	2 (0.7)	0 (0.0)	5 (1.3)	6 (2.0)	10 (2.8)
R, n (%)	847 (46.3)	532 (62.0)	866 (47.6)	370 (66.7)	136 (46.9)	38 (48.1)	272 (70.8)	208 (70.0)	214 (59.0)
S, n (%)	45 (2.5)	53 (6.2)	60 (3.3)	25 (4.5)	12 (4.1)	13 (16.5)	22 (5.7)	18 (6.1)	40 (11.0)
V, n (%)	21 (1.1)	22 (2.6)	25 (1.4)	14 (2.5)	4 (1.4)	0 (0.0)	7 (1.8)	7 (2.4)	14 (3.9)

A: Alimentary tract and metabolism; B: Blood and blood forming organs; C: Cardiovascular system; D: Dermatologicals; G: Genito urinary system and sex hormones; H: Systemic hormonal preparations, excl. sex hormones and insulins; J: Antiinfectives for systemic use; L: Antineoplastic and Immunomodulating agents; M: Musculoskeletal system; N: Nervous system; P: Antiparasitic products, insecticides and repellents; R: Respiratory system; S: Sensory organs; V: Various.

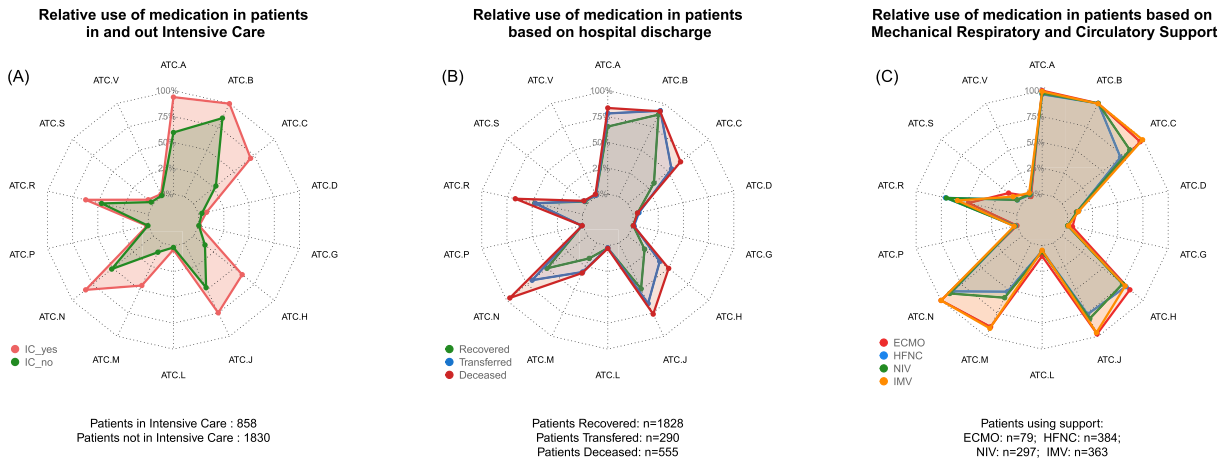

Fig. 2. Radar plots representing medication usage in subgroups: (A) ICU-admitted patients, (B) type of hospital discharge, and (C) type of MRCS. In each radar, the lines represent distinct patient categories, and the distance from each point to the origin indicates the percentage of patients using drugs from a specific ATC group. For instance, a line extending to the 75% marker under the label "ATC.A" suggests that 75% of those patients are being medicated with drugs from the ATC.A group. It's important to note that comparisons between lines within the same radar provide insights into discrepancies in medication usage among the subgroups; however, specific values and detailed interpretation should be derived from the study's context.

utilization, medications used for supportive care in COVID-19 patients, and other miscellaneous medications relevant to patients with COVID-19.

Our analysis showed a positive association between ICU admission and the use of all 1st level ATC drug groups, even after adjusting for age, sex, and baseline comorbidities. These results suggest a comprehensive interaction between COVID-19 and various organ systems, as critical cases generally require multifaceted pharmacological interventions. This is further evidenced when our model adjusts for patients' baseline comorbidities. The strongest association was with the blood and blood forming organs (B) category, where ICU patients were 52 times more likely to be on these medications than non-ICU patients. Additionally, there was an 11-fold increase in the odds for the use of alimentary tract and metabolism (A) drugs, and a 10-fold increase for cardiovascular system (C) drugs in the ICU population. The elevated use of antithrombotic agents (B01) in our cohort aligns with the established higher prevalence of these drugs among COVID-19 patients, likely due to their cardiovascular and metabolic comorbidities [35]. Given the recognized hypercoagulable state associated with COVID-19 [36] and the subsequent clinical recommendations for venous thromboembolism prophylaxis in hospitalized patients [37,38], our findings may reflect vigilant thromboembolism monitoring and preventive treatment in those at increased risk. This has led to an increased use of group B drugs, specifically anticoagulants and blood-related drugs, in ICU patients to manage the risk of thrombotic events associated with severe COVID-19 [39,40]. In the ICU setting, the pronounced use of group B drugs could also stem from interventions like blood transfusions or the administration of hematopoietic growth factors, which are included in this category [41]. Additionally, early protocols suggest therapeutic anticoagulation (B01AB) for COVID-19 patients [42], which may further explain the high incidence of these medications in our study population. In critical cases, a hypercoagulable state arises from heightened inflammation and endothelial dysfunction, leading to increased thrombus formation. Category B drugs, particularly anticoagulants, play a critical role in mitigating this risk by inhibiting clot formation and stabilizing blood flow [43].

The increased utilization of A drugs in our ICU cohort likely reflects the need for specialized nutrition support, such as enteral or parenteral feeding. This need often emerges from the hypermetabolic state of critically ill COVID-19 patients who may struggle with oral intake or have impaired nutrient absorption [42,44,45]. This state, characterized by increased carbon dioxide production and greater oxygen demands, exacerbates respiratory challenges like hypercapnia and hypoxia. Therapeutic hypothermia has been suggested as a method to reduce metabolic demands, thus lowering carbon dioxide production and aiding oxygenation [46]. From another clinical perspective, a meta-analysis demonstrated that enteral nutrition significantly reduces mortality risk in such patients, with a risk ratio of 0.89 (95% CI, 0.79–0.99, $p = 0.04$) [42]. The early initiation of enteral nutrition, preferably within 24–48 h of ICU admission, is particularly effective [47,48]. It not only meets the increased metabolic demands but also mitigates the risk of gastrointestinal symptoms and impaired nutrient absorption often seen in COVID-19 [49]. Additionally, enteral nutrition supports early gut function and reduces the incidence of nosocomial infections, compared to parenteral nutrition. It's important to note that COVID-19, while primarily a respiratory disease, can disrupt the intestinal mucosa, highlighting the importance of nutritional support in management [47,48,50]. Furthermore, the incidence of lower GI bleeding, which affects about 1.5% to 3.0% of hospitalized COVID-19 patients, must also be considered. Although typically mild to moderate due to mucosal inflammation, in the context of severe COVID-19 pneumonia, conditions such as peptic ulcer disease or stress gastritis can lead to severe, even life-threatening, bleeding [51]. Moreover, lower GI bleeding in these patients is often associated with ischemic colitis, a condition linked to COVID-19-related hypercoagulability and thromboembolism [52].

The pronounced prescription of C drugs in our study may indicate an increased occurrence of cardiovascular issues in severe COVID-19 cases, reinforced by Baranovskii et al.'s correlation between coagulation abnormalities and severe respiratory distress, which can exacerbate cardiovascular complications [53]. This is possibly due to the direct impact of COVID-19 on endothelial cells causing dysfunction and inflammation in the cardiovascular system, exacerbating pre-existing conditions like atherosclerosis, and increasing the risk of cardiac events [54,55]. The systemic inflammatory response, including cytokine release, can lead to myocardial injury, and the virus-induced hypercoagulable state heightens the risk of thrombotic complications. These mechanisms demand the increased use of C medications to manage exacerbated cardiovascular issues in COVID-19 patients [56]. Preexisting conditions like arrhythmias and hypertension could escalate the risk for severe COVID-19, leading to ICU admissions. Moreover, the stress of critical illness might worsen these conditions [57–60]. Though hypertension data were absent in our cohort, we noted that 17% had a history of heart failure and 7.8% had cerebrovascular disease pre-admission, which could partially explain the high use of C drugs. Heart failure in these patients might arise from direct cardiac injury or secondary to cytokine storms that impair cardiac function [61]. Furthermore, drugs such as

Table 6
Multivariable logistic regression analysis on the association between 1st ATC codes and each clinical severity outcomes.

	A		B		C		D		G		H		J	
	OR	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
Intensive Care														
No	1		1		1		1		1		1		1	
Yes	10.877	7.996-14.796	52.230	16.323-167.128	9.752	7.812-12.173	2.874	1.923-4.294	1.264	0.178-8.998	8.905	7.220-10.983	3.440	2.823-4.191
Hospital discharge														
Recovered	1		1		1		1		1		1		1	
Died	2.458	1.882-3.211	0.829	0.563-1.220	3.203	2.557-4.012	0.988	0.601-1.626	20.874	1.583-275.314	5.814	4.558-7.416	3.107	2.456-3.929
Other hospitals	1.774	1.307-2.408	1.113	0.679-1.823	2.145	1.637-2.811	1.319	0.758-2.295	11.254	1.790-70.740	2.326	1.751-3.091	1.772	1.356-2.315
ECMO														
No	-	-	-	-	1		1		1		1		1	
Yes	-	-	-	-	7.409	1.726-31.801	1.478	0.565-3.869	56.825	2.349-1374.385	2.388	1.169-4.877	6.785	1.511-30.472
HFNC														
No	1		-	-	1		1		1		1		1	
Yes	6.037	3.368-10.822	-	-	2.193	1.477-3.255	1.885	1.096-3.244	0.488	0.036-5.531	7.747	5.618-10.683	1.344	0.957-1.886
NIV														
No	1		-	-	1		1		1		1		1	
Yes	3.876	1.810-8.298	-	-	3.877	2.461-6.107	1.193	0.673-2.114	0.802	0.049-13.179	2.125	1.477-3.059	1.481	0.993-2.209
IMV														
No	1		1		1		1		1		1		1	
Yes	25.554	8.020-81.425	15.524	2.034-118.507	265.947	83.225-849.841	2.734	1.622-4.610	1.105	0.083-14.651	5.904	4.222-8.255	19.322	0.993-2.209

	L		M		N		P		R		S		V	
	OR	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**	**OR**	**95%CI**
Intensive Care														
No	1		1		1		1		1		1		1	
Yes	1.804	1.011-3.220	6.693	5.344-8.383	6.405	5.119-8.013	4.667	1.439-15.141	1.990	1.643-2.411	2.371	1.513-3.715	2.382	1.217-4.661
Hospital discharge														
Recovered	1		1		1		1		1		1		1	
Died	1.533	0.764-3.077	5.036	3.829-6.623	29.939	18.908-47.404	0.962	0.190-4.873	1.608	1.288-2.007	1.406	0.836-2.364	1.832	0.877-3.829
Other hospitals	1.307	0.509-3.355	2.270	1.664-3.095	2.106	1.598-2.776	1.674	0.335-8.361	0.793	0.605-1.040	1.171	0.608-2.258	1.056	0.353-3.165
ECMO														
No	1		1		1		1		1		1		1	
Yes	1.209	0.546-2.679	1.163	0.754-1.792	2.455	1.681-3.585	0.697	0.165-2.940	2.833	2.103-3.816	0.787	0.426-1.454	0.686	0.244-1.930
HFNC														
No	1		1		1		1		1		1		1	
Yes	6.144	1.903-19.837	1.163	0.754-1.792	2.455	1.681-3.585	0.697	0.165-2.940	2.833	2.103-3.816	0.787	0.426-1.454	0.686	0.244-1.930
NIV														
No	1		1		1		1		1		1		1	
Yes	2.194	0.946-5.089	1.989	1.243-3.181	2.059	1.296-3.272	1.430	0.366-5.594	1.384	0.987-1.942	0.991	0.511-1.925	0.872	0.307-2.482
IMV														
No	1		1		-	-	1		1		1		1	
Yes	0.935	0.411-2.128	76.067	48.458-119.408	-	-	21.499	5.067-91.216	0.964	0.712-1.306	4.548	2.562-8.076	5.926	2.588

A: Alimentary tract and metabolism; B: Blood and blood forming organs; C: Cardiovascular system; D: Dermatologicals; G: Genito urinary system and sex hormones; H: Systemic hormonal preparations, excl. sex hormones and insulins; J: Antiinfectives for systemic use; L: Antineoplastic and Immunomodulating agents; M: Musculoskeletal system; N: Nervous system; P: Antiparasitic products, insecticides and repellents; R: Respiratory system; S: Sensory organs; V: Various.
The multivariate logistic regression model was adjusted for age, sex, and comorbidity. For the variables for which estimates have not been provided, it's important to note that due to the low frequency of individuals in this group, coefficient values (odds ratios) may be subject to statistical instabilities stemming from data scarcity, which can lead to numerically elevated and less reliable estimates.

norepinephrine or vasopressin from C drugs are often used to maintain hemodynamic stability in critical situations [62–64].

A distinctive pattern was evident among patients who died in the hospital, with significantly higher use of nervous system drugs (N) and genitourinary system drugs and sex hormones (G) - nearly 30 and 21 times respectively - compared to those who survived. In our study, 40% of those who died had pre-existing neurological conditions. However, according to research by Salahuddin H., et al (2020) [65], the presence of pre-existing neurological diseases did not impact mortality; instead, the occurrence of major neurological complications during the illness

Table 7
Pattern use of medicines of interest for COVID-19 by clinical severity outcomes.

	Antiviral	Immunomodulators		
	Remdesivir (n = 7)	**Dexamethasone (n = 527)**	**Tocilizumab (n = 9)**	**Non-dexamethasone corticotherapy † (n = 201)**
Intensive care, n (%)				
No	1 (14.3)	123 (23.3)	0 (0.0)	60 (29.9)
Yes	6 (85.7)	404 (76.7)	9 (100.0)	141 (70.1)
*p-value**	**0.002**	**< 0.001**	**< 0.001**	**< 0.001**
Hospital discharge, n (%)				
Recovered	5 (71.4)	253 (48.2)	4 (44.4)	89 (44.5)
Died	0 (0.0)	188 (35.8)	1 (11.1)	82 (41.0)
Other hospitals	2 (28.6)	84 (16.0)	4 (44.4)	29 (14.5)
*p-value**	0.174	**< 0.001**	**0.005**	**< 0.001**
MRCS, n (%)				
ECMO				
No	6 (85.7)	474 (89.9)	3 (33.3)	185 (92.0)
Yes	1 (14.3)	53 (10.1)	6 (66.7%)	16 (8.0)
*p-value**	0.075	**< 0.001**	**< 0.001**	**< 0.001**
HFNC				
No	2 (28.6)	258 (49.0)	1 (11.1)	129 (64.2)
Yes	5 (71.4)	269 (51.0)	8 (88.9)	72 (35.8)
*p-value**	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**
NIV				
No	4 (57.1)	346 (65.7)	2 (22.2)	138 (68.7)
Yes	3 (42.9)	181 (34.3)	7 (77.8)	63 (31.3)
*p-value**	**0.007**	**< 0.001**	**< 0.001**	**< 0.001**
IMV				
No	4 (57.1)	315 (59.8)	5 (55.6)	111 (55.2)
Yes	3 (42.9)	212 (40.2)	4 (44.4)	90 (44.8)
*p-value**	**0.023**	**< 0.001**	**0.007**	**< 0.001**

*Pearson's chi-squared test.
† Includes all patients treated with methylprednisolone or prednisolone.
This table includes all patients treated with at least one of the drugs of interest during the study period.

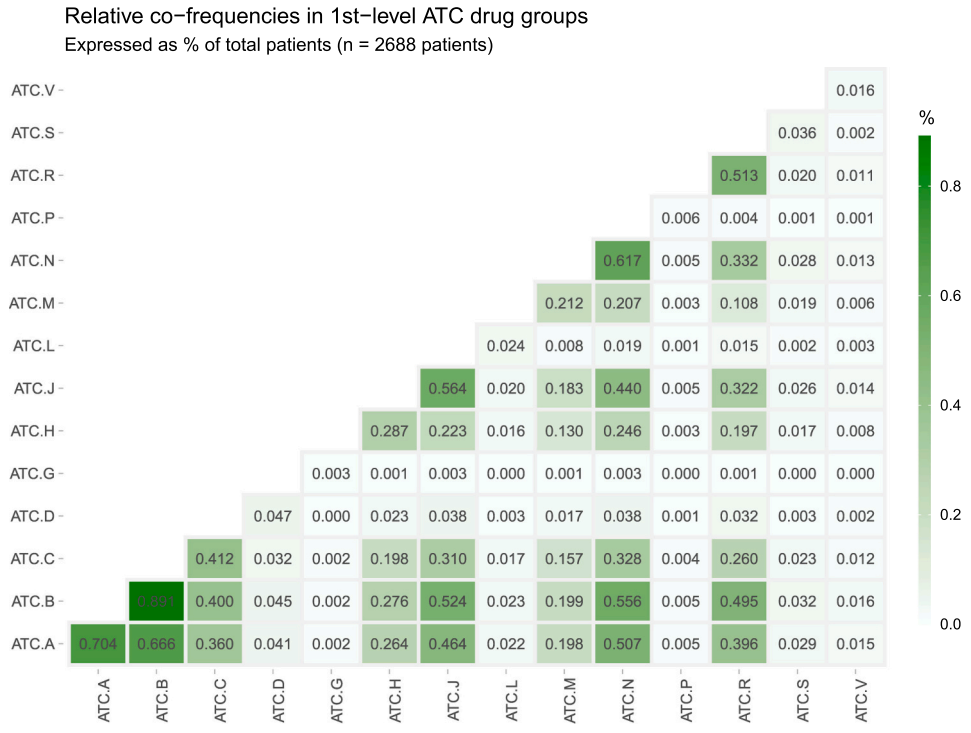

Fig. 3. Heatmap illustrating co-frequencies of exposure among 1st level ATC drug groups. Each cell represents the relative co-frequency of patients using two drug groups concurrently. For instance, the cell "ATC.A x ATC.C", with a value of 0.360, indicates that 36% of the total patients (n = 2688) are simultaneously prescribed drugs from ATC groups A and C. The diagonal line, like the cell "ATC.C x ATC.C" showing 0.412, can be interpreted as the relative frequency of the use of that specific ATC drug group on its own, signifying that 41.2% of the total patients are prescribed only drugs from ATC group C.

was an independent predictor of death. The NeuroCOV project underscores the need for continued research into post-COVID neurological conditions, aiming to tackle the enduring impacts and societal challenges through a series of multi-disciplinary clinical studies across Europe [66]. Corroborating our results, Larrosa-Garcia et al. (2023) reported similar associations between high mortality odds and pre-use of drugs like benzodiazepines in COVID-19 patients [67]. This suggests a complex interaction between COVID-19 and neurological complications

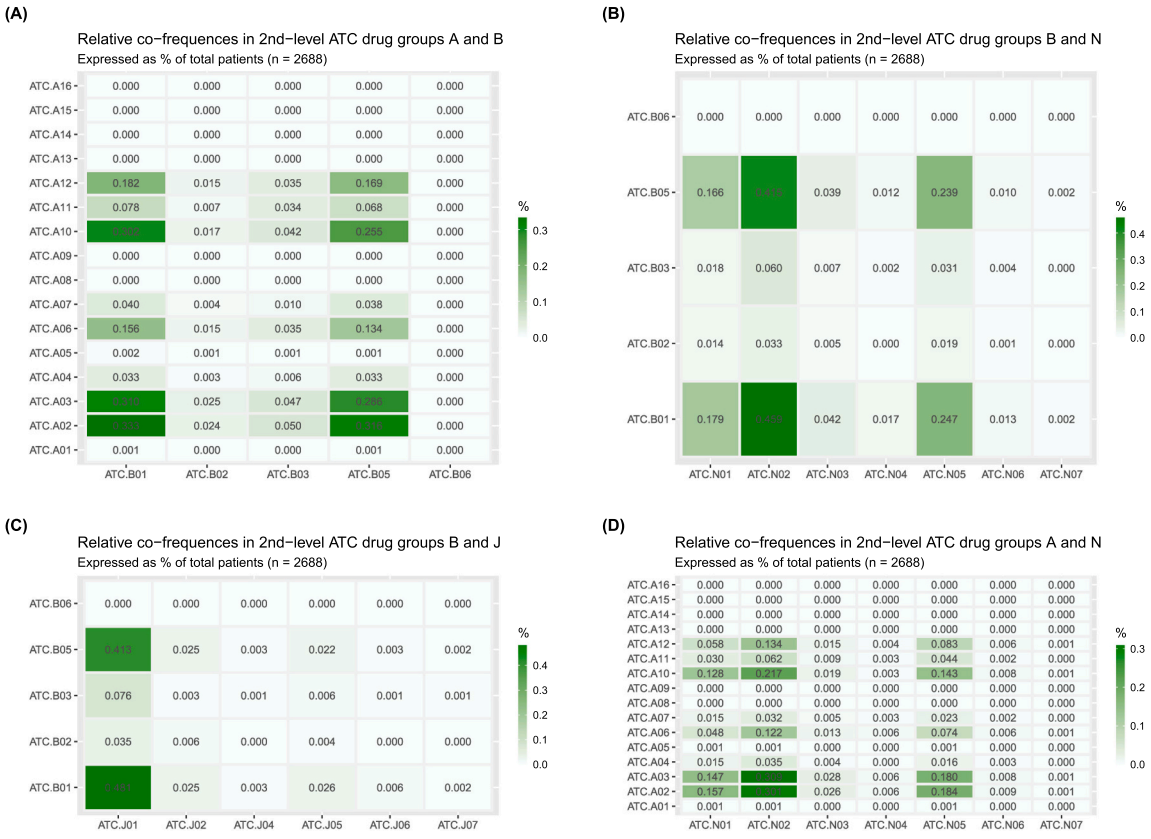

Fig. 4. Heatmaps illustrating co-frequencies among 2nd level ATC drug groups for the most prevalent associations from the 1st level ATC drug group heatmap: (A) ATC A and B, (B) ATC A and N, (C) ATC B and N, and (D) ATC B and J. Each cell represents the relative co-frequency of patients using two drug groups concurrently. For instance, in the heatmap (A), the cell "ATC.B01 x ATC.A02″ with a value of 0.333 indicates that 33.3% of the total patients (n = 2688) are concurrently prescribed drugs from 2nd level ATC groups B01 and A02.

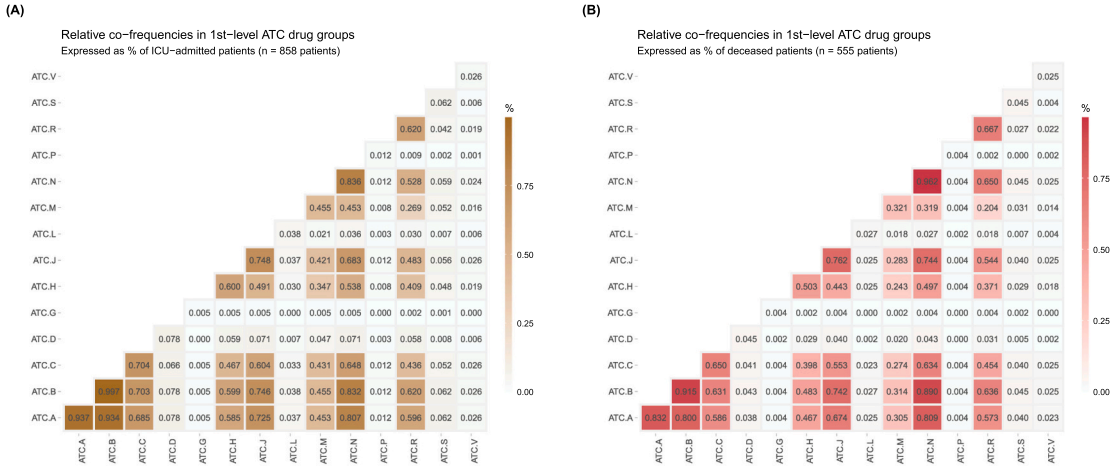

Fig. 5. Heatmaps illustrating co-frequencies of exposure among 1st level ATC drug groups for (A) ICU-admitted patients and (B) deceased patients. Each cell represents the relative co-frequency of patients using two drug groups concurrently. Taking the heatmap (A) as an example, the cell "ATC.B x ATC.A", with a value of 0.934, indicates that 93.4% of ICU-admitted patients (n = 858) are simultaneously prescribed drugs from ATC groups B and A. The diagonal cells, such as the cell "ATC.B x ATC.B" showing 0.997, can be interpreted as the relative frequency of the use of that specific ATC drug group alone, signifying that 99.7% of ICU-admitted patients are prescribed only drugs from ATC group B.

[68], highlighting the need for further research to confirm these findings and to elucidate the impact of neurological symptoms on COVID-19 outcomes. Benzodiazepines, often used for their sedative effects, might have been administered in response to COVID-19 related neurological symptoms such as anxiety, agitation, or sleep disturbances [69]. Furthermore, it is important to note that some of these medications, such as benzodiazepines, may contribute to the incidence of delirium in hospitalized and ICU patients, a condition linked to worse outcomes. Bun TP et al. (2021) found that 64.0% of critically ill COVID-19 patients received benzodiazepines and this was associated with increased delirium - a condition experienced by 54.9% of patients. The data suggest revisiting sedation protocols to minimize benzodiazepine use,

which could reduce delirium and its potential for long-term cognitive decline [70]. The study also reported that other drug groups – A, J (anti-infectives for systemic use), and L (antineoplastic and immunomodulating agents) - were associated with higher mortality odds, although the association was not as strong as with groups N and G, suggesting a wider range of medications may influence the course and outcomes of COVID-19.

Regarding MRCS, the use of medications was notably distinct based on the interventions received. Specifically, ECMO was associated with a 57-fold increase in the prescription of G drugs, suggesting a potential link between the management of severe respiratory or cardiac failure and hormonal balance or renal function [71–74]. ECMO affects hormonal pathways, leading to renal homeostasis disruption and exacerbating fluid overload in patients. This is compounded by inflammatory damage from the primary disease or ECMO therapy, increasing the risk of acute kidney injury. To address these issues, renal replacement therapy is often integrated into the ECMO circuit, aiding in optimal fluid management and the removal of inflammatory mediators [75]. Interestingly, the requirement for IMV escalated the odds of medication use across several categories, including a 266-fold increase for C drugs and a 76-fold increase for musculoskeletal system drugs (M). These findings may reflect the heightened cardiovascular strain and musculoskeletal complications associated with critical COVID-19 [76,77]. The increased reliance on systemic anti-infectives (J) by nearly 19 times and B drugs by 16 times in IMV patients could be indicative of the rigorous management of co-infections and the necessity for anticoagulation due to the recognized risks of thromboembolic events in severe COVID-19 cases [78]. Notably, ECMO patients had seven times the likelihood of being on C drugs, aligning with literature that indicates vasoactive drugs are frequently administered prior to initiating ECMO to manage hemodynamic instability [79–81]. Our study further identifies that within our patient cohort, anticoagulation practices were prevalent, reflecting the standard of care in managing the prothrombotic state of severe COVID-19 [82]. However, it is important to note that due to the lower representation of patients on ECMO, our model could not conclusively determine the association with A drugs. As we consider the broader context, it is important to acknowledge the variability of patient management across different waves of the pandemic. In Spain and Portugal, patients during the second wave experienced higher rates of co-infections at the start and during ECMO treatment, which could have significantly influenced their clinical journey. Our data does not differentiate between the waves of COVID-19; thus, we cannot ascertain the potential variations in medication use influenced by different virus strains and their associated complications.

Other clinical variables not included in our study, such as C-reactive protein (CRP) levels at hospital admission, have been identified as poor prognostic factors for COVID-19. Elevated CRP is indicative of systemic inflammation, often seen in severe COVID-19 cases, and may exacerbate lung damage leading to acute respiratory distress syndrome [53]. Additionally, prothrombin time and elevated levels of D-dimer and fibrin degradation products point to coagulation abnormalities, with a prolonged PT reflecting a disrupted clotting process, a known complication in severe COVID-19. These factors, combined with respiratory rate and age, contribute to predicting outcomes in COVID-19 [39]. The lower platelet counts observed in deceased patients might suggest platelet consumption in the context of widespread thrombosis, a key aspect of COVID-19′s pathology [39,83,84]. Choi YJ et al. [85] also identified several key factors predicting severe COVID-19 outcomes, such as dyspnea, lymphopenia, monocytopenia, elevated levels of CRP and LDH, hypoalbuminemia, and increased pro-BNP levels. These findings suggest that systemic inflammation, immune response dysregulation, and cardiac stress play significant roles in patient prognosis. The authors also found that oxygen saturation, anemia, and cardiac dysfunction are crucial in determining the severity of COVID-19, highlighting the importance of comprehensive clinical assessment in managing the disease. Despite that, our model included age, sex, and chronic conditions, which were identified by Bellou V et al. [86] as key prognostic factors for COVID-19, which strengthens the foundation of our analysis. This alignment implies that additional factors, including medication types explored in our study, might also play a significant role in influencing the disease's trajectory. However, the possibility of other, yet unidentified factors impacting COVID-19 outcomes cannot be ruled out, emphasizing the complexity and the multifactorial nature of the disease's progression and response to treatment.

Additionally, the potential for genetic factors influencing COVID-19 severity warrants consideration. Literature suggests that specific genetic variations, such as HLA alleles (e.g., HLA-A25:01, -B15:27) and genes like ACE2 and TMPRSS2, are linked to COVID-19 susceptibility and severity. These genetic factors can impact how the body responds to the virus and might explain differences in disease progression among individuals [87,88]. For instance, certain cytokine gene variants, like IL1B and IL6, could be related to the severity of the cytokine storm, a critical factor in severe COVID-19 cases [89]. Additionally, blood group associations, such as those with the ABO blood group system, have been observed to influence the risk of contracting the virus [90]. These genetic insights not only offer a deeper understanding of COVID-19 pathophysiology but also raise questions about pharmacogenetics in COVID-19, particularly how genetic variations might affect responses to medications like remdesivir and dexamethasone [91,92]. The potential for these genetic factors to contribute to disease progression underscores the need for more comprehensive research, including pharmacogenetic data, to fully understand the interplay between genetics and medication in COVID-19 management.

In our cohort, dexamethasone was the dominant therapy, prescribed to 19.6% of patients, reflecting a strong disparity with the lesser use of tocilizumab and remdesivir, at 0.33% and 0.26%, respectively. This predominance of dexamethasone mirrors the patterns observed by Mueller T et al., who reported dexamethasone use in 76.2% of their subjects, compared to 3.6% for tocilizumab, and 1.7% for remdesivir [9]. This discrepancy in usage rates may be explained by Portuguese guidelines that recommend dexamethasone only for severe disease [8]. Our analysis does not include temporal medication data, which constrains our ability to infer direct causal relationships between medication administration, ICU admissions, and subsequent hospital discharges. The interplay between drug effectiveness and the clinical course of COVID-19, including disease progression and related complications, is complex. Yet, there is a consistent thread across studies highlighting the extensive incorporation of corticosteroids in COVID-19 treatment protocols. The RECOVERY trial from the UK corroborates this with data showing 76.2% of patients on supplemental oxygen were treated with corticosteroids [93]. An international multicenter study further supports this trend, indicating that 68.5% of ICU patients were administered steroids [94], and a Pakistani cohort reported an even higher prevalence of systemic steroid treatment at 93.9%, with dexamethasone being the choice for 96.2% [10]. Our results on dexamethasone utilization resonate with data from Spain and Peru [95–97], where methylprednisolone was the preferred corticosteroid. This variation underscores the heterogeneous adoption of corticosteroids globally, influenced by regional protocols and evolving clinical evidence.

As expected, remdesivir, dexamethasone, tocilizumab and non-dexamethasone corticotherapy were administered in the majority of ICU-admitted patients. The effectiveness of remdesivir on survival in COVID-19, especially in cases treated in the ICU is controversial [98]. It is known that patients treated with remdesivir alone had a shorter length of hospital stay. The use of corticosteroids (such as dexamethasone) as adjunctive therapy of remdesivir is not associated with improvement in mortality of COVID-19 patients [99]. Hanafusa et al. (2023) have noticed that among COVID-19 patients who received corticosteroids in ICU, remdesivir use within 9 days from symptom onset was associated with reduced in-hospital mortality risk [100]. Nonetheless, the use of dexamethasone in patients hospitalized with COVID-19 resulted in lower 28-day mortality among those who were receiving either invasive

mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support [101]. Furthermore, we observed that among the patients who died, both dexamethasone and non-dexamethasone corticosteroid treatments were administered in most cases.

A recent study, which assessed the use of corticosteroids in hospitalized COVID-19 patients, with all-cause mortality as the primary outcome, revealed the frequent utilization of this type of medication in treating hospitalized COVID-19 patients. The study found a higher all-cause mortality rate among older and critically ill patients, while it was lower among smokers and those receiving treatment for more than 7 days. Additionally, the occurrence of side effects, particularly superinfections, contributed to an increased all-cause mortality rate among patients treated with corticosteroids [102]. In advanced COVID-19 cases, hypoxia and ground-glass infiltrates precipitate acute respiratory distress syndrome, primarily through viral invasion of alveolar type II cells. This infection results in the production of a harmful pulmonary toxin and significant loss of these cells, triggering alternative pathways for epithelial repair. Notably, type II cells are precursors to type I cells, essential for lung repair. Effective recuperation hinges on a strong immune response and epithelial regeneration, processes that can be compromised by the ill-timed administration of corticosteroids [103]. Our findings suggested that tocilizumab was administrated in most patients in ECMO. It is known that tocilizumab treatment is associated with a lower risk of mortality and mechanical ventilation requirement among COVID-19 patients, having a substantial effectiveness in reducing mortality among COVID-19 patients, especially among critical cases [104]. Tocilizumab therapy has been associated with accelerated recovery and significantly reduced lengths of hospital stay and mechanical ventilation in patients with severe COVID-19 pneumonia on ECMO, particularly those on veno-venous ECMO [105].

Analyzing co-occurrences among 1st level ATC groups, we observed group B frequently, including B+A, B+N, and B+J. B01 drugs, in particular, were often prescribed alongside treatments for acid-related disorders (e.g., dyspepsia, peptic ulcer, gastroesophageal reflux disease) (A02), analgesics (N02), and antibacterials (J01), with these combinations linked to increased ICU admissions, ECMO, and other intensive procedures, or death. This pairing suggests a strategy addressing secondary infections in critically ill patients, particularly in those undergoing invasive interventions. Conversely, antiparasitic and insecticide drugs (P) were less linked to such intensive care scenarios. Sun F et al [106] identified that, globally, the co-occurrence of medication administration was antiviral therapy (J05) with glucocorticoids (H02), which was not consistent with our study. However, the study mentioned only considered for analysis the pharmacological groups typically prescribed for COVID-19, without examining supportive medications. Wang Y et al. [107] found lower mortality rates in patients who received combination antiviral therapies and supportive treatment compared to those on single-agent therapies.

4.1. Study strengths and weaknesses

This pioneering study offers a comprehensive analysis of ATC data, encompassing a broad spectrum of medications, including those usually designated for supportive therapy, with the stratification by clinical severity criteria adding depth to its findings. The diverse patient cohort from a central hospital in Portugal enhances the study's external validity, boosting generalizability.

Nevertheless, certain limitations must be considered. The retrospective observational design has inherent constraints, limiting the ability to establish causality. Indeed, the available data do not allow for an assessment of causality or the directionality of outcomes concerning drug exposure and event occurrence. Furthermore, the observed correlations, despite being statistically significant, might be influenced by unmeasured confounding factors. Missing variables might potentially impact outcomes. The absence of effective antiviral medications in the early stages of the disease may have influenced clinical outcomes negatively. Outpatient medication data are lacking, making it challenging to differentiate new hospital-introduced drugs from prior treatments. Temporal data on in-hospital medication administration is also missing.

While we highlight the statistical significance of elevated OR values, further investigation is needed to establish causality and pinpoint specific drugs responsible for outcomes. The elevated OR values estimated in our study may be influenced by the inherent imbalance in the frequency of patients between the exposure and non-exposure groups, particularly concerning specific medical procedures such as intubation, mechanical ventilation, and ICU admission, which could impact the precision of our estimates in these scenarios. It's important to note that this imbalance is inherent to the study population and beyond our control.

5. Conclusion

This study shows that distinct drug patterns are correlated with clinical severity of the disease. Positive correlations have been identified between most 1st level ATC drug groups and severe clinical outcomes, particularly drugs related to the blood, often co-prescribed with other medications in severe cases. The frequent co-prescription of antithrombotic agents with drugs for acid-related disorders, analgesics, and antibacterials indicates complex treatment regimens in severe cases, associated with higher ICU admission and mortality rates. Our findings support the optimization of treatment plans, clinical guidelines, and active pharmacovigilance for safer medication use, providing valuable insights to minimize risks in common co-prescriptions. Future research should explore specific drug subgroups, administration timing, and the influence of pre-hospital medications to enhance treatment optimization.

Ethical Approval

All procedures followed the ethical standards of the ethics committee of the São João University Hospital Centre and the Helsinki Declaration of 1964 and its later amendments. This ethics committee approved the study (CES nr. 417/2020).

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CRediT authorship contribution statement

Renato Ferreira da Silva: Writing – review & editing, Writing – original draft, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Priscila Maranhão:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Cláudia Camila Dias:** Writing – review & editing, Validation, Formal analysis. **João Miguel Alves:** Writing – review & editing, Formal analysis. **Lígia Pires:** Writing – review & editing, Investigation. **Manuela Morato:** Writing – review & editing, Validation, Supervision, Conceptualization. **Jorge Junqueira Polónia:** Writing – review & editing, Validation, Supervision, Conceptualization. **Inês Ribeiro-Vaz:** Writing – review & editing, Validation, Supervision, Conceptualization..

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Consent to participate

Not applicable.

Consent for publication

Not applicable.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2024.116242.

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