Drug-utilisation Profiles and COVID-19: Retrospective Cohort Study in Italy

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Research Article

Keywords: COVID-19, SARS-Cov-2, Drug-utilisation study, Real-world data, Drug use

Posted Date: May 29th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-31829/v1

Abstract

Coronavirus disease 2019 (COVID-19) has wrought havoc on healthcare systems worldwide. Age, chronic diseases, use of drugs acting on the renin-angiotensin system (RAS), male sex and genetic predisposition have been postulated as risk factors for adverse outcomes in COVID-19 cases. A retrospective drug-utilisation study was carried out using information collected routinely in a healthcare database (CaReDB) in Campania (Southern Italy). We wished to discover the prevalence of drug utilisation (monotherapy and polytherapy) in COVID-19 *vs*. non-COVID-19 patients in Campania (~6 million inhabitants). The study cohort was 1,532 individuals who tested positive for COVID-19. Drugs were grouped according to the Anatomical Therapeutic Chemical (ATC) classification system. We noted a higher prevalence of use of drugs in the ATC category C01, B01 and M04, and this was probably linked to related comorbidities (i.e., cardiovascular, metabolic). Nevertheless, the prevalence of use of drugs acting on the RAS, such as antihypertensive drugs, was not higher among COVID-19 patients compared with that in non-COVID-19 patients. These results highlight the need for further case–control studies to define the effect of medications and comorbidities on susceptibility to, and associated mortality from, COVID-19.

Introduction

As of 24 April 2020, coronavirus disease 2019 (COVID-19) has been responsible for ~3,000,000 cases and >200,000 deaths worldwide[1]. COVID-19 is very contagious and has a wide spectrum of presentation. COVID-19 can range from an absence of symptoms to severe illness, and includes three phases (i.e., viral infection, pulmonary, hyperinflammation/systemic)[2]. Aging and underlying disease (e.g., heart disease, diabetes mellitus) have been reported to be risk factors for adverse outcomes, but, being male and a genetic predisposition to infection are under investigation as potential contributors[3–7]. Moreover, initial reports have suggested a potential pro-infective effect of drugs. Two classes of drugs that have been implicated are angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers. This action may be due to interaction between the virus that causes COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and ACE-2 receptors in the lungs, though this theory is controversial [8–12].

However, there is a lack of data on drug use (monotherapy and polytherapy) in COVID-19 patients. The main aims of this study were to: (i) discover the prevalence of drug utilisation (monotherapy and polytherapy) in COVID-19 *vs*. non-COVID-19 patients in Campania, Southern Italy; (ii) ascertain the epidemiology and profiles of patients affected in relation to drug utilisation.

Methods

Study design

A retrospective drug-utilisation study was carried out using information collected routinely in healthcare databases in Campania. The Campania Region Database (CaReDB) includes information on patient

demographics, and the electronic records of outpatient pharmacy dispensing for ~6 million residents of a well-defined population in Italy (~10% of the population of Italy). CaReDB is complete and includes validated data in previous drug-utilisation studies [13–20]. The characteristics of CaReDB are described in Supplemental Table S1.

From the beginning of the COVID-19 epidemic, a surveillance system was implemented to collect all cases identified by reverse transcription-polymerase chain reaction (RT-PCR) testing for SARS-CoV-2. These archives can be linked together by a unique anonymous identifier that is encrypted to protect patient privacy. Our research protocol adhered to the tenets of the Declaration of Helsinki 1975 and its later amendments. Permission use anonymized data to this study was granted to the researchers of the Centro di Ricerca in Farmacoeconomia e Farmacoutilizzazione (CIRFF) by the governance board of Unità del Farmaco della Regione Campania. The research does not contain clinical studies, and all patients' data were fully anonymized and were analysed retrospectively. For this type of study, formal consent is not required according to current national law from Italian Medicines Agency and according to the Italian Data Protection Authority, neither Ethical Committee approval nor informed consent were required for our study[21]. Our research protocol adhered to the tenets of the Declaration of Helsinki 1975 and its later amendments.

Study population

People who had been dispensed medication according to CaReDB during 2019 formed the study cohort. From the regional surveillance system, we obtained information on confirmed cases of COVID-19 from the beginning of the epidemic (26 February 2020) to 30 March 2020 who were linked to the population identified in CaReDB. For the purposes of our investigation, the study population diagnosed as having SARS-CoV-2 infection at the date of the analysis was referred to as the "COVID-19 group" (C19G). The remaining individuals were used as a comparator group for the analysis and were referred to as the "general population group" (GPG).

Patient characteristics

The study population was categorised by sex and subdivided into four age groups in years; 0–39; 40–59; 60–79; ≥80. The number of drug prescriptions, prevalence of drug use and polypharmacy regimens (classified as 'no-polypharmacy'; 'polypharmacy'; 'excessive polypharmacy') were ascertained in 2019. Drugs were grouped according to the Anatomical Therapeutic Chemical (ATC) classification system. ATC II and ATC IV codes with a prevalence ≥3% in the C19G were included in the analysis.

Outcome

The drug-utilisation profile was evaluated as the prevalence of drug use. Prevalent users were estimated as individuals dispensed ≥1 drug prescription per 100 inhabitants in 2019. The prevalence of drug use was evaluated in the C19G and GPG. Prevalence was stratified by age group and sex. Prevalence was

probably influenced by the heterogeneous demographic distribution among the age groups, so we provide to use direct standardization.

Statistical methods

Baseline characteristics of the study population were analysed using descriptive statistics. Quantitative variables are described by the mean ± standard deviation. Categorical variables are described by counts and percentages. Crude and age-adjusted prevalence was calculated. Differences in prevalence between the C19G and GPG are expressed as risk ratios (RRs) adjusted for sex and age with 95% confidence intervals (CIs). Standardisation was done using a direct method whereby the Italian population up to 1 January 2019 was used as the standard population (available on the Demo Istat website [22]).

$$\text{standardised rate} = \frac{\sum_{i=1}^{m} w_i \cdot T_i}{\sum_{i=1}^{m} w_i} \cdot k$$

where

($T_i = n_i / n$) = rate in stratum 'i' of the study population;

n_i = number of cases in stratum 'i' of the study population;

N = size of the study population in stratum 'i';

$\frac{\sum w_i \cdot T_i}{\sum w_i} \cdot k$ = size of stratum 'i' of the reference population;

m = number of considered strata;

k = multiplicative constant

The 95%CI age-adjusted RRs were computed using standard methods. Data management was undertaken with SQL server v2018 (Microsoft, Redmond, WA, USA). Analyses were carried out with SPSS v17.1 (IBM, Armonk, NY, USA).

Results

C19G characteristics

A total of 1,532 individuals in Campania who tested positive for COVID-19 on 30 March 2020 were identified. Of these, 926 (60.4%) were males and the median age of the entire sample was 55±19 years. Among the C19G, 20.8% were aged 0–39 years, 36.1% aged 40–59 years, 33.6% aged 60–79 years and 9.5% aged >80 years. The percentage of males was higher in all age groups except for people aged >80 years (43.8% males).

The prevalence of drug use among the C19G was 74.5% and increased with age, reaching 93.8% in those aged >80 years. The median number of prescriptions per patient (overall: 16 [interquartile range, IQR]: 5–

42) ranged from 3 (IQR, 1–6) among people aged 0–39 years and 51 (IQR, 29–71) among individuals aged >80 years.

Half of COVID-19 cases aged 0–39 years had no exposure to any medication, whereas 45.5% of COVID-19 patients were prescribed ≤4 medications and 4.1% had polypharmacy regimens (5–9 drugs). The percentage of participants undergoing polypharmacy increased with increasing age, reaching 18.3% among those aged 40–59 years, 34.8% in those aged 60–79 years and ~80% of participants aged >80 years were in polypharmacy or excessive polypharmacy (≥10 drugs) regimens. C19G characteristics are shown in Table 1.

		Age groups N (%)			
	Overall 1,532	0–39 years 319 (20.8)	40–59 years 553 (36.1)	60–79 years 514 (33.6)	≥80 years 146 (9.5)
Sex N (%)					
Male	926 (60.4)	189 (59.2)	335 (60.6)	338 (65.8)	64 (43.8)
Female	606 (39.6)	130 (40.8)	218 (39.4)	176 (34.2)	82 (56.2)
Mean age ± SD	55 (±19)	27 (±9)	51 (±5)	68 (± 6)	85 (±4)
Prevalence of drug use (%)	74.54	49.53	69.98	89.49	93.84
Median number of prescriptions (IQR)	16 (5 - 42)	3 (1–6)	9 (3–20)	28 (13–54)	51 (29–71)
Polypharmacy group, N (%)					
0 drugs	387 (25.5)	161 (50.5)	163 (29.5)	54 (10.5)	9 (6.2)
No polypharmacy (1–4 drugs)	600 (39.2)	145 (45.5)	264 (47.7)	168 (32.7)	23 (15.8)
Polypharmacy (5–9 drugs)	351 (22.9)	13 (4.1)	101 (18.3)	179 (34.8)	58 (39.7)
Excessive polypharmacy (≥10 drugs)	194 (12.7)	–	25 (4.5)	113 (22.0)	56 (38.4)

Table 1. Characteristics of the COVID-19 population

Drug-utilisation profiles of the C19G

Twenty-three pharmacological ATC II groups and 39 ATC IV groups resulted had a prevalence >3% in the C19G. The highest unadjusted and adjusted prevalence of drug use in ATC II groups was for drug category J01, A02, C09, M01, B01 and R03 in the C19G and GPG (Figure 1).

Crude differences (in terms of at least ±20% in the overall prevalence of drug use between the C19G and GPG) were found in all 23 pharmacological ATC II groups and in 30 of 39 ATC IV groups included in the analysis (Figure 1, Table 2). After adjustment, differences remained in six ATC II groups and eight ATC IV groups. With respect to Drugs Acting on the Renin–Angiotensin System (RAS) (C09), Beta-Blockers (C07),

Antibacterial Drugs for Systemic Use (J01) and Anti-inflammatory and Antirheumatic Drugs (M01), the differences disappeared after adjustment. The large differences in Antithrombotic Agents (B01), Cardiac Therapy (C01) and Antiepileptics (N03) diminished after adjustment, even though they were more common in the C19G after adjustment.

ATC IV	Chemical subgroup	Prevalence of drug use (%)				Adjusted RR C19G/GPG (95%CI)
		Unadjusted		Adjusted		
		C19G	GPG	C19G	GPG	
A02AD	Aluminium, calcium and magnesium	4.6	3.1	3.7	3.4	1.10 (1.099–1.109)
A02BC	Proton pump inhibitors	36.8	23.4	29.6	26.0	1.14 (1.136–1.140)
A02BX	Other drugs for peptic ulcers	6.9	5.1	6.1	5.5	1.10 (1.098–1.106)
A07AA	Antibiotics	7.2	5.4	6.1	5.9	1.03 (1.026–1.033)
A10BA	Biguanides	6.9	3.8	4.6	4.3	1.09 (1.083–1.092)
A11CC	Vitamin D and analogues	16.4	13.3	15.0	14.7	1.02 (1.016–1.021)
B01AB	Heparin group	5.2	2.2	4.7	2.5	1.88 (1.874–1.895)
B01AC	Platelet-aggregation inhibitors	17.2	8.1	12.2	9.4	1.29 (1.286–1.294)
B03BB	Folic acid and derivatives	4.0	2.8	3.9	3.0	1.31 (1.303–1.316)
C03CA	Sulfonamides	5.9	3.6	4.7	4.4	1.07 (1.063–1.072)
C07AB	β-blocking agents, selective	14.8	9.3	10.5	10.6	0.99 (0.988–0.994)
C08CA	Dihydropyridine derivatives	9.6	5.2	6.7	6.0	1.11 (1.105–1.113)
C09AA	ACE inhibitors	8.8	5.9	6.1	6.7	0.91 (0.902–0.909)
C09BA	ACE inhibitors and diuretics	5.0	3.2	3.6	3.7	0.97 (0.962–0.971)
C09CA	Angiotensin-II receptor blockers	10.2	5.7	7.4	6.5	1.13 (1.129–1.137)
C09DA	Angiotensin-II receptor blockers and diuretics	8.6	5.2	6.5	5.9	1.10 (1.099–1.107)
C10AA	HMG CoA reductase inhibitors	17.0	11.5	12.1	13.1	0.92 (0.922–0.926)
H02AB	Glucocorticoids	16.8	14.8	15.3	15.3	1.00 (1.001–1.006)
H03AA	Thyroid hormones	4.2	3.6	4.0	3.8	1.05 (1.044–1.053)
J01CA	Penicillins with extended spectrum	3.7	4.0	3.4	4.1	0.83 (0.831–

						0.838)
J01CR	Combinations of penicillins	22.8	21.3	21.2	21.8	0.97 (0.970–0.973)
J01DD	Third-generation cephalosporins	16.8	13.4	15.5	14.1	1.10 (1.097–1.102)
J01FA	Macrolides	14.2	12.7	13.8	12.9	1.07 (1.067–1.072)
J01MA	Fluoroquinolones	14.6	10.1	12.0	11.0	1.09 (1.082–1.088)
J01XX	Other antibacterials	5.6	4.5	5.4	4.9	1.11 (1.101–1.110)
J02AC	Antimycotic for systemic use	3.1	2.5	3.0	2.6	1.17 (1.160–1.172)
M01AB	Acetic acid derivatives	10.8	8.3	9.0	9.1	1.00 (0.994–1.000)
M01AE	Propionic acid derivatives	12.3	10.8	10.7	11.7	0.92 (0.913–0.918)
M01AH	Coxibs	4.1	3.2	3.3	3.5	0.94 (0.938–0.947)
M01AX	Other anti-inflammatory and antirheumatic agents, non-steroidal anti-inflammatory drugs	4.0	4.3	3.0	4.7	0.63 (0.632–0.637)
M04AA	Preparations inhibiting uric acid	5.9	2.7	4.2	3.2	1.29 (1.286–1.299)
N03AX	Other antiepileptics	4.0	2.3	3.4	2.6	1.30 (1.294–1.308)
N06AB	Selective serotonin reuptake inhibitors	3.9	3.4	3.3	3.8	0.86 (0.853–0.860)
N06AX	Other antidepressants	3.8	1.7	3.0	2.0	1.54 (1.531–1.550)
R03AK	Adrenergics in combination with corticosteroids	5.9	4.2	4.8	4.5	1.06 (1.058–1.066)
R03BA	Glucocorticoids	11.2	10.4	10.7	10.3	1.03 (1.030–1.036)
R03BB	Anticholinergics	4.0	1.9	2.8	2.2	1.25 (1.241–1.256)
R06AE	Piperazine derivatives	4.8	4.5	5.0	4.6	1.10 (1.093–1.101)
R06AX	Other antihistamines for systemic use	4.6	4.6	4.8	4.7	1.02 (1.016–1.023)

Table 2. Differences in prevalence of drug use between the C19G and GPG according to Chemical Subgroup (ATC IV).

ATC A: Drugs for the alimentary tract and metabolism

Drugs for Acid-related Disorders (ATC II: A02) had an adjusted prevalence of 32.2% in the C19G *vs*. 28.8% in the GPG (RR, 1.12; 95%CI, 1.116–1.120) (Figure 1). This difference increased mainly in those aged 40–59 years (32.4% *vs*. 26.5%; RR, 1.22) (Figure 2). Focusing on the Chemical Subgroup, Proton Pump Inhibitors (ATC IV: A02BC) had a higher prevalence in the C19G, mainly in those aged 0–39 years (6.8% *vs*. 5.2%; RR, 1.36) and 40–59 years (30.1% *vs*. 22.8%; RR, 1.32) (Supplementary Tables S4, S5). The prevalence of Drugs Used in Diabetes Mellitus (ATC II: A10) after adjustment showed a very small difference between the C19G and GPG. With regard to ATC IV, Biguanides (A10BA) had a higher prevalence in the C19G, mainly in those aged ≥80 years (14.6% *vs*. 10.7%; RR, 1.36) (Supplementary Tables S4, S5).

ATC B: Drugs for blood and blood-forming organs

Antithrombotic Agents (ATC II: B01) was the therapeutic group with the highest adjusted difference in prevalence between the C19G and GPG (17.1% *vs*. 11.6%; RR: 1.47; 95%CI: 1.467–1.475) (Figure 1). All age groups showed a difference in adjusted prevalence between the C19G and GPG, with a higher RR found in younger age groups (Supplementary Tables S2, S3). An identical trend was observed for ATC IV. Heparin (B01AB) and Platelet-aggregation Inhibitors (B01AC) had a higher adjusted prevalence in the C19G *vs*. the GPG, with a higher RR in participants <60 years of age (Heparin: RR, 3.19 for 0–39 years and RR, 2.27 for 40–59 years; Platelet-aggregation Inhibitors: RR, 1.94 for 0–39 years and RR, 1.52 for 40–59 years) (Figure 3). Folic Acid and Derivatives (B03BB) had a higher prevalence in the C19G *vs*. GPG mainly for those aged 0–39 years (3.3% *vs*. 1.5%; RR, 2.22) (Supplementary Tables S4, S5).

ATC C: Drugs for the cardiovascular system

Among drugs for cardiovascular system, Cardiac Therapy (ATC II: C01) showed the highest adjusted difference in prevalence between the C19G and GPG overall and by age group, and decreased with age (0–39 years: RR, 4.63; 40–59 years: RR, 2.09; 60–79 years: RR, 1.50) (Supplementary Table S3).

The other ATC II therapeutic group, which pertained to the cardiovascular system, did not show relevant differences in the overall adjusted prevalence between the C19G and GPG (Figure 1). Nevertheless, looking at values stratified by age group, a higher RR (C19G/GPG) in people aged <60 years was noted. Focusing on people older than 80 years, differences disappeared or reversed, such as for Agents acting on the RAS (ATC II: C09) and Lipid-modifying Agents (ATC II: C10) (65.6% *vs*. 71.2% and 34.6 % *vs*. 42.7% in the C19G *vs*. GPG, respectively) (Figure 2).

ATC J: Anti-infectives for systemic use

Relevant differences were not observed in overall adjusted prevalence between the C19G and GPG for therapeutic groups (ATC II) pertaining to this drug category (Figure 1). Nevertheless, focusing on the

Chemical Subgroups (ATC IV), among people under 40 years of age, Third-generation Cephalosporins (J01DD) had a higher prevalence in the C19G than in the GPG (11.8% *vs*. 9.8%; RR, 1.20). In the 40–59 years group, Macrolides (J01FA) and Fluoroquinolones (J01MA) had a higher prevalence in the C19G *vs*. GPG (16.2% *vs*. 11.9%, RR, 1.37; 13.1% *vs*. 10.2%, RR, 1.29, respectively). Among those aged >80 years, Third-generation Cephalosporins (J01DD) had a higher prevalence in the C19G than in the CPG (37.3% *vs*. 29.1%, RR, 1.28) (Figure 3 and Supplementary Tables S4, S5).

With regard to Antimycotics for Systemic Use (ATC IV: J02AC), greater sex differences in overall adjusted prevalence in the C19G was noted (male RR: 1.41) (Supplementary Tables S5).

ATC M: Drugs for the musculoskeletal system

Among Anti-inflammatory and Antirheumatic Drugs (ATC II: M01), no significant differences were observed in overall adjusted prevalence between the C10G and CPG (Figure 1). Focusing on the Chemical Subgroup (ATC IV), Acetic Acid Derivatives and Related Substances (M01AB; RR, 2.07) and Propionic Acid Derivatives (M01AE; RR, 1.75) showed a higher prevalence in those aged >40 years (Figure 3).

Anti-gout Preparations (ATC II: M04) had an adjusted prevalence of 4.5% in the C19G *vs*. 3.3% in the GPG (RR, 1.37; 95%CI, 1.36–1.37) (Figure 1). Greater sex differences in overall adjusted prevalence in the C19G were observed (female RR, 1.55) (Supplementary Table S3).

Focusing on the Chemical Subgroup (ATC IV), Preparations Inhibiting Uric Acid Production (M04AA) recorded a higher prevalence in the C19G in those aged 40–59 years (2.8% *vs*. 1.2%; RR, 2.36) and 60–79 years (8.5% *vs*. 7.1%; RR, 1.21) (Supplementary Tables S4, S5).

ATC N: Drugs for the nervous system

Among drugs for the nervous system, Antiepileptics (ATC II: N03) recorded the largest difference in prevalence between the C19G and GPG (5.0% *vs*. 3.6%; RR, 1.39) (Figure 1). For its pertaining Chemical Subgroup of Other Antiepileptics (ATC VI: N03AX), the RR in COVID-19 patients increased with age, reaching the highest difference in those aged >80 years (11.7% *vs*. 7.2%; RR, 1.62) (Supplementary Tables S4, S5). Psychoanaleptics (ATC II: N06) had an adjusted prevalence of 6.2% in the C19G *vs*. 5.5% in the GPG (RR, 1.12; 95%CI, 1.114–1.122) (Figure 1).

Focusing on the Chemical Subgroup, Other Antidepressants (ATC IV: N06AX) recorded high risk of exposure for COVID-19 patients in all age groups except for those aged 40–59 years (Figure 3).

Sex differences were observed for Analgesic Drugs (N02) (male RR, 1.41), Other Antiepileptics (N03AX) (female RR, 1.55) and Selective Serotonin Reuptake Inhibitors (N06AB) (male RR, 0.67) (Supplementary Tables S3, S5).

ATC R: Drugs for the respiratory system

Marked differences were not observed in prevalence for the therapeutic group (ATC II) between the C19G and GPG (Figure 1).

However, focusing on the Chemical Subgroup (ATC IV), Anticholinergic Inhalation (R03BB) recorded a higher sex difference in overall adjusted prevalence in the C19G (male RR, 1.44) (Supplementary Table S5) Adrenergic Agents in Combination with Corticosteroids (R03AK) had the highest prevalence in the C19G (6.1% *vs*. 4.0%; RR, 1.53) among those aged 40–59 years (Supplementary Table S5). Glucocorticoids (R03BA) had the highest prevalence in the C19G among those aged 40–59 years (10.4% *vs*. 7.3%; RR, 1.42) (Supplementary Table S5) and those aged 60–79 years (14.9% *vs*. 11.4%; RR, 1.31) (Supplementary Table S5). A higher prevalence in the C19G was recorded for Anticholinergics (R03BB) (11.9% *vs*. 9.8%; RR, 1.23) and Piperazine Derivatives (R06AE) (7.1% *vs*. 5.5%; RR, 1.30) among those aged >80 years (Supplementary Table S5).

Discussion

The COVID-19 pandemic has wrought havoc on healthcare systems worldwide. A body of literature has been produced on the clinical aspects, possible treatments and risk factors of patients with COVID-19 [23–26]. Nevertheless, apart from a few studies, the epidemiology and profile of drug use in patients with COVID-19 has not been studied. To our knowledge, this is the first study dealing with this topic.

Most of our COVID-19 population were middle-aged men (55±19 years; 80% were >40 years of age) and taking ≥1 drug (74.5% of cases; including 35% exposed to a polypharmacy regimen).

In general, from our results we can describe four profiles. The first is an age range of 0–39 (median age, 27±9) years, male, half of patients with no exposure to any drug and a very low prevalence of polytherapy. The second is an age range of 40–59 (median age, 51±5) years, male, nearly half of patients taking 1–4 drugs and a low prevalence of polytherapy (<25%). The third is an age range of 60–79 (median age, 68±6) years, male, 90% of patients taking ≥1 drug and more than half of patients having polytherapy. The final profile is age >80 (median age 85±4) years, female, 94% of patients taking ≥1 drug, including 78% taking polytherapy.

Analyses of drug-utilisation profiles highlighted differences between the C19G and GPG in terms of prevalence of drug exposure. Drug categories showing a variation of ≥30% were Antithrombotic Agents (B01), Antiepileptics (N03), Anti-hyperuricemics/Anti-gout (M04) and cardiac therapy (C01). The higher prevalence of use of drug category C01, B01 and M04 is a proxy of a more frequent pattern of cardiovascular and metabolic comorbidity in COVID-19 populations, as reported from other studies [4,5,8]. It is of some relevance that B01 drugs showed the highest difference in drug exposure between COVID -19 and General population. This therapeutic profile can be a proxy for cardiovascular complications (including venous thromboembolism), supporting the hypothesis of an increased risk associated with COVID -19 infection in these patients [8].

With regard to greater exposure to drugs in the M04 category, a retrospective cohort study on 131,565 patients and 252,763 controls, using data from the UK Clinical Practice Research Datalink, reported an increased risk of pneumonia (hazard ratio, 1.27; 95%CI 1.18–1.36) in patients with gout[27].

There is no clear association between epilepsy and the risk of developing COVID-19. Nevertheless, epilepsy may be associated with other comorbidities, or as part of congenital/inherited syndromes that may affect the immune system. Also, antiepileptic agents can be used in association with other medications that can influence the immune system (e.g., adrenocorticotropic hormone, corticosteroids, everolimus, immunotherapy), and this may increase the infection risk[28]. Moreover, these patients may require frequent clinical evaluation, which may explain (at least in part) greater exposure to potential healthcare infections.

Notably, the adjusted prevalence of Drugs Acting on the RAS (C09) did not show differences between the C19G and GPG (RR, 1.02; 95%CI, 1.01–1.02). This result is in accordance with evidence from a retrospective study undertaken on a COVID-19 cohort in Italy [29], and supports the position of the European Society of Cardiology[30]. Furthermore, no major differences were noted for any category of antihypertensive drugs.

Stratification by age showed a higher prevalence of exposure to drugs of category B01, B03, C09 and C10 in people aged <40 years. This evidence should be interpreted with caution because the number of such patients was very small. Nevertheless, a similar morbidity pattern to that for older patients could be hypothesised for these patients. Conversely, in patients aged >60 years, there was no significant difference in use of drugs for cardiometabolic diseases compared with that in the CPG, but the prevalence of use of drugs for respiratory disease and drugs for neurological disease increased in the C19G.

A high number of males took Analgesics (N02) and drugs for Cardiac Therapy (C01). A high number of females took Anti-anemia Agents (B03) and Anti-epileptic Agents (N03). Early descriptions of COVID-19 suggested a male preponderance for this disease[23, 24, 31]. Sex-based immunological, genetic, or lifestyle differences (e.g., tobacco smoking) have been postulated for the male preponderance for COVID-19[32]. In a population of 507 patients with COVID-19 reported between 13 January and 31 January 2020 (including 364 from mainland China), 281 patients were male (55%) and the median age was 46 (IQR, 35–60) years[33]. Zhou and colleagues described 191 COVID-19 patients from Wuhan (Hubei Province, China) during the first month of the outbreak. That cohort had a median age of 56 (IQR, 46.0–67.0) years, with 62% of men and 48% of patients with comorbidities[23]. Also, data from Italy have shown a higher prevalence of males *vs*. females with COVID-19[34, 35]. However, sex- and age-disaggregated data revealed the opposite to be true for women aged >80 years in Campania. National data for Italy reveals that, in those aged 20–29 years, 56.5% of diagnosed cases are female, and only after the age of 50 years does the male preponderance for COVID-19 increase. Thus, caution should be employed regarding the male

preponderance for COVID-19 because sex-disaggregated data are incomplete, and evidence that is more robust is needed.

Our study was not designed to define the association between drug use, comorbidities risk of adverse outcome and outcome in COVID-19 patients. The association between use of certain drugs and susceptibility to SARS-CoV-2 infection (e.g., predictive factors for poor outcome) must be studied using a large cohort, a control group and robust clinical data. This was a retrospective study of health records. More detailed patient information (mainly regarding clinical outcomes) was not available at the time of analyses. Despite these limitations, we delineated the drug, epidemiological and demographic characteristics of 1,532 Italian patients with COVID-19. This information delineates the first picture of the association between drug utilization and Covid-19 risk, giving us a solid background for further analysis and interpretation using upcoming data.

Conclusions

In conclusion, the current data provide a picture of baseline complexity of patients affected by COVID-19 showing frequencies and differences of drug utilization profiles in COVID-19 patients compared with the general population. The higher prevalence of C01, B01 and M04 is probably linked to related comorbidities (i.e. cardiovascular, metabolic). Nevertheless, prevalence of drugs acting on RAS, such as other antihypertensive drugs, didn't show higher prevalence among COVID-19 patients than observed in the general population. Since these pilot data derived from the first month of documented COVID-19 cases in Campania Region (Southern Italy), our results highlight the need for further case-control studies to define the effect of medications and comorbidities on susceptibility to, and associated mortality from, COVID-19 infection. Finally, to better understand the global epidemiology of COVID-19, reproducible and comparable results are needed from cohorts of multiple countries and multiple regions for further investigation and metanalysis.

Declarations

Funding

The authors declare no funding for this work.

Competing interests

The authors declare no competing interests.

Author contributions

V.O. and E.M. conceived the study. I.G. and S.M. conducted the study. V.O., E.M. and G.L. analysed the results and wrote the original draft. E.C., A.P. and U.T. reviewed the manuscript. All authors agreed with the final version of the manuscript.

Our research protocol adhered to the tenets of the Declaration of Helsinki 1975 and its later amendments.

Permission use anonymized data to this study was granted to the researchers of the Centro di Ricerca in Farmacoeconomia e Farmacoutilizzazione (CIRFF) by the governance board of Unità del Farmaco della Regione Campania. The CIRFF has a regional decree that allow for conducting research by making secondary use of administrative data (DGRC n 276 23/05/2017).

The research does not contain clinical studies, and all patients' data were fully anonymized and were analysed retrospectively.

For this type of study, formal consent is not required according to current national law from Italian Medicines Agency and according to the Italian Data Protection Authority, neither Ethical

Committee approval nor informed consent were required for our study.

References

1. World Health Organization. Coronavirus disease 2019 (COVID-19), Situation Report – 95. Available from: www.who.int/docs/default-source/coronaviruse/situation-reports/20200424-sitrep-95-covid-19.pdf?sfvrsn=e8065831_4. Accessed on 4 April 2020.
2. Yuen, K. S., Ye, Z. W., Fung, S. Y., Chan, C. P., & Jin, D. Y. SARS-CoV-2 and COVID-19: the most important research questions. *Cell Biosci.* **10**(1), 1–5 (2020).
3. Wenham, C., Smith, J., & Morgan, R. COVID-19: the gendered impacts of the outbreak. *Lancet*. **395**(10227), 846–848 (2020).
4. Yang, X., et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir. Med*. pii: S2213-2600(20)30079-5 (2020) [Epub ahead of print].
5. Li, B., et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Res. Cardiol.* **109**(5), 531–538 (2020).
6. Tignanelli, C. J., et al. Antihypertensive drugs and risk of COVID-19? *Lancet Respir. Med*. pii: S2213-2600(20)30153-3 (2020) [Epub ahead of print].
7. Gandhi, R. T., Lynch, J. B., & del Rio, C. Mild or moderate Covid-19. *New England Journal of Medicine*. (2020). doi: 10.1056/NEJMcp2009249.
8. Guo, T., et al. Cardiovascular implications of fatal outcomes of patients with coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. (2020) doi: 10.1001/jamacardio.2020.1017. [Epub ahead of print].
9. Rossi, G. P., Sanga, V., & Barton, M. Potential harmful effects of discontinuing ACE-inhibitors and ARBs in COVID-19 patients. **9**, e57278. (2020).
10. South, A. M., Diz, D., & Chappell, M. C. COVID-19, ACE2 and the cardiovascular consequences. *J. Physiol. Heart Circ. Physiol*. **318**(5), H1084-H1090 (2020).

11. Aronson, J. K., & Ferner, R. E. Drugs and the renin-angiotensin system in covid-19. *BMJ*. **369**, m1313. (2020).
12. Sommerstein, R., Kochen, M. M., Messerli, F. H., & Gräni, C. Coronavirus disease 2019 (COVID-19): do angiotensin-converting enzyme inhibitors/angiotensin receptor blockers have a biphasic effect? *Am. Heart Assoc.* **9**(7), e016509 (2020).
13. Moreno-Juste, A., et al. Treatment patterns of diabetes in Italy: a population-based study. *Pharmacol.* **10**, 870 (2019).
14. Guerriero, F., et al. Biological therapy utilization, switching, and cost among patients with psoriasis: retrospective analysis of administrative databases in Southern Italy. *Outcomes Res*. **9**, 741 (2017).
15. Putignano, D., et al. Differences in drug use between men and women: an Italian cross sectional study. *BMC Women's Health*. **17**(1), 73 (2017).
16. Iolascon, G., et al. Osteoporosis drugs in real-world clinical practice: an analysis of persistence. *Aging Clin. Exp. Res*. **25**(1), 137–141 (2013).
17. Orlando, V., et al. Prescription patterns of antidiabetic treatment in the elderly. Results from Southern Italy. *Diabetes Rev.***12**(2), 100–106 (2016).
18. Menditto, E., et al. Adherence to chronic medication in older populations: application of a common protocol among three European cohorts. *Patient Prefer. Adherence.* **12**, 1975 (2018).
19. Casula, M., et al. Assessment and potential determinants of compliance and persistence to antiosteoporosis therapy in Italy. *Am J Manag. Care*. **20**(5), e138–e145 (2014).
20. Orlando, V., et al. Drug utilization pattern of antibiotics: the role of age, sex and municipalities in determining variation. *Risk Manag. Healthc. Policy.* **13**, 63 (2020).
21. Italian Data Protection Authority. General authorisation to process personal data for scientific research purposes – 1 March 2012 [1884019]. 10.1094/PDIS-11-11-0999-PDN.
22. Demo-Geodemo. Mappe, Popolazione, Statistiche Demografiche dell'ISTAT. Available from: http://demo.istat.it/. Accessed on 2020, March 1.
23. Zhou, F., et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. **395**(10229):1054–1062 (2020).
24. Chen, N., et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. **395**(10223), 507–513 (2020).
25. Shoenfeld, Y. Corona (COVID-19) time musings: our involvement in COVID-19 pathogenesis, diagnosis, treatment and vaccine planning. *Rev*. (2020). 102538. doi: 10.1016/j.autrev.2020.102538. [Epub ahead of print].
26. Vellingiri, B., et al. COVID-19: a promising cure for the global panic. *Total Environ.* **725**, 138277 (2020).
27. Spaetgens, B., et al. Risk of infections in patients with gout: a population-based cohort study. *Rep.* **7**(1), 1–9 (2017).
28. Beghi, E., & Shorvon, S. Antiepileptic drugs and the immune system. *Epilepsia*. **52**, 40–44 (2011).

29. Mancia, G., Rea, F., Ludergnani, M., Apolone, G. & Corrao, G. Renin-Angiotensin-Aldosterone System Blockers and the Risk of Covid-19. *N Engl J Med*. (2020). doi: 10.1056/NEJMoa2006923. [Epub ahead of print].
30. The European Society of Cardiology. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic. 2020. Available from: escardio.org/static_file/Escardio/Education-General/Topic%20pages/Covid-19/ESC%20Guidance%20Document/ESC-Guidance-COVID-19-Pandemic.pdf. Accessed on 21 April 2020.
31. Chen, T., et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. **368** (2020).
32. Cai, H. Sex difference and smoking predisposition in patients with COVID-19. *Lancet Respir. Med*. **8**(4), e20 (2020).
33. Sun, K., Chen, J., & Viboud, C. Early epidemiological analysis of the coronavirus disease 2019 outbreak based on crowdsourced data: a population-level observational study. *Lancet Digit. Health*. **2**(4), e201–e208 (2020).
34. Riccardo, F., et al. Epidemiological characteristics of COVID-19 cases in Italy and estimates of the reproductive numbers one month into the epidemic. *medRxiv*. (2020). doi: 10.1101/2020.04.08.20056861
35. Onder, G., Rezza, G., & Brusaferro, S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *Jama*. (2020). doi: 10.1001/jama.2020.4683. [Epub ahead of print].

Figures

ATC II	Therapeutic subgroup	Prevalence of drug use (%)			
		Unadjusted		Adjusted	
		C19G	GPG	C19G	GPG
B01	Antithrombotic agents	22.8	10.1	17.1	11.6
N03	Antiepileptics	5.9	3.3	5	3.6
M04	Anti-gout Preparations	6.3	2.8	4.5	3.3
C01	Cardiac therapy	4.9	2.2	3.5	2.6
B03	Anti-anemia Agents	6.2	4.7	6.4	5
N02	Analgesic Drugs	6.3	3.9	5.2	4.4
A07	Antidiarrheals, Intestinal Antiinflammatory/Antiinfective Agents	9.7	6.5	8.3	7.1
J02	Antimycotics for systemic use	3.1	2.5	3	2.6
N06	Psychoanaleptics	7.5	5.0	6.2	5.5
C03	Diuretics	8.0	4.7	6.3	5.6
C08	Calcium channel blockers	10.4	5.6	7.2	6.4
A02	Acid-related Disorders	39.3	26.1	32.2	28.8
A10	Drugs Used in Diabetes Mellitus	10.3	5.8	7.1	6.7
R06	Antihistamines for systemic use	9.0	8.7	9.3	8.8
R03	Drugs for obstructive airway diseases	18.9	15.9	17	16.3
J01	Antibacterial Drugs for Systemic Use	50.3	44.7	47	45.9
H03	Thyroid therapy	4.6	3.9	4.3	4.2
A11	Vitamins	16.4	13.3	15	14.7
C09	Drugs Acting on the Renin–Angiotensin System (RAS)	33.2	20.7	23.9	23.5
H02	Corticosteroids for systemic use	16.8	14.8	15.3	15.3
C07	Beta-Blockers	18.7	12.1	13.5	13.7
C10	Lipid-modifying Agents	20.0	13.3	14.4	15.1
M01	Anti-inflammatory and Antirheumatic Drugs	24.9	20.5	21.2	22.3

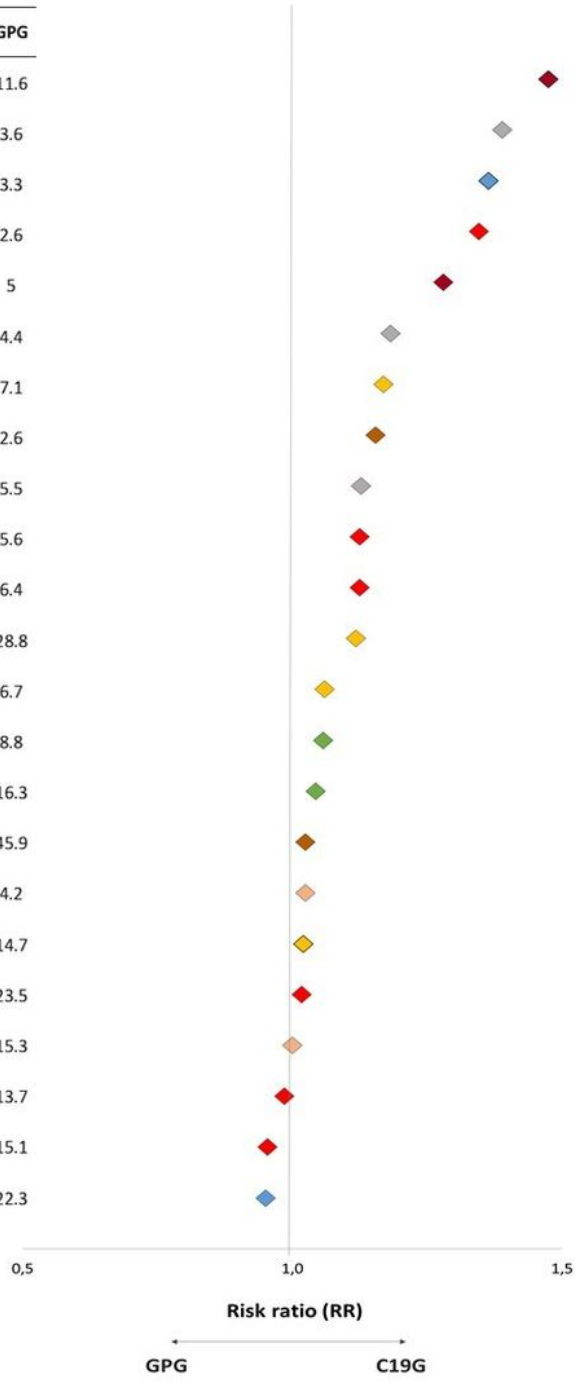

Figure 1

Differences in prevalence of drug use between the C19G and GPG according to Therapeutic Group (ATC II).

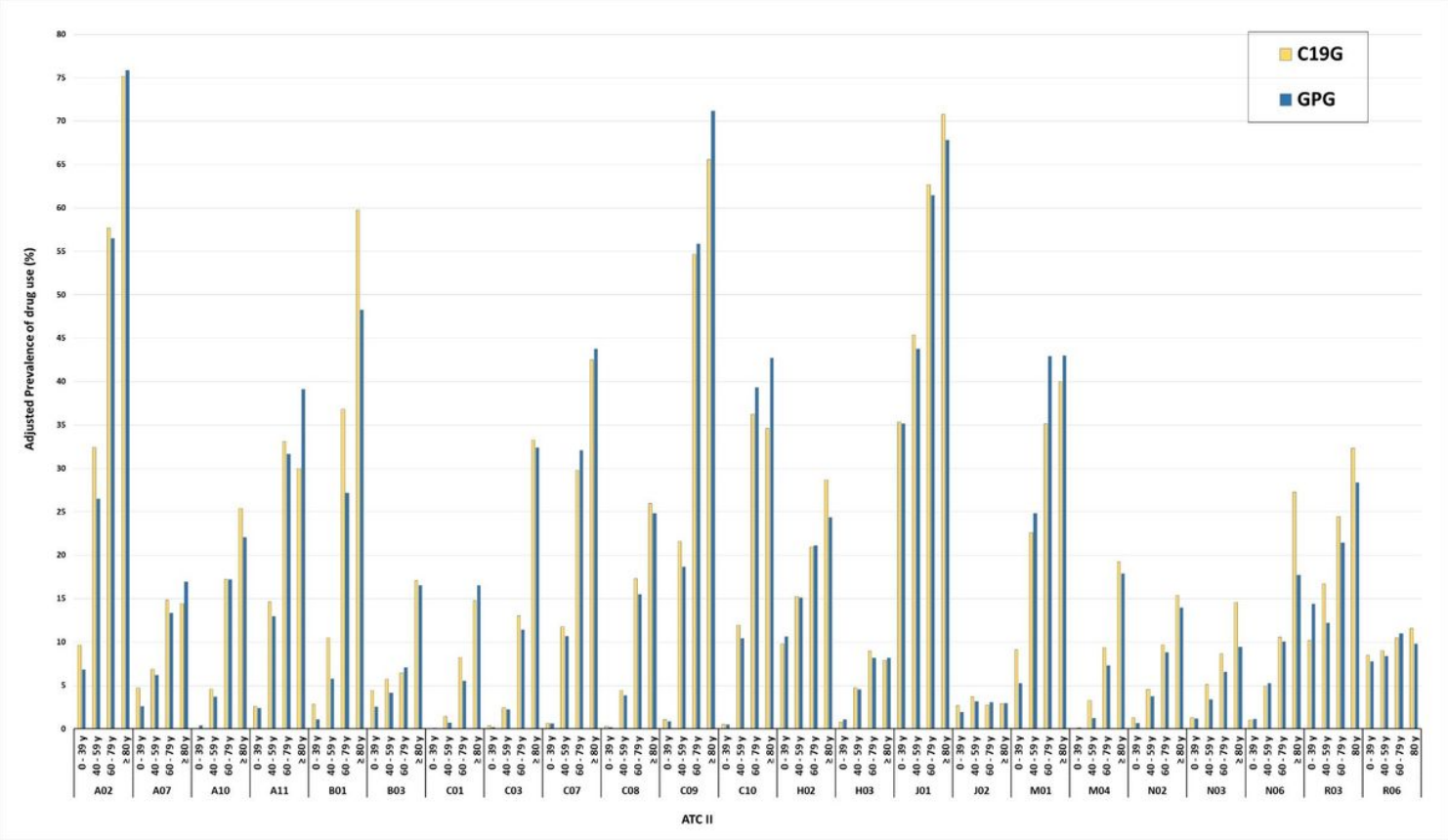

Figure 2

Prevalence of drug use between the C19G and GPG stratified by age group.

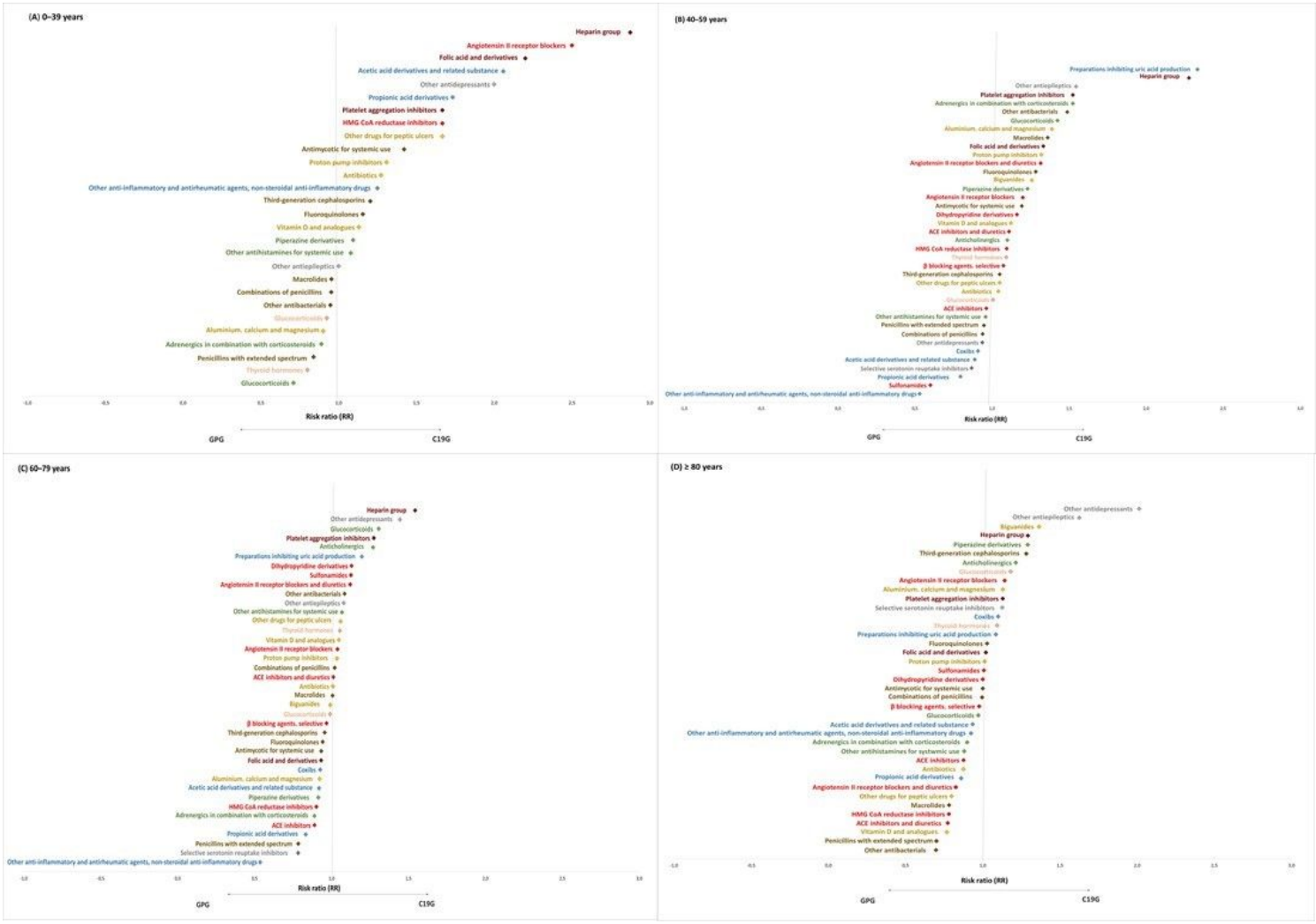

Figure 3

Chemical Subgroup of the C19G with the highest adjusted relative differences in prevalence stratified by age group. (A) Patients aged 0–39 years. (B) Patients aged 40–59 years. (C) Patients aged 60–79 years. (D) Patients aged >80

Supplementary Files

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