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ORIGINAL ARTICLE
Hypertension

Association between renin–angiotensin system inhibitors and COVID-19 complications

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Aims To describe the characteristics of patients hospitalized with COVID-19 (including their long-term at-home medication use), and compare them with regard to the course of the disease. To assess the association between renin–angiotensin system inhibitors (RASIs) and disease progression and critical outcomes.

Methods and results All consecutive hospitalized patients with laboratory-confirmed COVID-19 in a university hospital in Amiens (France) were included in this study. The primary composite endpoint was admission to an intensive care unit (ICU) or death before ICU admission. Univariable and multivariable logistic regression models were used to identify factors associated with the composite endpoint. Between 28 February 2020 and 30 March 2020, a total of 499 local patients tested positive for SARS-CoV-2. Of these, 231 were not hospitalized {males 33%; median [interquartile range (IQR)] age: 44 (32–54)}, and 268 were hospitalized [males 58%; median (IQR) age: 73 (61–84)]. A total of 116 patients met the primary endpoint: 47 died before ICU admission, and 69 were admitted to the ICU. Patients meeting the primary endpoint were more likely than patients not meeting the primary endpoint to have coronary heart disease and to have been taking RASIs; however, the two subsets of patients did not differ with regard to median age. After adjustment for other associated variables, the risk of meeting the composite endpoint was 1.73 times higher (odds ratio 1.73, 95% confidence interval 1.02–2.93) in patients treated at baseline with a RASI than in patients not treated with this drug class. This association was confirmed when the analysis was restricted to patients treated with antihypertensive agents.

Conclusions We highlighted a potential safety signal for RASIs, the long-term use of which was independently associated with a higher risk of severe COVID-19 and a poor outcome. Due to the widespread use of this important drug class, formal proof based on clinical trials is needed to better understand the association between RASIs and complications of COVID-19.

Keywords COVID-19 • Renin–angiotensin system inhibitors • Associated factors • Critical outcomes

Introduction

In December 2019, an outbreak of a previously unknown form of pneumonia was identified in Wuhan, China. Coronavirus RNA was detected in some patients. The novel coronavirus has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the resulting disease is referred to as coronavirus disease 2019 (COVID-19). The World Health Organization declared COVID-19

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to be a pandemic in March 2020. As of 17 April 2020, >2 million cases of COVID-19 (including 135 000 fatal cases) had been reported in 213 countries and territories.[1]

In a report on 72 314 cases of COVID-19 by the Chinese Center for Disease Control and Prevention, 81% were classified as mild (i.e. no pneumonia or mild pneumonia only), 14% developed severe illness requiring oxygen therapy, and 5% developed very severe illness requiring admission to an intensive care unit (ICU).[2] Due to SARS-CoV-2's high contagiousness, even the most advanced healthcare systems are likely to be overwhelmed in the absence of lockdown policies. Furthermore, it recently emerged that a large proportion of people infected by SARS-CoV-2 remained asymptomatic—making it even more difficult to control the pandemic. Although the estimated overall death rate from COVID-19 is 0.66%, the value is as high as 7.8% in people aged 80 and as low as 0.0016% in children aged 9 and under.[3]

Identifying the at-risk groups is essential for patient care and the implementation of protective strategies (e.g. social distancing and longer lockdown). Retrospective cohort studies in China, Italy, and the USA have found that several clinical characteristics are risk factors for severe COVID-19, including older age and the presence of one or more of several underlying health conditions.[4,5] In critically ill patients, hypertension and diabetes are associated with more severe COVID-19.[6–8] Unfortunately, prevalent diseases are not readily modifiable, and so it is essential to identify more easily modifiable factors. Little is known about the potential impact of at-home drug treatments on the severity and course of COVID-19. Some drugs might have harmful effects; for example, anti-inflammatory agents might aggravate the infection by 'damping down' the immune system. This point prompted the French Minister for Health to claim that people showing symptoms of COVID-19 should use paracetamol (acetaminophen) rather than other non-steroidal anti-inflammatory drugs such as ibuprofen.[9] Some other concerns relate to renin–angiotensin system inhibitors [RASIs; i.e. angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II type I receptor blockers (ARBs)], which are cornerstone treatments for hypertension, coronary heart disease, and diabetic nephropathy. Indeed, the target receptor for SARS-CoV and SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE2), which is expressed by epithelial cells in the lung, intestine, kidney, and blood vessels.[10] Given that RASI use may up-regulate ACE2,[11] treatment with these medications could increase the risk of developing severe/fatal COVID-19.[12] Although epidemiologists have started to investigate RASI use by patients hospitalized for COVID-19 and potential associations with disease severity,[13,14] we considered that this topic warrants evaluations in different countries with different patient populations.

Hence, the objectives of the present study were to describe the characteristics of patients hospitalized with COVID-19 (including long-term at-home medication use), compare them with regard to the course of the disease, and assess factors (including medications) associated with poor outcomes.

Methods

Study population

This retrospective, observational study was performed at Amiens University Hospital (Amiens, France). The hospital was one of the first to admit patients with COVID-19 at the start of the epidemic phase in northern France. We extracted data from the medical records of hospitalized patients (admission between 28 February 2020 and 30 March 2020) and outpatients with laboratory-confirmed COVID-19. Laboratory confirmation for SARS-CoV-2 was defined according to the WHO guidelines, i.e. a positive result in a real-time reverse transcription–PCR (RT–PCR) assay of nasal and pharyngeal swabs.[15] The clinical outcomes were recorded up until 14 April 2020.

In line with French legislation on retrospective analyses of routine medical care, informed consent by patients was not required. On admission to hospital, however, patients could refuse the use of their medical data for research purposes. This protocol was approved by an institutional committee (with competency for studies not requiring approval by an independent ethics committee) and was registered with the French National Data Protection Commission (Commission Nationale de l'Informatique et des Libertés, Paris, France; reference: PI2020_843_0032.)

Data collection

The clinical data reported here were collected by three pharmacologists (S.L., J.M., and V.G.-C.), on the basis of an electronic chart review. For hospitalized patients, the following data were collected: age, sex, body mass index (BMI), comorbidities (*Table 1*), home drug prescriptions (if noted), death in hospital, ICU admission, and discharge (up until 14 April 2020). Regarding at-home drug prescriptions considered as long-term at-home medication use, we specifically recorded the use of drugs that could potentially aggravate infections (such as anti-inflammatories, corticosteroids, immunosuppressive agents, and antineoplastic agents) or the complications of infection (such as benzodiazepines and opiates). Furthermore, we collected data on all types of antihypertensive agent, including beta-blockers, calcium channel blockers, diuretics, aldosterone antagonists, and RASIs. Long-term treatment with a RASI was defined as a prescription of an ACE inhibitor or an angiotensin II type I receptor blocker (ARB) alone or combined with another antihypertensive agent.

For outpatients, we collected data on comorbidities and the signs and symptoms at the time of the COVID-19 diagnosis (including fever, asthenia, myalgia, headache, cough, dyspnoea, diarrhoea, rhinorrhoea, odynophagia, ageusia, and anosmia). Information on drug prescriptions was not present in their electronic medical records.

Study outcomes

The primary study outcome was a composite endpoint: ICU admission or death before ICU admission. The two events comprising the composite endpoint were also evaluated separately as secondary outcomes.

Statistical analysis

Continuous and categorical variables were described as the median [interquartile range (IQR)] or the frequency (percentage), respectively. We used the Mann–Whitney *U*-test, the χ^2 test, or Fisher's exact test to compare groups, as appropriate. Univariable and multivariable logistic regression models were used to identify factors associated with the composite endpoint. Given that we sought to identify relationships between a large number of variables and outcomes, a starting hypothesis was not pre-specified. Only literature variables with $P < 0.20$ in the univariate

Table 1 Baseline characteristics of the study population

	All hospitalized (n = 268)	Achievement of the composite endpoint		*P*-value	Type of composite endpoint		Patients with missing data
		No (n = 152)	Yes (n = 116)		Death before ICU admission (n = 47)	ICU admission (n = 69)	
Age (years)	73 (61–84)	73 (58–82)	73 (63–86)	0.124	86 (81–89)	66 (57–74)	0%
<18	4 (2)	4 (3)	0 (0)		0 (0)	0 (0)	
18 to 44	17 (6)	11 (7)	6 (5)		0 (0)	6 (8)	
45 to 64	62 (23)	34 (22)	28 (25)		1 (2)	27 (39)	
65 to 74	60 (22)	34 (22)	26 (22)		7 (15)	19 (28)	
≥75	125 (47)	69 (46)	56 (48)		39 (83)	17 (25)	
Male sex	156 (58)	83 (55)	73 (63)	0.171	24 (51)	49 (71)	0%
Body mass index (kg/m^2)	28 (24–33)	28 (23–33)	28 (24–33)	0.348	25 (21–30)	29 (26–34)	20%
≥ 30 kg/m^2	82 (39)	44 (38)	38 (40)		10 (27)	28 (47)	
Lean	69 (32)	41 (35)	28 (30)		20 (56)	8 (14)	
Overweight	61 (29)	32 (27)	29 (30)		6 (17)	23 (39)	
Moderately obese	51 (24)	29 (25)	22 (23)		7 (19)	15 (25)	
Severely obese	31 (15)	15 (13)	16 (17)		3 (8)	13 (22)	
Smoking status				0.699			0%
Non-smoker	215 (80)	124 (82)	91 (78)		41 (87)	50 (73)	
Former smoker	44 (17)	4 (3)	20 (17)		4 (9)	16 (23)	
Current smoker	9 (3)	24 (15)	5 (4)		2 (4)	3 (4)	
Pregnancy	1 (1)	0 (0)	1 (1)	0.247	0 (0)	1 (1)	0%
Concomitant disorder							0.7%
Any disorder	221 (83)	121 (79)	100 (87)	0.115	45 (98)	55 (80)	
Hypertension	152 (57)	80 (53)	71 (62)	0.116	29 (61)	42 (62)	
Coronary heart disease	33 (12)	11 (7)	22 (19)	0.003	10 (23)	12 (18)	
Stroke	37 (14)	22 (15)	15 (13)	0.743	8 (18)	7 (10)	
Cardiac insufficiency	30 (11)	17 (11)	13 (11)	0.955	5 (13)	8 (12)	
Cardiac surgery	26 (10)	13 (9)	13 (11)	0.438	4 (10)	9 (13)	
Other cardiovascular disease	74 (28)	40 (26)	34 (30)	0.527	15 (38)	19 (28)	
Chronic obstructive pulmonary disease	26 (10)	11 (7)	13 (13)	0.108	10 (25)	3 (4)	
Asthma	14 (5)	8 (5)	5 (5)	0.989	3 (8)	2 (3)	
Restrictive lung disease	16 (6)	7 (5)	7 (7)	0.264	2 (5)	5 (7)	
Active cancer	16 (6)	12 (8)	3 (4)	0.137	2 (5)	1 (1)	
Cured cancer	22 (8)	10 (7)	11 (11)	0.247	7 (18)	4 (6)	
Chronic kidney disease	19 (7)	9 (6)	10 (9)	0.372	4 (10)	6 (9)	
Dialysis	5 (2)	3 (2)	2 (2)	0.896	0 (0)	2 (3)	
Cirrhosis	1 (1)	0 (0)	1 (1)	0.247	1 (2)	0 (0)	
Type 1 diabetes mellitus	8 (3)	3 (2)	5 (4)	0.254	1 (2)	4 (6)	
Type 2 diabetes mellitus	47 (18)	27 (18)	20 (18)	0.603	1 (2)	19 (27)	
Hypothyroidism	26 (10)	16 (11)	10 (9)	0.633	7 (18)	3 (4)	
Chronic inflammatory disease	9 (3)	4 (3)	5 (4)	0.434	1 (2)	4 (6)	
Immunosuppressant drugs	10 (4)	8 (5)	2 (2)	0.402	1 (2)	1 (1)	
Immunosuppression due to HIV	1 (1)	1 (1)	1 (1)	0.353	0 (0)	0 (0)	
Immunosuppression due to transplantation	2 (1)	1 (1)	1 (1)	0.501	0 (0)	1 (1)	
Treated haematological malignancy	3 (1)	3 (1)	0 (0)	0.165	0 (0)	0 (0)	
Neurodegenerative disease	60 (23)	35 (23)	24 (21)	0.479	23 (51)	1 (1)	

Median (IQR) or *n* (%).
Body mass index category: lean (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), moderately obese (30 to 35 kg/m^2), and severely obese (≥35 kg/m^2).

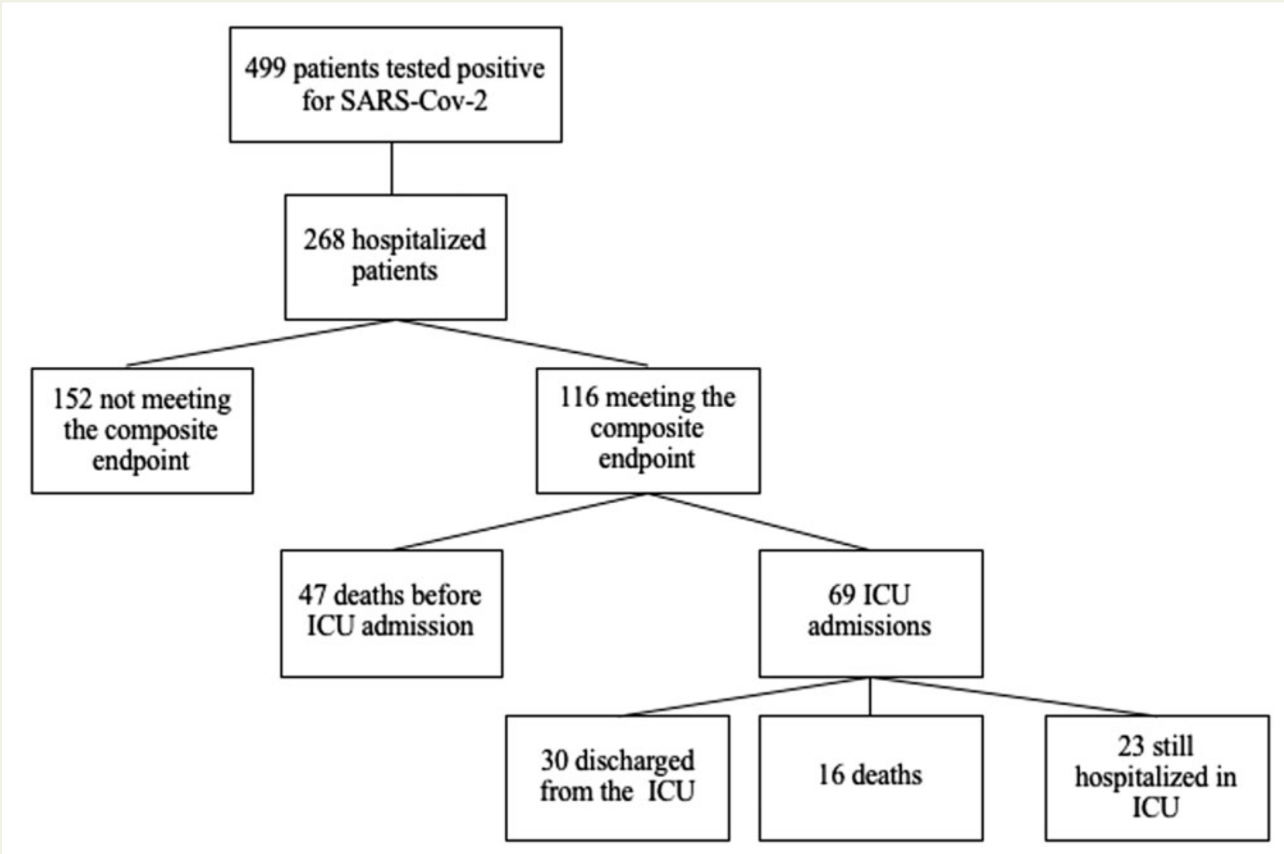

Figure 1 Study flow chart.

analysis were included in the multivariable analysis. For the analysis of the primary endpoint, age, sex, coronary heart disease, hypertension, chronic obstructive pulmonary disease, beta-blockers, diuretics, RASIs, and anti-inflammatory drugs were included in the multivariate analysis. In contrast, the following variables [odds ratios (ORs) with $P > 0.2$ in the univariate analysis] were not included in the multivariate model: BMI, smoking status, pregnancy, stroke, heart failure, cardiac surgery, other cardiovascular disease, asthma, restrictive lung disease, active cancer, cured cancer, chronic kidney disease, dialysis, cirrhosis, type 1 diabetes mellitus, type 2 diabetes mellitus, hypothyroidism, chronic inflammatory disease, immunosuppressant drugs, immunosuppression due to HIV, immunosuppression due to transplantation, treated haematological malignancy, neurodegenerative disease, calcium channel blockers, other antihypertensive agents, aldosterone antagonists, systemic corticosteroids, inhaled corticosteroids, antineoplastic agents, opioids, and benzodiazepines. To avoid overfitting, the number of variables included in the multivariable analysis also took into account the number of patients meeting the primary endpoint ($n = 116$). A sensitivity analysis (based on the same analysis plan) was performed by restricting the population to patients treated with at least one antihypertensive agent. Multivariate logistic regression models were also applied to the two secondary endpoints [ICU admission ($n = 69$) and death before ICU admission ($n = 47$)], using the methods described above. For the multivariate analysis of ICU admissions, age, sex, BMI, diabetes mellitus, diuretics, and RASIs were included. For the multivariate analysis of death before admission to the ICU, age, BMI, coronary heart disease, chronic obstructive pulmonary disease, and cognitive disorder were included. In addition, a Kaplan–Meier actuarial curve was used to estimate ICU admission according to RASI at baseline. Patients were censored at death before ICU admission or the last news date. The log-rank test was used to compare survival curves. All statistical analyses were performed with SAS software (version 9.2; SAS Institute Inc., Cary, NC, USA) and SPSS software (version 18.0; SPSS Inc., Chicago, IL, USA).

Results

Between 28 February 2020 and 30 March 2020, a total of 499 local patients tested positive for SARS-CoV-2. Of these, 231 were not hospitalized [males 33%; median (IQR) age: 44 (32–54)] and 268 were hospitalized [males 58%; median (IQR) age: 73 (61–84)]. Among the hospitalized patients, 116 met the primary outcome (47 died before ICU admission and 69 were admitted to the ICU) (*Figure 1*).

Demographic and clinical characteristics

The non-hospitalized patients had tested positive for the presence of SARS-CoV-2 genomic material a median (IQR) of 5 (3–7) days after symptom onset. All presented minor symptoms, with cough in 141 patients (65%) and fever in 132 (61%). Other symptoms included digestive symptoms, with diarrhoea in 40 (17%) patients, ageusia in 40 (17%), and anosmia in 52 (23%). The great majority of non-hospitalized individuals had unremarkable medical histories (68; 31%)

Table 2 Characteristics of the patients' medications at baseline

	All hospitalized patients (n = 268)	Achievement of the composite endpoint		P-value	Type of composite endpoint		Patients with missing data
		No (n = 152)	Yes (n = 116)		Death before ICU admission (n = 47)	ICU admission (n = 69)	
At least one antihypertensive drugs	164 (62)	86 (57)	78 (68)	0.071	31 (67)	47 (68)	0.7%
Beta-blockers	73 (27)	36 (24)	37 (32)	0.231	18 (39)	19 (28)	0.7%
Calcium channel blockers	57 (21)	30 (20)	27 (23)	0.477	11 (24)	16 (23)	0.7%
Diuretics	58 (22)	28 (19)	30 (26)	0.140	8 (17)	22 (33)	0.7%
RASIs	96 (36)	44 (29)	52 (45)	0.007	17 (37)	35 (51)	0.7%
Other antihypertensive agents	2 (1)	0 (0)	2 (1)	0.104	0 (0)	2 (3)	0.7%
Aldosterone antagonist	15 (6)	8 (5)	7 (6)	0.785	2 (4)	5 (7)	0.7%
Corticosteroids for systemic use	18 (7)	9 (6)	9 (8)	0.548	6 (13)	3 (4)	0.7%
Corticosteroids for respiratory use	17 (6)	8 (5)	9 (8)	0.404	5 (11)	4 (6)	0.7%
Antineoplastic agents	15 (6)	9 (6)	6 (5)	0.795	2 (4)	4 (6)	0.7%
Immunosuppressive agents	13 (5)	7 (5)	6 (5)	0.827	2 (4)	4 (6)	0.7%
Anti-inflammatory drugs	9 (3)	3 (2)	6 (5)	0.149	1 (2)	5 (7)	0.7%
Opioids	19 (8)	10 (7)	9 (8)	0.765	5 (11)	4 (6)	0.7%
Benzodiazepines	71 (28)	46 (32)	25 (22)	0.088	13 (28)	12 (18)	0.7%

Median (IQR) or *n* (%).

(Supplementary material online, *Table S1*). Relative to hospitalized patients, outpatients were younger [with 185 (69%) vs. 12 (13%) patients below the age of 65 years, respectively; $P < 0.0001$], less likely to be male [156 (58%) vs. 77 (33%) respectively; $P < 0.0001$], and less likely to have concomitant disorders [221 (83%) vs. 68 (31%), respectively; $P < 0.0001$]. The demographic and clinical characteristics of the 268 hospitalized patients are summarized in *Table 1*. One hundred and twenty-five (47%) were aged 75 or over, and 21 (8%) were younger than 45. Eighty-three percent of the hospitalized patients had at least one comorbidity—mainly cardiovascular disease, with hypertension in 152 (57%) cases. The second most common comorbidity was diabetes mellitus (55 patients, 21%). We observed at least one comorbidity in 110 of the 125 over-75 patients (88%) and in 173 of the 185 over-65 patients (94%). The median (IQR) BMI was 28 (24–33), and 82 patients (39%) were considered to be obese. Regarding at-home medications, 164 patients (62%) were undergoing long-term treatment with an antihypertensive, including 96 (36%) taking RASIs (*Table 2*).

Clinical outcomes

In the cohort of hospitalized patients, the median (IQR) duration between symptom onset and hospitalization was 6 (3–8) days. This information was not available for 17% of the hospitalized patients. One hundred and eighty-two patients (68%) had lung damage on imaging, and 202 patients (75%) required oxygen therapy. Of the 268 hospitalized patients, 116 met the primary outcome: 47 patients died before ICU admission and 69 patients were admitted to the ICU. As of 14 April 2020, 145 of the 152 patients who did not reach the primary outcome (95%) were discharged from the hospital after a median (IQR) stay of 9 (6–12) days, and 7 (5%) were still hospitalized. In the patients who died before ICU admission, the median (IQR) time interval between hospitalization and death was 7 (4–14) days. Nine of these 47 patients were already hospitalized in a geriatric ward. Among the 69 patients admitted to the ICU, 30 (44%) were discharged from the ICU after a median (IQR) stay in the unit of 8 (4–15) days, 16 (23%) died in the ICU after a median ICU stay of 9 (6–19) days, and 23 (33%) were still in the ICU as of 14 April 14 2020. During their stay in the ICU, a 53 of the 69 patients (77%) presented an acute respiratory distress syndrome, 11 (16%) presented a heart rhythm disorder, 17 (25%) presented septic shock, and 36 (52%) developed acute kidney injury.

Patients meeting the primary (composite) outcome were more likely to have coronary heart disease and to have been taking RASIs (*Tables 1* and *2*). Patients who died before ICU admission were older ($P < 0.001$), had a lower BMI ($P = 0.004$), and were more likely to have at least one comorbidity ($P < 0.001$) than patients who did not die before ICU admission.

Patients who were admitted to the ICU were younger ($P <0$ .0001), had a higher BMI ($P = 0.001$, and 47% had a BMI ≥ 30 kg/m^2), and were more likely to be male (71%) than patients not admitted to the ICU (29% male; $P = 0.016$).

Factors associated with meeting the composite endpoint

After adjustment for other associated variables, the risk of meeting the composite endpoint was 1.73 times higher [OR 1.73, 95% confidence interval (CI) 1.02–2.93] in patients treated at baseline with a RASI than in patients not treated with this drug class (*Table 3*). Furthermore, the risk of severe COVID-19 was significantly and

Table 3 Odds ratios for composite endpoints, as a function of the patients' characteristics and medications at baseline

	N (%) with endpoints (n = 116)	Crude model		Adjusted model	
		OR (95% CI)	P-value	OR (95% CI)	P-value
Age (years)		1.01 (0.99–1.03)	0.126	1.01 (0.99–1.02)	0.342
Sex					
Female	53 (37)	Reference		Reference	
Male	73 (63)	1.41 (0.86–2.31)	0.141	1.54 (0.91–2.61)	0.148
Coronary heart disease					
Absence of CHD	88 (81)	Reference		Reference	
Presence of CHD	22 (19)	**3.07 (1.42–6.62)**	**0.004**	**2.32 (1.04–5.19)**	**0.041**
Hypertension					
Absence of hypertension	45 (38)	Reference		Reference	
Presence of hypertension	71 (62)	1.49 (0.91–2.44)	0.117	1.22 (0.63–1.73)	0.795
COPD					
Absence of COPD	102 (88)	Reference		Reference	
Presence of COPD	13 (12)	1.94 (0.86–4.41)	0.112	1.60 (0.68–3.78)	0.209
Beta-blockers					
No	89 (73)	Reference		Reference	
Yes	73 (27)	1.52 (0.88–2.61)	0.132	1.18 (0.64–2.19)	0.533
Diuretics					
No	88 (76)	Reference		Reference	
Yes	28 (24)	1.55 (0.86–2.78)	0.141	1.35 (0.71–2.56)	0.331
RASIs					
No	64 (55)	Reference		Reference	
Yes	52 (45)	**2.01 (1.21–3.34)**	**0.007**	**1.73 (1.02–2.93)**	**0.042**
Anti-inflammatory drugs					
No	110 (95)	Reference		Reference	
Yes	6 (5)	2.72 (0.66–11.1)	0.164	2.93 (0.68–12.57)	0.153

BMI, body mass index; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; OR, odds ratio; RASI, renin–angiotensin system inhibitor.
Hypertension, body mass index, smoking status, pregnancy, stroke, heart failure, cardiac surgery, other cardiovascular disease, COPD, asthma, restrictive lung disease, active cancer, cured cancer, chronic kidney disease, dialysis, cirrhosis, type 1 diabetes mellitus, type 2 diabetes mellitus, hypothyroidism, chronic, inflammatory disease, immunosuppressant drugs, immunosuppression due to HIV, immunosuppression due to transplantation, treated haematological malignancy, neurodegenerative disease, calcium channel blockers, other antihypertensive agents, aldosterone antagonist, systemic corticosteroids, inhaled corticosteroids, antineoplastic agents, anti-inflammatories, opioids, and benzodiazepines had an odds ratio with $P > 0.2$ and were not included in the multivariate model.

independently associated with a history of coronary heart disease (OR 2.32, 95% CI 1.04–5.19).

In a sensitivity analysis, we restricted the population to 164 patients having been treated with at least one antihypertensive drug. After adjustment for age, sex, coronary heart disease, and other antihypertensive drugs, the risk of severe COVID-19 was higher in patients treated with a RASI (OR 1.97, 95% CI 1.03–3.78) than in patients not treated with a RASI.

Factors associated with death before ICU admission

The only two independent factors associated with death before ICU admission were older age (OR 1.06, 95% CI 1.01–1.10) and the presence of a cognitive disorder (OR 2.63, 95% CI 1.00–7.13). None of the drugs taken at baseline (including RASIs) was associated with death before ICU admission (Supplementary material online, *Table S2*).

Factors associated with ICU admission

In crude analysis, RASI at baseline was a predictor of ICU admission ($P = 0.002$) (*Figure 2*). After adjustment for age, sex, BMI, and coronary heart disease, patients treated at baseline with a RASI had a higher risk of ICU admission (OR 2.28, 95% CI 1.17–4.42). BMI and male gender were the other independently associated factors (OR 1.06, 95% CI 1.01–1.11; and OR 2.15, 95% CI 1.05–4.42, respectively) (Supplementary material online, *Table S3*).

Discussion

We provided a comprehensive description of the epidemiological, demographic, and clinical characteristics, long-term home treatments, and outcomes for patients hospitalized for COVID-19 in a university hospital in France. Of the 268 hospitalized patients, 69 (26%) were admitted to the ICU and 63 (24%) died (47 before ICU admission and 16 afterwards). Our study's main finding was that

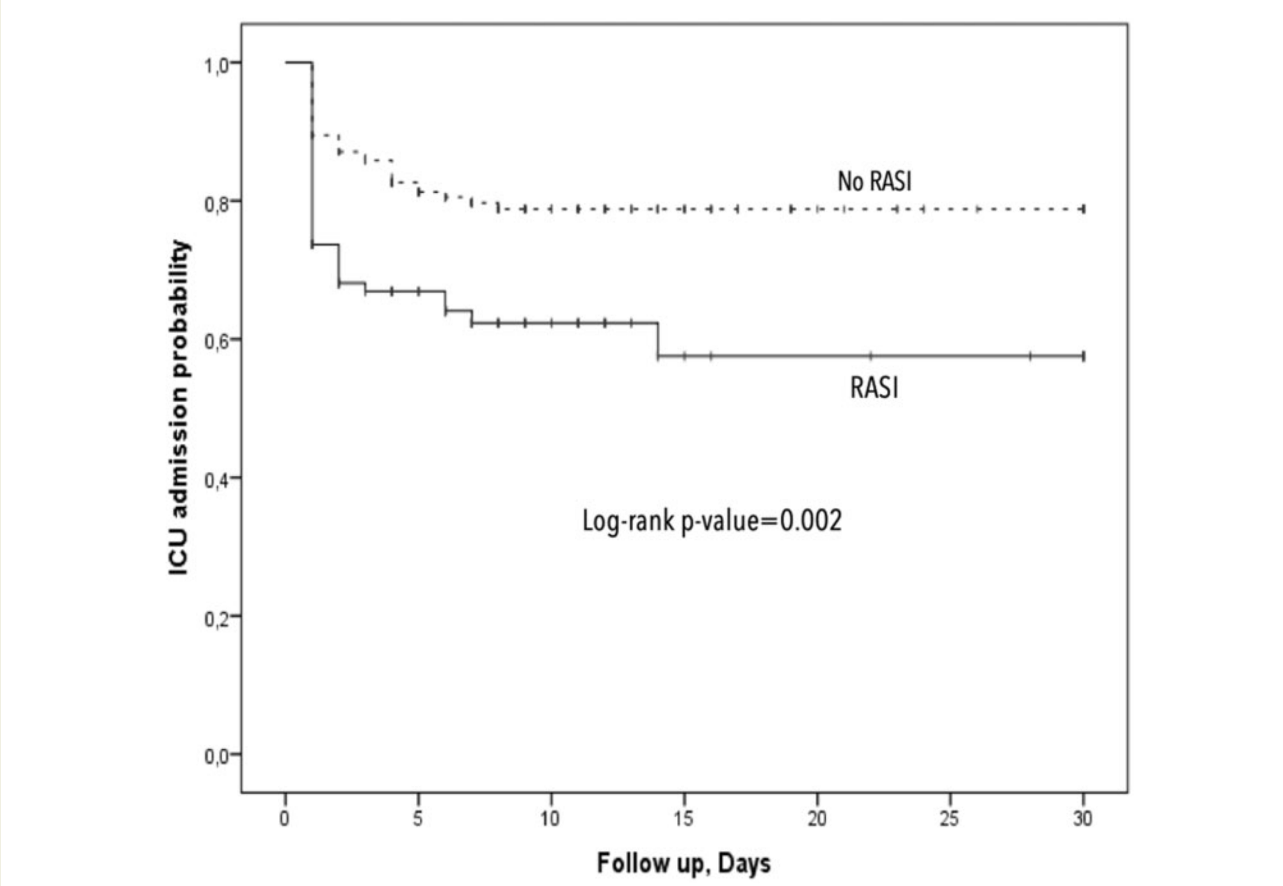

Figure 2 Kaplan–Meier estimates of intensive care unit (ICU) admission as function of renin–angiotensin system inhibitor (RASI) use at baseline.

patients having been treated with RASIs before COVID-19 were more likely to meet the composite endpoint (ICU admission or death before ICU admission). This relationship persisted after multivariate adjustment, and was observed consistently in secondary and sensitivity analyses.

We observed high comorbidity rates among patients hospitalized for COVID-19 pneumonia—up to 69% in those aged 65 and over. These findings are in line with the literature data. In a study of 72 314 patients infected with COVID-19 in China, a greater likelihood of severe disease was found in older adults with comorbidities such as hypertension, cardiovascular disease, and diabetes mellitus.[2,16,17]

Identification of the most at-risk groups of patients is crucial. Knowledge of risk factors can help clinicians to optimize treatment early in the course of COVID-19. Furthermore, governments worldwide have implemented restrictive measures (including mass quarantine) aimed at containing the spread of COVID-19. Lifting these restrictions will be challenging, and might increase pressure on healthcare systems (and especially ICUs). Differentiated strategies for lifting these restrictions could be based on population risk factors; people more at risk (i.e. more likely to need critical care) could remain in quarantine for longer.

It has been reported that ∼5% of people with COVID-19 will require ICU admission or (in the absence of treatment) will die. The identification of factors associated with critical disease progression is a major challenge for the future management of COVID-19 patients. In the present analysis, we identified a history of coronary heart disease as an independent risk factor. This is in line with literature reports of an association between cardiovascular disease and severe disease or death,[5,18] although these studies were performed outside Europe (in China) on the basis of univariate analyses that did not consider potential confounding factors.

In the present cohort of hospitalized patients with severe COVID-19, 57% had hypertension. The proportion was 62% among those admitted to the ICU. A recent report from the European Society of Hypertension stated that 75% of the patients who died in Italy had hypertension, and that the median age among the deceased patients was 79.[17] There are several possible explanations for an association between hypertension and the severity of COVID-19. First, the proportion of patients with hypertension increases with age. Given that age is one of the most important risk factors for COVID-19, the association between hypertension and COVID-19 severity might be due to confounding bias. Secondly, recent research suggests that hypertension is associated with immune dysregulation;[19] rapid deterioration in COVID-19 patients is associated with a proinflammatory cytokine storm. Lastly, the SARS-CoV-2 spike protein facilitates viral entry into target cells by binding to ACE2. Treatment with a

RASI—one of the cornerstones of hypertension treatment—might up-regulate ACE2.[20] Indeed, patients undergoing long-term treatment with RASIs for cardiovascular disease might express higher levels of ACE2 throughout their cardiopulmonary systems, as has been observed in animal models.[11] Two recent studies failed to show an association between ACE inhibitors or ARBs and an increased risk of developing COVID-19.[21,22]

The present analysis highlighted long-term RASI use as a factor potentially associated with more severe COVID-19. It is important to note that this association was maintained after adjustment for various risk factors (including hypertension). After restriction of the analysis to patients treated with antihypertensive agents, the risk of meeting our composite endpoint was 1.97 times higher among patients having undergone long-term treatment with a RASI than among patient treated with another antihypertensive agent. In contrast, a recent retrospective cohort study in China evaluated the association between in-hospital use of RASIs and all-cause mortality in COVID-19 among patients with hypertension.[13] However, this study looked at hospital prescriptions (rather than home prescriptions), and RASI use in the study population was lower (17%) than in our population. Furthermore, the Chinese patients were younger than our patients. Furthermore, the use of ACE inhibitors or ARBs was not associated with an increased risk of in-hospital death in an international multicentre retrospective cohort.[14] Once again, the mean ± SD age in the latter study (49 ± 16) was much lower than in the present study. It is important to evaluate the relationship with RASI use in different ethnic cohorts, as the Asiatic and European populations appear to differ markedly with regard to the mortality rate. Indeed, a recent assessment of primary care electronic health records in the UK showed that compared with people of Caucasian ethnic origin, people of Asian and African origin were more at risk of death by COVID-19.[23] Even though the Chinese and American researchers evaluated a hard outcome (mortality), we consider that looking at other outcomes related to severe COVID-19 (especially ICU admission, as in our study) is important. Indeed, we found a significant relationship between RASI use and ICU admission but not between RASI use and death before ICU admission. On the same lines, Mehta *et al*. recently reported on a higher likelihood of hospital admission or ICU admission among COVID-19 patients who had been treated with RASIs.[22]

Until formal proof is provided by a clinical trial of RASI discontinuation vs. continuation (e.g. trial NCT04351581, currently recruiting), it is important to continue to perform case–control studies in populations of various ethnic origin. In order to optimize overall outcomes, the risk and benefits of RASIs should be assessed carefully on a case by case basis. At present, withdrawal of RASIs is not recommended by cardiologists.[20,24] Indeed, some patients (e.g. those with heart failure) may deteriorate rapidly if they stop taking the RASI, and so withdrawal of this key medication would be problematic in this context. However, if our present finding is confirmed by clinical trial results, physicians could consider (i) the temporary withdrawal in patients using RASIs for their cardiovascular benefits; and (ii) avoiding the initiation of RASI treatment during the course of COVID-19.[25]

In the present study, we looked at a number of other drug classes that might be associated with the exacerbation of COVID-19. We did not find evidence of an association with anti-inflammatory agents, although the small proportion of patients taking these drugs at baseline would have reduced the statistical power of our analysis; hence, a larger study is needed to identify other potential signals. Furthermore, we cannot rule out self-medication with anti-inflammatory agents. Indeed, our recent survey of 1257 university students demonstrated that analgesics were the most frequently self-administrated drugs (anti-inflammatories reported in 20% of participants).[26] In France, however, a major media campaign about the danger of anti-inflammatories was initiated at the beginning of the pandemic.[9]

When focusing on patients who died in hospital but were not admitted to the ICU, the main determinants were age and cognitive disorders. Indeed, the median age in this group was 86, and 51% displayed cognitive impairment. The decision not to transfer to the ICU was mainly based on advanced age and the likely lack of benefit of management in the ICU.

In patients admitted to the ICU, the OR (95% CI) associated with RASI use was 2.28 (1.17–4.42). Another important associated factor was BMI: 47% of the patients admitted to the ICU were obese. This factor has not been greatly studied in China, although a recent study performed in northern France found a high frequency of obesity (47.6%) among patients receiving intensive care for SARS-CoV-2.[27] Obesity is generally acknowledged to be a risk factor for severe infection[28] and is associated with low lung capacities and restrictive patterns.[29,30] Lastly, obesity predisposes to a proinflammatory state via elevated levels of inflammatory mediators [e.g. interleukin-6 (IL-6) and tumour necrosis factor (TNF)-α] and low levels of anti-inflammatory mediators (e.g. adiponectin).[31]

The major strengths of the present study include the presentation of the clinical characteristics of hospitalized patients with COVID-19 and the identification of a potential association between RASIs and critical forms of the disease. The old age of the study population and our adjustments for other associated factors (including hypertension) indicate that RASI use is an independent associated factor.

This study also had several limitations. First, limited medical resources prevented us from defining endpoints for patients with non-severe COVID-19, and so our findings might not apply to the general population. Secondly, the study was conducted at a single university hospital, and the sample size was relatively small. Thirdly, the descriptive nature of our data meant that attack rates among patients taking vs. not taking RASIs could not be compared, and thus the difference in the risk of critical disease progression between these groups could not be estimated. Lastly, the observational nature of the present study prevented us from demonstrating a causal relationship. Although we considered known, recorded covariables in our analyses, the observed associations might be due to unknown or unmeasured residual confounders.

Conclusions

In a retrospective cohort study of 268 patients hospitalized for COVID-19, we observed a high proportion of critical outcomes. We highlighted a potential safety signal for RASIs, the long-term use of which was independently associated with a higher risk of severe COVID-19 and a poor outcome. Due to the widespread use of this important drug class, large-scale, prospective cohort studies and randomized controlled trials are needed in ethnically and geographically diverse populations, with a view to better understand the association between RASIs and complications of COVID-19.

Author contributions

Concept and design: S.L., Y.B., K.M., and V.G.-C. Acquisition, analysis, or interpretation of data: S.L., J.M, V.G.-C., and K. M. Drafting of the manuscript: S.L. Critical revision of the manuscript for important intellectual content: J.M., Y.B., B.B., E.B., J.L.S., J.-P.L., C.A., O.G., M.S., J.M., Y.M., K.M., and V.G.-C. Statistical analysis: S.L.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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