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Clinical factors associated with hospitalization and mortality from COVID-19 in hypertensive patients in primary care: a multicenter study in Spain

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Abstract

Objective To identify clinical factors independently associated with COVID-19-related hospitalization and short-term mortality among hypertensive patients managed in Primary Care in Spain.

Methods Multicenter retrospective cohort study including 1,372 hypertensive adults (≥ 18 years) with PCR-confirmed SARS-CoV-2 infection between May 2021 and February 2022. Multivariable logistic regression models adjusted for predefined confounders (age, sex, smoking status, and obesity) were used to evaluate factors independently associated with hospital admission and 3-month all-cause mortality.

Results Hospital admission occurred in 29.2% of patients, ICU admission in 5.0%, and 3-month mortality was 4.0%. Chronic kidney disease (aOR 1.52; 95% CI 1.08–2.14), heart failure (aOR 2.55; 95% CI 1.74–3.74), atrial fibrillation (aOR 2.16; 95% CI 1.50–3.12), diabetes in patients aged < 60 years (aOR 2.54; 95% CI 1.41–4.60), peripheral arterial disease (aOR 2.17; 95% CI 1.31–3.58), chronic obstructive pulmonary disease (aOR 1.83; 95% CI 1.33–2.51), and immunocompromised status (aOR 3.19; 95% CI 1.89–5.53) were independently associated with hospital admission. A significant interaction between smoking and chronic kidney disease was observed (aOR 6.80; 95% CI 2.37–19.48). RAAS inhibitor use was not associated with hospitalization.

For mortality, chronic kidney disease (aOR 4.34; 95% CI 2.37–7.94), atrial fibrillation (aOR 4.09; 95% CI 2.18–7.68), heart failure (aOR 3.66; 95% CI 1.91–7.02), chronic obstructive pulmonary disease (aOR 2.95; 95% CI 1.59–5.47), and peripheral arterial disease (aOR 2.05; 95% CI 1.21–3.47) were independently associated with death. Estimates for mortality should be interpreted in light of the limited number of events.

Conclusions In hypertensive patients with COVID-19 managed in Primary Care, cardiovascular and renal comorbidities were independently associated with hospitalization and short-term mortality. Chronic kidney disease

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and heart failure showed the strongest and most consistent associations across outcomes. RAAS inhibitor use was not associated with increased risk.

Keywords Primary Health Care, Hypertension, COVID-19, Hospitalization, Mortality, Comorbidity, Chronic Kidney Disease, Risk Factors

Introduction

Coronavirus disease 2019 (COVID-19) has posed an unprecedented challenge to healthcare systems worldwide, particularly for primary care services responsible for the longitudinal management of patients with chronic conditions. From the earliest phases of the pandemic, observational studies and meta-analyses consistently identified older age, male sex, and pre-existing comorbidities as key determinants of severe disease and mortality [1, 2].

Arterial hypertension is one of the most prevalent chronic conditions among patients infected with SARS-CoV-2 and frequently coexists with other cardiometabolic disorders, including diabetes mellitus, obesity, chronic kidney disease, and established cardiovascular disease [1–3]. Hypertension has consistently been recognized as an important risk factor for severe COVID-19 outcomes, particularly in older adults. Several systematic reviews and meta-analyses have reported an association between hypertension and an increased risk of hospitalization, critical illness, and death from COVID-19 [3–5]. However, the extent to which hypertension independently contributes to adverse outcomes remains debated, as this association appears to be strongly influenced by age and the burden of coexisting comorbidities [4, 6].

This uncertainty has led to increasing interest in multimorbidity-based risk stratification approaches, particularly in real-world primary care populations, where patients commonly present with complex clinical profiles rather than isolated risk factors. In this context, it is clinically relevant to explore how the coexistence of cardiovascular, renal, metabolic, and lifestyle-related comorbidities contributes to adverse outcomes among patients with arterial hypertension.

Several pathophysiological mechanisms may link hypertension and worse COVID-19 outcomes, including endothelial dysfunction, chronic low-grade inflammation, impaired immune responses, and dysregulation of the renin–angiotensin–aldosterone system (RAAS) [7]. Early in the pandemic, the interaction between SARS-CoV-2 and angiotensin-converting enzyme 2 (ACE2) raised concerns regarding the safety of RAAS inhibitors, prompting extensive investigation into their potential impact on COVID-19 prognosis [8]. Although subsequent evidence has largely alleviated these concerns, their role remains of clinical interest, particularly in hypertensive patients managed in the community.

Beyond hypertension, comorbid conditions such as chronic kidney disease, heart failure, ischemic heart disease, atrial fibrillation, and smoking have consistently been associated with worse clinical outcomes in COVID-19 [6, 9]. Recent meta-analyses emphasize the cumulative effect of multimorbidity and lifestyle factors, particularly tobacco use, on disease severity and mortality [9, 10]. These observations highlight the importance of integrated risk assessment strategies that reflect the complexity of patients typically encountered in primary care settings.

Despite the growing body of literature on COVID-19 outcomes, most available evidence derives from hospital-based cohorts. Data focusing on community-managed hypertensive patients remain limited. Understanding how hypertension and associated comorbidities influence the risk of hospitalization and all-cause mortality in primary care populations is essential to improve early risk stratification and guide clinical decision-making. Therefore, the aim of this study was to identify clinical factors independently associated with COVID-19–related hospitalization and all-cause mortality among hypertensive patients attended in primary care in Spain, with particular emphasis on cardiovascular and renal multimorbidity, smoking status, and the use of RAAS inhibitors.

Methods

Study design and population

A multicenter, observational, retrospective cohort study was conducted in primary care settings across Spain. Adult patients (≥ 18 years) with a previous diagnosis of arterial hypertension and confirmed SARS-CoV-2 infection by polymerase chain reaction (PCR) were included. Patients were managed in primary care between May 2021 and February 2022.

Participants were recruited by 119 primary care physicians from 30 health centers distributed across 10 Spanish autonomous regions. Eligible patients were identified through electronic health record searches at each participating center and included consecutively until the required sample size was achieved. Figure 1 shows the flow diagram of patient selection and inclusion.

An a priori assessment of sample size adequacy was performed primarily based on the expected COVID-19–related hospitalization rate (approximately 25–30%), which was the most frequent outcome. A minimum sample size of 1,200 participants was considered sufficient to support multivariable modelling for hospitalization

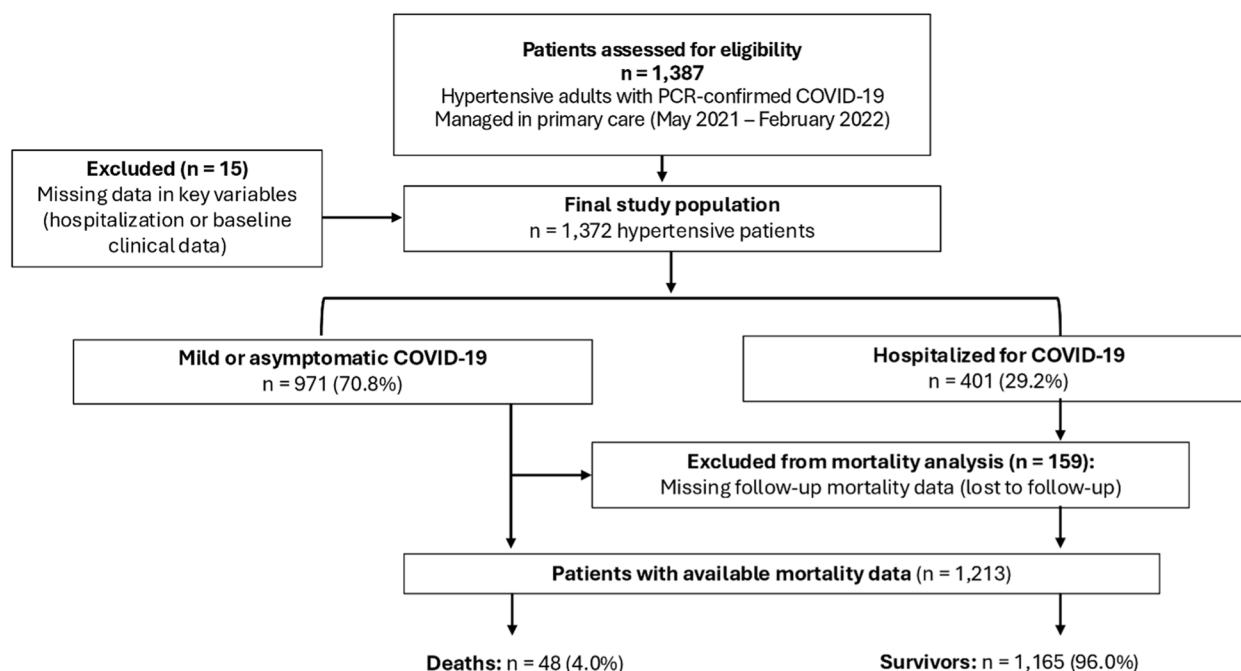


Fig. 1 Flow diagram of patient selection and inclusion in the study. Hypertensive adult patients with PCR-confirmed SARS-CoV-2 infection managed in primary care between May 2021 and February 2022 were assessed for eligibility. After exclusion of patients with missing key baseline data, 1,372 participants were included in the analysis of COVID-19–related hospitalization. Mortality follow-up data were available for 1,213 patients, who constituted the population included in the 3-month all-cause mortality analyses

analyses. The final study population ($n = 1,372$) exceeded this threshold. For mortality analyses, the number of events was lower than initially anticipated; therefore, findings should be interpreted with caution given the limited events-per-variable ratio.

Data collection and variables

Data were collected using a structured electronic case report form completed by the investigators based on routinely recorded information in primary care electronic health records. No additional diagnostic or laboratory tests were performed for the purposes of this study.

Sociodemographic variables included age, sex, and type of housing. Lifestyle factors comprised smoking status, alcohol consumption, and physical activity level. Anthropometric measurements included weight, height, and body mass index (BMI). Clinical parameters recorded were systolic and diastolic blood pressure and heart rate.

Baseline laboratory data obtained prior to SARS-CoV-2 infection included fasting plasma glucose, HbA1c (in patients with diabetes), lipid profile (total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides), serum creatinine, estimated glomerular filtration rate (eGFR), uric acid, and urine albumin-to-creatinine ratio (ACR). These values corresponded to the most recent measurements available before infection and were not updated during follow-up.

Comorbidities assessed included diabetes mellitus, dyslipidemia, chronic kidney disease, chronic obstructive pulmonary disease, atrial fibrillation, heart failure, ischemic heart disease, peripheral arterial disease, stroke, and immunocompromised status. Immunocompromised status referred to patients receiving immunosuppressive treatments and/or presenting clinically relevant conditions associated with impaired immune function.

Information on chronic pharmacological treatments (antihypertensive, antidiabetic, lipid-lowering, and anti-thrombotic therapy) prescribed at least six months before COVID-19 diagnosis was also collected. Use of renin–angiotensin–aldosterone system inhibitors (ACE inhibitors or angiotensin receptor blockers) was specifically recorded due to their clinical relevance and prior controversy regarding COVID-19 outcomes.

No patients were excluded based on the degree of blood pressure or glycemic control, as reliable information on adequate versus inadequate control was not consistently available.

Outcomes

The primary outcomes were COVID-19–related hospitalization and all-cause mortality within three months following SARS-CoV-2 diagnosis.

Hospitalization analyses were conducted in the full cohort ($n = 1,372$). Mortality outcome data were available for 1,213 patients with complete follow-up information.

Secondary outcomes included admission to an intensive care unit (ICU) and clinical course of COVID-19 (mild or asymptomatic evolution versus hospitalization).

Operational definitions

Hypertension was defined as systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg, or current antihypertensive treatment.

Diabetes mellitus was defined as a previous diagnosis or the use of antidiabetic medication.

Dyslipidemia was defined by elevated lipid values in untreated patients (total cholesterol ≥ 200 mg/dL, LDL-cholesterol ≥ 150 mg/dL, triglycerides ≥ 150 mg/dL, or low HDL-cholesterol) or the use of lipid-lowering therapy.

Chronic kidney disease was defined as an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² for at least three months, calculated using the CKD-EPI equation, or the presence of albuminuria (albumin-to-creatinine ratio ≥ 30 mg/g), according to Kidney Disease Quality Outcome Initiative criteria. Estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m² was additionally reported descriptively as an indicator of reduced renal function.

Obesity was defined as body mass index (BMI) ≥ 30 kg/m². Current smoking was defined as active tobacco use at the time of data collection.

Sedentary lifestyle was defined as less than 150 min of moderate physical activity per week. Excessive alcohol consumption was defined as > 40 g/day in men and > 24 g/day in women.

Statistical analysis

Continuous variables were assessed for normality using Q–Q plots and are presented as mean and standard deviation or median and interquartile range, as appropriate. Categorical variables are expressed as absolute frequencies and percentages.

Comparisons between groups were performed using the chi-square test or Fisher's exact test for categorical variables, and Student's t-test or Mann–Whitney U test for continuous variables, depending on data distribution.

Missing values in independent variables were handled using multiple imputation under the assumption of missing at random (MAR). Linear regression models were used for continuous variables and logistic regression models for categorical variables. Patients with missing outcome data were excluded from the corresponding analyses.

Multivariable logistic regression models were constructed using simultaneous entry of prespecified predictors (enter method) to identify factors independently associated with COVID-19–related hospitalization in the full cohort ($n = 1,372$). A separate multivariable logistic

regression model was performed for 3-month all-cause mortality among patients with complete follow-up data ($n = 1,213$). No automated stepwise procedures were applied.

Given the limited number of mortality events ($n = 48$), model complexity was restricted to clinically relevant prespecified variables to reduce the risk of overfitting, and mortality estimates should be interpreted with caution.

Collinearity among predictors was evaluated through inspection of correlation matrices and assessment of model stability; no evidence of problematic multicollinearity was identified.

Models were adjusted for predefined confounders (age, sex, smoking status, and obesity), selected based on clinical relevance and prior evidence of association with COVID-19 severity. Results are reported as adjusted odds ratios (aORs) with 95% confidence intervals (CIs). Model goodness-of-fit was assessed using the likelihood ratio test and the Hosmer–Lemeshow test. Model discrimination was evaluated using the area under the receiver operating characteristic curve (AUC).

Based on biological plausibility and prior evidence, interaction terms with smoking status were pre-specified for selected vascular comorbidities, including chronic kidney disease, ischemic heart disease, and prior stroke, to explore potential effect modification. Interaction terms were included in the final multivariable models only when statistically significant ($p < 0.05$).

Statistical significance was set at $p < 0.05$. All analyses were performed using Stata version 13.1 (StataCorp, College Station, TX, USA).

Ethics approval

The study was approved by the Research Ethics Committees of all participating Spanish regions and was conducted in accordance with the Declaration of Helsinki and national regulations on data protection. Written informed consent was obtained from all participants prior to inclusion in the study.

Results

Study population

A total of 1,372 hypertensive adult patients with PCR-confirmed SARS-CoV-2 infection managed in primary care were included in the analysis of COVID-19–related hospitalization (Table 1). Mortality follow-up data at 3 months were available for 1,213 patients, among whom 48 deaths were recorded, as shown in the flow diagram (Fig. 1).

The mean age of the study population was 67.1 ± 13.6 years, and 697 participants (50.8%) were women. Most patients (68.3%) were aged ≥ 60 years. Baseline sociodemographic characteristics and clinical

Table 1 Baseline sociodemographic characteristics and clinical history of the study population according to COVID-19 severity

Variable	Total (n = 1,372)	Mild/ asymptomatic (n = 971)	Hospitalized (n = 401)	p value
Age, mean (SD), years	67.09 (13.59)	65.10 (13.78)	71.92 (11.81)	< 0.001 ^a
Sex, n (%)				< 0.001 ^b
Female	697 (50.8)	529 (54.5)	168 (41.9)	
Male	675 (49.2)	442 (45.5)	233 (58.1)	
Current smoking, n (%)	171 (12.5)	135 (13.9)	36 (9.0)	< 0.05 ^b
Alcohol consumption, n (%)				NS ^b
No	1,103 (80.4)	779 (80.2)	324 (80.8)	
Yes	269 (19.6)	192 (19.8)	77 (19.2)	
Physical activity < 150 min/week, n (%)	794 (57.9)	557 (57.4)	237 (59.1)	NS ^b
BMI, mean (SD), kg/m ²	29.65 (4.91)	29.28 (4.72)	30.52 (5.23)	< 0.001 ^a
BMI categories, n (%)				< 0.001 ^b
Underweight	7 (0.5)	7 (0.7)	0 (0.0)	
Normal weight	208 (15.2)	165 (17.0)	43 (10.7)	
Overweight	554 (40.4)	401 (41.3)	153 (38.2)	
Obesity	603 (44.0)	398 (41.0)	205 (51.1)	
Chronic kidney disease, n (%)	194 (14.1)	108 (11.1)	86 (21.5)	< 0.001 ^b
eGFR < 60 mL/min/1.73 m ² , n (%)	250 (18.2)	140 (14.4)	110 (27.4)	< 0.001 ^b
COPD, n (%)	203 (14.8)	116 (12.0)	87 (21.7)	< 0.001 ^b
Immunocompromised status, n (%)	54 (3.9)	24 (2.5)	30 (7.5)	< 0.001 ^b
Diabetes mellitus, n (%)	377 (27.5)	242 (24.9)	135 (33.7)	< 0.05 ^b
Dyslipidemia, n (%)	821 (59.8)	562 (57.9)	259 (64.6)	< 0.05 ^b
Atrial fibrillation, n (%)	141 (10.3)	70 (7.2)	71 (17.7)	< 0.001 ^b
Heart failure, n (%)	124 (9.0)	56 (5.8)	68 (17.0)	< 0.001 ^b
Ischemic heart disease, n (%)	98 (7.1)	45 (4.6)	53 (13.2)	< 0.001 ^b
Peripheral arterial disease, n (%)	70 (5.1)	35 (3.6)	35 (8.7)	< 0.001 ^b
Prior stroke, n (%)	91 (6.6)	53 (5.5)	38 (9.5)	< 0.05 ^b

Values are presented as mean (SD) for continuous variables and as n (%) for categorical variables

BMI categories: underweight < 18.5 kg/m²; normal weight 18.5–24.9 kg/m²; overweight 25.0–29.9 kg/m²; obesity ≥ 30 kg/m²

Hospitalization outcomes were available for all 1,372 patients

SD, standard deviation, BMI body mass index, eGFR estimated glomerular filtration rate, COPD chronic obstructive pulmonary disease

^aStudent's t test

^bPearson's chi-square test

history according to hospitalization status are presented in Table 1.

Mortality follow-up data were unavailable for 159 patients from one autonomous community due to administrative restrictions on data access. No clinically

meaningful differences were observed in baseline demographic characteristics or major comorbidities between included and excluded individuals (data not shown).

Baseline characteristics and comorbidity burden

Comorbidities were highly prevalent in this cohort. Dyslipidemia was present in 821 patients (59.8%), diabetes mellitus in 377 (27.5%), and obesity in 603 (44.0%). Chronic kidney disease was identified in 194 patients (14.1%), while reduced renal function (eGFR < 60 mL/min/1.73 m²) was observed in 250 patients (18.2%).

Other common conditions included chronic obstructive pulmonary disease (14.8%), atrial fibrillation (10.3%), heart failure (9.0%), ischemic heart disease (7.1%), peripheral arterial disease (5.1%), prior stroke (6.6%), and immunocompromised status (3.9%). Current smoking was reported by 171 patients (12.5%).

COVID-19 clinical course and outcomes

Overall, 401 patients (29.2%) required hospitalization due to COVID-19. A total of 69 patients (5.0% of the full cohort) required admission to an intensive care unit. During the three-month follow-up period after SARS-CoV-2 diagnosis, 48 deaths (4.0%) were recorded among the 1,213 patients with available mortality data.

Factors associated with COVID-19-related hospitalization

In unadjusted analyses (Table 1), hospitalized patients were significantly older and more frequently male than those managed exclusively in primary care (both $p < 0.001$). They also exhibited a higher prevalence of chronic kidney disease, chronic obstructive pulmonary disease, atrial fibrillation, heart failure, ischemic heart disease, peripheral arterial disease, prior stroke, immunocompromised status, and diabetes mellitus (all $p < 0.05$). No significant differences were observed according to chronic antihypertensive therapy, including renin-angiotensin-aldosterone system inhibitor use.

In multivariable logistic regression analyses adjusted for age, sex, smoking status, and obesity (Table 2; Fig. 2), chronic obstructive pulmonary disease (aOR 1.83; 95% CI 1.33–2.51), heart failure (aOR 2.55; 95% CI 1.74–3.74), atrial fibrillation (aOR 2.16; 95% CI 1.50–3.12), peripheral arterial disease (aOR 2.17; 95% CI 1.31–3.58), and immunocompromised status (aOR 3.19; 95% CI 1.89–5.53) were independently associated with hospitalization.

A significant interaction between age and diabetes mellitus was observed. Diabetes was independently associated with hospitalization among patients younger than 60 years (aOR 2.54; 95% CI 1.41–4.60), whereas no significant association was observed in older individuals. Effect modification by smoking status was identified for chronic kidney disease, ischemic heart disease, and prior stroke.

Table 2 Multivariable logistic regression analysis of baseline clinical predictors of COVID-19–related hospitalization among hypertensive patients

Variable	Adjusted OR	95% CI	p value
Chronic obstructive pulmonary disease (COPD)	1.83	1.33–2.51	<0.001
Diabetes mellitus			
Age < 60 years	2.54	1.41–4.60	<0.05
Age ≥ 60 years	1.06	0.79–1.41	NS
Chronic kidney disease			
Non-smoker	1.52	1.08–2.14	<0.05
Current smoker	6.80	2.37–19.48	<0.001
Stroke			
Non-smoker	1.14	0.70–1.84	NS
Current smoker	7.73	1.80–33.28	<0.05
Atrial fibrillation	2.16	1.50–3.12	<0.001
Heart failure	2.55	1.74–3.74	<0.001
Ischemic heart disease			
Non-smoker	1.89	1.19–3.00	<0.05
Current smoker	11.36	3.24–39.87	<0.001
Peripheral arterial disease	2.17	1.31–3.58	<0.05
Immunocompromised status	3.19	1.89–5.53	<0.001
RAAS inhibitors (ACEI/ARB)	0.87	0.68–1.12	NS

Adjusted odds ratios (aORs) and 95% confidence intervals were derived from a multivariable logistic regression model evaluating predictors of COVID-19–related hospitalization. The model was adjusted for age, sex, smoking status, and obesity. Interaction terms with smoking status were pre-specified for selected vascular comorbidities (chronic kidney disease, ischemic heart disease, and stroke) based on biological plausibility and prior evidence. Stratified estimates are presented when statistically significant interaction terms were identified in the final model. RAAS inhibitor use was specifically evaluated due to its proposed interaction with SARS-CoV-2 pathophysiology

OR odds ratio, CI confidence interval, COPD chronic obstructive pulmonary disease, RAAS renin–angiotensin–aldosterone system, ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin II receptor blocker

Use of RAAS inhibitors was not associated with hospitalization (aOR 0.87; 95% CI 0.68–1.12).

Adjusted predicted probabilities and absolute risk differences were estimated (Table 3). Heart failure was associated with an adjusted predicted probability of hospitalization of 47% (95% CI 39–56), corresponding to an absolute increase of 18 percentage points. Chronic obstructive pulmonary disease showed a predicted probability of 40% (95% CI 33–46), corresponding to an 11 percentage-point increase. Among patients younger than 60 years with diabetes mellitus, the adjusted predicted probability was 24% (95% CI 15–34), representing an absolute increase of 13 percentage points.

The final hospitalization model demonstrated acceptable discrimination (AUC 0.72; 95% CI 0.69–0.74), and calibration assessed by the Hosmer–Lemeshow test did not indicate lack of fit.

Factors associated with 3-month all-cause mortality

In descriptive analyses (Table 4), non-survivors were significantly older (78.4 vs 66.6 years, $p < 0.001$) and more

frequently male. Mortality was markedly more frequent among patients who required hospitalization or ICU admission. Chronic kidney disease, atrial fibrillation, heart failure, chronic obstructive pulmonary disease, prior stroke, and peripheral arterial disease were significantly more prevalent among non-survivors.

In the multivariable model adjusted for predefined confounders (Table 5), chronic kidney disease (aOR 4.34; 95% CI 2.37–7.94), atrial fibrillation (aOR 4.09; 95% CI 2.18–7.68), heart failure (aOR 3.66; 95% CI 1.91–7.02), chronic obstructive pulmonary disease (aOR 2.95; 95% CI 1.59–5.47), and peripheral arterial disease (aOR 2.05; 95% CI 1.21–3.47) were independently associated with 3-month all-cause mortality. Other variables were not independently associated with mortality in the adjusted model. Given the limited number of mortality events ($n = 48$), these estimates should be interpreted with caution.

Discussion

Principal findings

In this multicenter primary care cohort of hypertensive patients with confirmed COVID-19, several baseline cardiovascular and renal comorbidities were independently associated with an increased risk of hospitalization and short-term mortality. In multivariable analyses, chronic obstructive pulmonary disease, heart failure, atrial fibrillation, peripheral arterial disease, immunocompromised status, and diabetes mellitus in patients younger than 60 years were independently associated with COVID-19–related hospitalization. Chronic kidney disease, ischemic heart disease, and prior stroke showed significant effect modification by smoking status, with markedly higher risks among current smokers.

Regarding mortality, chronic kidney disease, atrial fibrillation, heart failure, chronic obstructive pulmonary disease, and peripheral arterial disease were independently associated with 3-month all-cause mortality after multivariable adjustment. These findings underscore the prognostic relevance of cardiovascular and renal multimorbidity in hypertensive patients managed in community settings.

Importantly, no association was observed between renin–angiotensin–aldosterone system (RAAS) inhibitor use and either hospitalization or mortality.

Hypertension and comorbidity burden in COVID-19

Hypertension has consistently been reported as one of the most prevalent comorbidities among patients with COVID-19, particularly in those with severe disease [1–4]. However, its independent contribution to adverse outcomes remains debated. Several systematic reviews and meta-analyses suggest that the association between hypertension and COVID-19 severity is strongly

Figure 2. Adjusted odds ratios for COVID-19-related hospitalization according to baseline comorbidities among hypertensive patients.

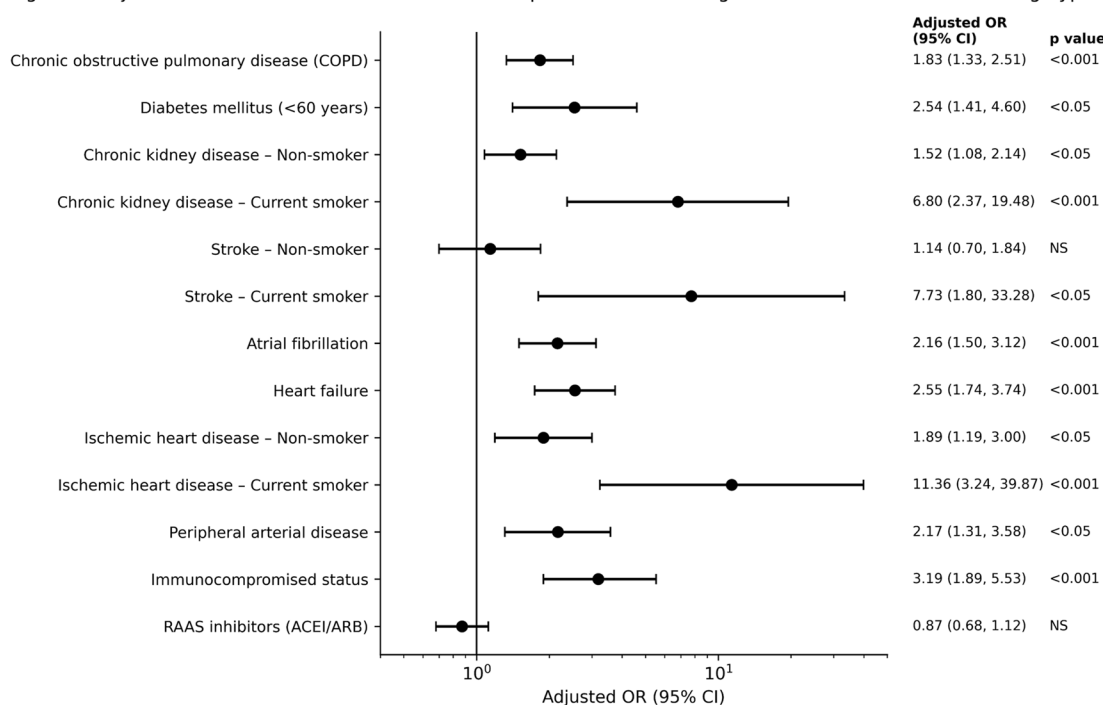


Fig. 2 Adjusted odds ratios for COVID-19-related hospitalization according to baseline comorbidities among hypertensive patients. Adjusted odds ratios (aORs) and 95% confidence intervals are shown for predictors of COVID-19-related hospitalization in the full cohort of hypertensive patients ($n = 1,372$). Estimates were obtained from multivariable logistic regression models adjusted for age, sex, smoking status, and obesity. Interaction terms with smoking status were included for selected vascular comorbidities. RAAS inhibitor use (ACE inhibitors or angiotensin receptor blockers) was included in the model

influenced by age and coexisting cardiometabolic and cardiovascular conditions rather than by elevated blood pressure itself [2–6].

Our findings align with this interpretation. Within a hypertensive population, adverse outcomes were primarily associated with established cardiovascular, cerebrovascular, and renal disease rather than with hypertension per se. Chronic kidney disease showed the strongest and most consistent association with both hospitalization and mortality, in agreement with previous evidence identifying impaired renal function as a major determinant of COVID-19 severity [5, 11]. Similarly, heart failure and atrial fibrillation were robust predictors across models, and peripheral arterial disease was independently associated with both hospitalization and mortality, supporting the concept that systemic vascular vulnerability contributes to worse outcomes [5, 11].

The observed interaction between age and diabetes suggests that diabetes may confer additional risk among younger hypertensive patients. In older individuals, the relative contribution of diabetes may be attenuated by competing comorbidities and age-related risk.

Smoking has also been associated with increased COVID-19 severity and mortality in prior meta-analyses [6, 8]. In our study, smoking significantly modified the association between several vascular comorbidities

and hospitalization, particularly chronic kidney disease, ischemic heart disease, and prior stroke. These findings suggest that smoking may amplify the vulnerability conferred by underlying vascular pathology, although subgroup-specific estimates should be interpreted cautiously.

Antihypertensive treatment and RAAS inhibitors

Early in the pandemic, concerns were raised regarding a potential interaction between RAAS inhibitors and SARS-CoV-2 entry through modulation of angiotensin-converting enzyme 2 [7]. However, accumulating evidence from observational studies, meta-analyses, and randomized controlled trials has consistently demonstrated that continuation of RAAS inhibitors does not increase the risk of severe COVID-19 or mortality [10, 12–14].

In agreement with this body of evidence, we found no association between RAAS inhibitor therapy and hospitalization or mortality. These results support current recommendations against routine discontinuation of antihypertensive treatment during SARS-CoV-2 infection. Nevertheless, residual confounding related to treatment indication cannot be entirely excluded.

Table 3 Baseline characteristics, comorbidities, and clinical course according to 3-month all-cause mortality among hypertensive patients with COVID-19 ($n = 1,213$; deaths = 48)

Characteristic	Total ($n = 1,213$)	Non-survivors ($n = 48$)	Survivors ($n = 1,165$)	<i>p</i> value
Sex, <i>n</i> (%)				< 0.05 ^a
Male	602 (49.6)	32 (66.7)	570 (48.9)	
Female	611 (50.4)	16 (33.3)	595 (51.1)	
Age group, <i>n</i> (%)				< 0.001 ^a
< 60 years	385 (31.7)	2 (4.2)	383 (32.9)	
≥ 60 years	828 (68.3)	46 (95.8)	782 (67.1)	
Current smoking, <i>n</i> (%)	153 (12.6)	6 (12.5)	147 (12.6)	NS ^a
Clinical course during follow-up, <i>n</i> (%)				
Mild or asymptomatic	839 (69.2)	5 (10.4)	834 (71.6)	< 0.001 ^a
Hospitalized	374 (30.8)	43 (89.6)	331 (28.4)	< 0.001 ^a
ICU admission	69 (5.7)	18 (37.5)	51 (4.4)	< 0.001 ^a
Baseline comorbidities, <i>n</i> (%)				
COPD	190 (15.7)	17 (35.4)	173 (14.9)	< 0.001 ^a
Diabetes mellitus	339 (28.0)	19 (39.6)	320 (27.5)	NS ^a
Chronic kidney disease	180 (14.8)	22 (45.8)	158 (13.6)	< 0.001 ^a
Atrial fibrillation	125 (10.3)	17 (35.4)	108 (9.3)	< 0.001 ^a
Heart failure	113 (9.3)	15 (31.3)	98 (8.4)	< 0.001 ^a
Ischemic heart disease	87 (7.2)	8 (16.7)	79 (6.8)	< 0.05 ^a
Peripheral arterial disease	63 (5.2)	7 (14.6)	56 (4.8)	< 0.05 ^a
Prior stroke	79 (6.5)	9 (18.8)	70 (6.0)	< 0.001 ^a
Chronic antihypertensive treatment, <i>n</i> (%)				
RAAS inhibitors (ACEI/ARB)	764 (63.0)	28 (58.3)	736 (63.2)	NS ^a

Values are presented as *n* (%). Comparisons are unadjusted and intended for descriptive purposes only. Categorical variables were compared using Pearson's chi-square test. Mortality was defined as all-cause death within 3 months following SARS-CoV-2 diagnosis. Clinical course variables (hospitalization and ICU admission) are presented to describe disease severity during follow-up and were not considered baseline exposures in multivariable analyses

ICU intensive care unit, COPD chronic obstructive pulmonary disease, RAAS renin-angiotensin-aldosterone system, ACEI, angiotensin-converting enzyme inhibitor, ARB angiotensin II receptor blocker

^aPearson's chi-square test

Clinical implications in primary care

The inclusion of adjusted predicted probabilities and absolute risk differences enhances the clinical interpretability of these findings. For example, heart failure and chronic obstructive pulmonary disease were associated with substantial absolute increases in hospitalization probability. Such estimates may assist primary care clinicians in identifying hypertensive patients at higher risk of clinical deterioration during acute SARS-CoV-2 infection, particularly in community settings where early risk stratification is essential.

Table 4 Multivariable logistic regression analysis of factors associated with 3-month all-cause mortality among hypertensive patients with COVID-19 ($n = 1,213$; deaths = 48)

Variable	Adjusted OR	95% CI	<i>p</i> value
COPD	2.95	1.59–5.47	< 0.001
Diabetes mellitus	1.45	0.80–2.64	0.22
Dyslipidemia	0.75	0.42–1.36	0.35
Chronic kidney disease	4.34	2.37–7.94	< 0.001
Stroke	2.17	0.97–4.88	0.06
Atrial fibrillation	4.09	2.18–7.68	< 0.001
Heart failure	3.66	1.91–7.02	< 0.001
Ischemic heart disease	1.91	0.85–4.29	0.12
Peripheral arterial disease	2.05	1.21–3.47	0.007
Immunocompromised status	1.39	0.42–4.70	0.60

Adjusted odds ratios (aORs) were derived from a multivariable logistic regression model adjusted for age, sex, smoking status, and obesity. Mortality was defined as all-cause death within 3 months of SARS-CoV-2 diagnosis. Given the limited number of events ($n = 48$), estimates should be interpreted cautiously

Table 5 Adjusted odds ratios, predicted probabilities, and absolute risk differences for hospital admission

Variable	Adjusted OR (95% CI)	Adjusted probability (95% CI)	Absolute difference (pp) (95% CI)
COPD	1.83 (1.33–2.51)	0.40 (0.33–0.46)	0.11 (0.05–0.17)
Diabetes mellitus (< 60 years)	2.54 (1.41–4.60)	0.24 (0.15–0.34)	0.13 (0.03–0.23)
Chronic kidney disease	1.52 (1.08–2.14)	0.37 (0.30–0.44)	0.09 (0.01–0.16)
Heart failure	2.55 (1.74–3.74)	0.47 (0.39–0.56)	0.18 (0.11–0.25)
Atrial fibrillation	2.16 (1.50–3.12)	0.42 (0.32–0.52)	0.13 (0.03–0.24)

Predicted probabilities were estimated using marginal post-estimation estimates derived from the final multivariable logistic regression model. Absolute differences are expressed in percentage points (pp) compared with patients without the corresponding comorbidity

Strengths and limitations

This study has several strengths, including its multi-center design, recruitment from primary care settings across different regions, and comprehensive assessment of cardiovascular and renal comorbidities. The use of multivariable modelling with prespecified predictors and reporting of both relative and absolute measures enhances methodological transparency and clinical applicability.

However, several limitations warrant consideration. The observational design precludes causal inference, and residual confounding cannot be entirely excluded. The number of mortality events was limited ($n = 48$), which may have affected the precision of mortality estimates and resulted in wide confidence intervals for some variables. Interaction findings, although statistically significant, should also be interpreted cautiously.

Information regarding SARS-CoV-2 variants, vaccination status, and specific in-hospital treatments was not

systematically available in primary care electronic health records and may have influenced outcomes. Blood pressure control status prior to infection was not consistently documented across centers and therefore could not be incorporated into analyses. Consequently, the potential impact of hypertension control or severity on COVID-19 outcomes could not be assessed. Finally, the study period (May 2021 to February 2022) encompassed different pandemic phases in Spain, potentially involving changes in circulating variants, vaccination coverage, and therapeutic strategies, which may have introduced temporal heterogeneity.

Conclusion

In this multicenter primary care cohort of hypertensive patients with COVID-19, hospitalization and short-term mortality were independently associated with cardiovascular and renal comorbidities, particularly chronic kidney disease, heart failure, atrial fibrillation, chronic obstructive pulmonary disease, and peripheral arterial disease. Diabetes mellitus increased hospitalization risk among younger patients, and smoking amplified the risk associated with selected vascular conditions. RAAS inhibitor therapy was not associated with adverse outcomes.

These findings highlight the importance of multimorbidity burden in risk stratification of hypertensive patients with COVID-19 managed in community settings, while reinforcing the safety of continuing established antihypertensive treatment.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12875-026-03263-z>.

Supplementary Material 1.

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Authors' contributions

JAA conceived and designed the study. ADV and JAA coordinated data collection and supervised the statistical analyses performed by MSA. ADV drafted the manuscript. All authors contributed to data interpretation, critically revised the manuscript for important intellectual content, and approved the final version.

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request, subject to applicable data protection regulations.

Declarations

Ethics approval and consent to participate

The study was approved by the Research Ethics Committees of all participating Spanish regions. It was conducted in accordance with the Declaration of Helsinki and national regulations on data protection. Written informed consent was obtained from all participants prior to inclusion in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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