Original article

# Association Between Common Comorbidities and Outcomes in COVID-19 Patients Hospitalised in General Hospital Našice – a Cross-Sectional Study

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## Abstract

**Aim:** The aim was to define the impact of comorbidities, specifically hypertension as one of the most common chronic diseases, on the outcome and length of stay for COVID-19 patients.

**Methods:** The cross-sectional study, carried out from October to December 2021, included 129 hospitalised COVID-19 patients who presented to the Emergency Department and were hospitalised and treated in the COVID ward in the General Hospital Našice. All patients tested positive for COVID-19 with a polymerase chain reaction (PCR) test. Clinical parameters were also recorded and they included demographic factors, comorbidities, type of antihypertensive therapy, new-onset hypertension, length of stay and the overall outcome.

**Results:** The most common comorbidity was hypertension (86, 66.7%). Hypertension was associated with women ($P = 0.03$) and age over 65 years ($P < 0.001$). Length of stay was longer for patients with hypertension ($P = 0.04$) and/or diabetes mellitus ($P = 0.04$). Higher mortality was associated with age over 65 years ($P < 0.001$) and a higher number of comorbidities ($P = 0.01$). New-onset hypertension was recorded in three patients. There was no significant difference in the outcome in relation to antihypertensive therapy.

**Conclusion:** Hypertension is the most common comorbidity in hospitalised COVID-19 patients. Although treated hypertension did not have a negative impact on the outcome, other potential risk factors, including a higher number of comorbidities and older age, are associated with mortality in COVID-19 patients.

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## Introduction

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes pneumonia and flu-like symptoms. The first case was reported in Wuhan, China in late 2019, after which the virus has spread around the world. Shortly afterwards, the coronavirus pandemic has been declared.

Since the first confirmed case of COVID-19, there have been approximately 418,650,474 confirmed cases worldwide, including 5,856,224 deaths, as reported by the WHO (1). The first case of COVID-19 in Croatia was reported in February 2020 in Zagreb. At the time of writing, there have been approximately 1,041,212 confirmed cases, 14,815 of which were fatal (2).

Several variants of SARS-CoV-2 with the far more dominant Alpha strain were recorded in early May 2021. In June, the Delta strain began to spread more rapidly, and by early September, it was responsible for more than 99% of all COVID-19 cases. In December 2021, the Omicron variant began to break through within the Delta strain and a few weeks later, it became the dominant strain (3).

Although the prognosis for patients with COVID-19 is generally good, it has been observed that some patients with comorbidities have a poor outcome (4,5). Previous studies on COVID-19 have reported that over 60% of COVID-19 patients have associated comorbidities (4,6). The most common comorbidities are hypertension (7–9), diabetes mellitus (DM) (8,10), cardiovascular diseases (10), chronic obstructive pulmonary disease (7), chronic kidney disease (11) and malignancy (12), which are associated with severe disease and mortality. However, there is conflicting data in this regard. A poor outcome in COVID-19 patients is also associated with a higher number of comorbidities (8). It has been observed that three or more comorbidities are the cut-off point for severe COVID-19 cases, while four or more comorbidities indicate a high rate of fatal outcomes (4). Older age is an independent risk factor for disease progression and higher mortality rates (13). It has been observed that many patients with rapid disease progression are 45-65 years old, while severe disease and most deaths were reported in patients aged 70 and above (14). In general, both age and the number of comorbidities could have a predictive role in disease severity and in the final outcome of COVID-19.

The length of stay for COVID-19 patients depends on several factors. Analyses have shown that age, gender, hypertension, DM, cardiovascular disease and renal failure are significantly associated with the length of stay (15). It has been observed that every additional comorbidity was significantly associated with an increase in the expected length of stay by 2%. Similarly, every one-year increase in age is also significantly associated with an increase in the expected length of stay by 2% (16).

Hypertension is one of the most common chronic diseases associated with hospitalised patients, but its impact on COVID-19 patients has not been well-defined (17). Previous studies indicate that hypertension is associated with a higher risk of all-cause mortality regardless of age, gender and other comorbidities (9). It is also assumed that antihypertensive drugs play a major role in the mechanism of interaction between the coronavirus and target cells in the body through the angiotensin-converting enzyme 2 (ACE2) (18,19). This hypothesis has come to light when the following two facts were related: the finding that the renin-angiotensin-aldosterone system (RAAS) inhibitors increase the expression of ACE2 and the observation that hypertension and diabetes were the most common comorbidity among patients with severe COVID-19, for which RAAS inhibitors are widely used (20). Although the treatment of hypertension with these drugs is thought to increase the risk of developing severe and fatal COVID-19, studies have found no such association so far (20–22).

The COVID-19 pandemic is a global health issue that has spread rapidly around the world with varying degrees of severity. This study aimed to define the significance of comorbidities in

hospitalised COVID-19 patients, specifically hypertension as one of the common chronic diseases worldwide. Understanding these factors is key to improve the accuracy of predicting disease outcomes as well as the length of stay for the purpose of optimising resources and providing better care for patients.

## Patients and Methods

This cross-sectional study, carried out from 1 October to 31 December 2021, included 129 hospitalised COVID-19 patients who presented to the Emergency Department in the General Hospital Našice, which has been a designated hospital for treating COVID-19 patients since November 2020. Inclusion criteria were as follows: patients admitted from the Emergency Department, hospitalised and treated in the COVID ward, who tested positive for SARS-CoV-2 with a nasal swab polymerase chain reaction (PCR) test (23) during the admission. Exclusion criteria included the following: eight patients transferred from the COVID ward to the University Hospital Centre Osijek during hospitalisation.

The data were reviewed based on the electronic medical records kept by the Emergency Department. Clinical parameters were also recorded, including demographic factors (age and gender), comorbidities (hypertension, DM, atrial fibrillation and respiratory comorbidities – asthma or chronic obstructive pulmonary disease), type of antihypertensive therapy (angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), calcium channel blockers and diuretics), length of stay and outcome (discharge or fatal outcome). With regard to the number of comorbidities, the patients were divided into five groups (0, 1, 2, 3 and 4 comorbidities). Depending on the combination of antihypertensive therapy, the patients were divided into four groups (1, 2, 3 and 4 types of antihypertensives). New-onset hypertension was defined as hypertension in patients who did not have hypertension as a comorbidity or who did not have any antihypertensive treatment during admission, but received hypertensive therapy at discharge. Regarding age, two groups of patients were defined (<65 and ≥65 years old). In terms of the length of stay, the patients were divided into two groups based on the number of days spent in the COVID ward (≤10 or >10 days). The study was approved by the Ethics Committee of the General Hospital Našice (Official Gazette 100/18, 147/2020).

*Statistical Analysis*

Categorical and numerical data were used for the statistical analysis. Categorical data were presented as absolute and relative frequencies. Numerical data were presented in the form of an arithmetic mean and standard deviation in case of normal distribution, and as a median and interquartile range for data not following the normal distribution. Differences in categorical variables were tested by the $\chi$2-test. The Student's t-test for independent values was used in case of normal distribution, while the Mann-Whitney U test and the Kruskal–Wallis test were used in case of deviations from the normal distribution to test the numerical data. All P-values were two-tailed. The significance level was set to Alpha = 0.05. The statistical analysis was performed using the MedCalc Statistical Software, version 20.027 (MedCalc Software Ltd, Ostend, Belgium, https://www.medcalc.org/, 2022).

## Results

The study included 129 patients, of whom 61 (47.3%) were male and 68 (52.7%) were female. The median age was 70 years (interquartile range from 60 to 83 years), while 46 (35.7%) patients were under 65 years of age. The most common comorbidity was hypertension (86, 66.7%), followed by diabetes mellitus (36, 27.9%) and atrial fibrillation (27, 20.9%), whereas only 14 patients (10.9%) had no comorbidities. The diagnosis of hypertension was significantly associated with gender – 75% of women had hypertension, in contrast to 57.4% of men (P = 0.03, $\chi$2 test), and with age – 80.7% of the patients aged 65 and above had hypertension (P < 0.001, $\chi$2 test) (Table 1).

**Table 1. Demographic findings in relation to presence of hypertension**

| | | Hypertension N (%) | | P* | Total N (%) |
|---|---|---|---|---|---|
| | | Yes | No | | |
| Gender | Male | 35 (57.4) | 26 (42.6) | **0.03** | 61 (47.3) |
| | Female | 51 (75) | 17 (25) | | 68 (52.7) |
| Age | < 65 | 19 (41.3) | 27 (58.7) | **<0.001** | 46 (35.7) |
| | ≥ 65 | 67 (80.7) | 16 (19.3) | | 83 (64.3) |
| Total N (%) | | 86 (66.7) | 43 (33.3) | | 129 (100) |

* $\chi$ 2 test

The patients stayed in the hospital for a median of 9 days (6 – 12 days). The majority of patients were discharged from the hospital (94, 72.9%), whereas 35 patients (27.1%) had a fatal outcome. A total of 83 patients (64.3%) stayed in the hospital less than 10 days, while 46 (35.7%) stayed longer. The length of stay was significantly associated with the presence of certain comorbidities. In particular, patients with hypertension (P = 0.04, $\chi$ 2 test) and diabetes mellitus (P = 0.04, $\chi$ 2 test) had a significantly longer stay. Healthy patients had a shorter length of stay, but there was no statistical significance (Table 2).

**Table 2. Length of stay in relation to different comorbidities**

| | | Length of stay (days) N (%) | | P* | Total N (%) |
|---|---|---|---|---|---|
| | | ≤10 | >10 | | |
| Comorbidity | | | | | |
| None | Yes | 11 (78.6) | 3 (21.4) | 0.24 | 14 (10.9) |
| | No | 72 (62.6) | 43 (37.4) | | 115 (89.1) |
| Hypertension | Yes | 50 (58.1) | 36 (41.9) | **0.04** | 86 (66.7) |
| | No | 33 (76.7) | 10 (23.3) | | 43 (33.3) |
| Diabetes mellitus | Yes | 18 (50) | 18 (50) | **0.04** | 36 (27.9) |
| | No | 65 (69.9) | 28 (30.1) | | 93 (72.1) |
| Respiratory† | Yes | 6 (60) | 4 (40) | 0.77 | 10 (7.8) |
| | No | 77 (64.7) | 42 (35.3) | | 119 (92.2) |
| Atrial fibrillation | Yes | 17 (63) | 10 (37) | 0.87 | 27 (20.9) |
| | No | 66 (64.7) | 36 (35.3) | | 102 (79.1) |
| Total N (%) | | 83 (64.3) | 46 (35.7) | | 129 (100) |

* $\chi$ 2 test; † Asthma and chronic obstructive pulmonary disease

The majority of patients used a combination of two antihypertensive drugs (34, 28.3%), the most common of which were ACE inhibitors (55, 45.8%) and diuretics (43, 35.8%). There was no significant difference in the outcome with regard to the type of antihypertensive therapy and the number of antihypertensives used (Table 3).

New-onset hypertension was detected in three (2.3%) patients. All three patients were under 65 years of age and were discharged. The patients with new-onset hypertension had a shorter mean length of stay.

**Table 3. Antihypertensive therapy in relation to outcome**

| | | Outcome N (%) | | *P** | Total N (%) |
|---|---|---|---|---|---|
| | | Discharge | Fatal | | |
| **Antihypertensive therapy** | | | | | |
| None | Yes | 33 (78.6) | 9 (21.4) | 0.42 | 42 (35) |
| | No | 56 (71.8) | 22 (28.2) | | 78 (65) |
| ACE inhibitor | Yes | 41 (74.5) | 14 (25.5) | 0.93 | 55 (45.8) |
| | No | 48 (73.8) | 17 (26.2) | | 65 (54.2) |
| ARB | Yes | 5 (62.5) | 3 (37.5) | 0.43 | 8 (6.7) |
| | No | 84 (75) | 28 (25) | | 112 (93.3) |
| Beta blocker | Yes | 24 (70.6) | 10 (29.4) | 0.58 | 34 (28.3) |
| | No | 65 (75.6) | 21 (24.4) | | 86 (71.7) |
| Calcium channel blocker | Yes | 21 (70) | 9 (30) | 0.55 | 30 (25) |
| | No | 68 (75.6) | 22 (24.4) | | 90 (75) |
| Diuretic | Yes | 29 (67.4) | 14 (32.6) | 0.21 | 43 (35.8) |
| | No | 60 (77.9) | 17 (22.1) | | 77 (64.2) |
| Combination of antihypertensives | | | | | |
| 0 | | 33 (78.6) | 9 (21.4) | | 42 (35) |
| 1 | | 11 (68.7) | 5 (31.2) | | 16 (13.3) |
| 2 | | 26 (76.5) | 8 (23.5) | 0.16† | 34 (28.3) |
| 3 | | 19 (73.1) | 7 (26.9) | | 26 (21.7) |
| 4 | | 0 | 2 (100) | | 2 (1.7) |
| Total N (%) | | 94 (72.9) | 35 (27.1) | | 129 (100) |

ACE = angiotensin-converting enzyme; ARB = Angiotensin receptor blocker; * $\chi$ 2 test; † Kruskal–Wallis test

Patients aged 65 and above had significantly higher mortality rates (P <0.001, $\chi$ 2 test), while gender-related differences in the outcome were not significant. There was no significant association between the investigated comorbidities and outcomes. Out of the 14 healthy patients, 1 (7.1%) had a fatal outcome. Regarding the hypertensive patient population, 61 patients (70.9%) were discharged and 25 (29.1%) had a fatal outcome. There was a significant association between the number of comorbidities and fatal outcome (P = 0.01, Kruskal–Wallis test), with patients with one and three comorbidities having the worst outcome (Table 4). In addition, the patients with a fatal outcome had a significantly shorter length of stay (median of 7 days), in contrast to discharged patients, whose length of stay was 10 days (P< 0.001, Mann–Whitney U test).

**Table 4. Demographic findings, presence and number of comorbidities in relation to outcome**

| | | Outcome N (%) | | *P** | Total N (%) |
|---|---|---|---|---|---|
| | | Discharge | Fatal | | |
| Gender | Male | 44 (72.1) | 17 (27.9) | 0.86 | 61 (47.3) |
| | Female | 50 (73.5) | 18 (26.5) | | 68 (52.7) |
| Age | < 65 | 42 (91.3) | 4 (8.7) | **<0.001** | 46 (35.7) |
| | ≥ 65 | 52 (62.7) | 31 (37.3) | | 83 (64.3) |
| Comorbidity | | | | | |
| None | Yes | 13 (92.9) | 1 (7.1) | 0.08 | 14 (10.9) |
| | No | 81 (70.4) | 34 (29.6) | | 115 (89.1) |
| Hypertension | Yes | 61 (70.9) | 25 (29.1) | 0.49 | 86 (66.7) |
| | No | 33 (76.7) | 10 (23.3) | | 43 (33.3) |
| Diabetes mellitus | Yes | 25 (69.4) | 11 (30.6) | 0.59 | 36 (27.9) |
| | No | 69 (74.2) | 24 (25.8) | | 93 (72.1) |
| Respiratory‡ | Yes | 8 (80) | 2 (20) | 0.6 | 10 (7.8) |
| | No | 86 (72.3) | 33 (27.7) | | 119 (92.2) |
| Atrial fibrillation | Yes | 18 (66.7) | 9 (33.3) | 0.42 | 27 (20.9) |
| | No | 76 (74.5) | 26 (25.5) | | 102 (79.1) |
| Number of comorbidities | | | | | |
| 0 | | 13 (92.9) | 1 (7.1) | | 14 (10.9) |
| 1 | | 27 (62.8) | 16 (37.2) | | 43 (33.3) |
| 2 | | 45 (80.4) | 11 (19.6) | **0.01**† | 56 (43.4) |
| 3 | | 6 (46.2) | 7 (53.8) | | 13 (10.1) |
| 4 | | 3 (100) | 0 | | 3 (2.3) |
| Total N (%) | | 94 (72.9) | 35 (27.1) | | 129 (100) |

* $\chi$ 2 test; † Kruskal–Wallis test; Difference between 0 and 2 to 1 and 3 comorbidities (Post hoc Conover); ‡ Asthma and chronic obstructive pulmonary disease

## Discussion

This research studied the demographic characteristics and comorbidities in COVID-19 patients hospitalised in the General Hospital Našice from 1 October to 31 December 2021, with a focus on the hypertensive population, in relation to the length of stay and outcome. Of 129 hospitalised COVID-19 patients included in the study, hypertension was identified as the most common chronic disease, followed by diabetes mellitus and atrial fibrillation, which is consistent with previous studies (6,7,10,11,17,24), including studies in Croatia (25–27).

In Croatia, the prevalence of hypertension is high, namely 37% (M – 35.2%, F – 39.7%) according to the 2005 EH-UH study (28). Accordingly, in this study, hypertension was significantly more common in females, which is consistent with research conducted in China (17) and the United States (16). Hospitalized COVID-19 patients with hypertension were also significantly older than those without hypertension, which is consistent with research conducted in Iran (6). The patients stayed in the hospital for a median of 9 days (6 – 12 days). The study found that comorbidities played a significant role in the length of stay. It was observed that hypertension and diabetes mellitus were more associated with a longer

stay than other detected comorbidities, corresponding with research conducted in the United States (16) and Ghana (15).

In this study, the majority of hospitalised COVID-19 patients with hypertension were treated with ACE inhibitors (55, 45.8%), but there was no significant association between the type of antihypertensive therapy and the outcome, which is consistent with previous studies (20–22). Since ACE2 plays a negative role in the RAAS system, a decrease in ACE2 and an increase in ANG2 levels can lead to higher blood pressure values (29). In this study, new-onset hypertension was detected in three (2.3%) patients. All three patients were under 65 years of age and were discharged. In the study conducted in Turkey (30), of 153 subjects, new-onset hypertension was observed in 18 (12%) patients, which is comparable to our study.

There are other potential risk factors, including age and the number of comorbidities, that could lead to more severe disease and increased mortality rates in hospitalised COVID-19 patients. The association between a fatal outcome and specific comorbidities was not determined in this study. However, a significant association was detected between a higher number of comorbidities and older age, which is consistent with previous research (7,24,31,32), including studies in Croatia (25,27).

This study identified hypertension as the most common comorbidity in hospitalized COVID-19 patients. Even though treated hypertension did not affect the outcome negatively, other potential factors, including the number of comorbidities and age, were shown to be associated with mortality among COVID-19 patients. Further studies of the mechanism in hypertensive COVID-19 population are needed.

## Study limitations

This study has a few limitations. First, only 129 subjects with confirmed COVID-19 were included in the study and more extensive research would help gain a better understanding of the role of hypertension in COVID-19 patients. Second, the study was conducted in a short period of time without a control group. Finally, the data on outcomes in a short-term and long-term follow-up period after COVID-19 are limited.

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## Disclosure

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**Competing interests.** None to declare.

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