

Impact of Hypertension and Antihypertensive Treatment on COVID-19 Severity: A Retrospective Observational Study in Ternopil Region, Ukraine

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Background: Hypertension (HP) may significantly affect the prognosis of COVID-19 illness. Understanding the epidemiological and clinical characteristics of post-COVID-19 patients with HP and other comorbidities is important for improving outcomes.

Methods: We conducted a retrospective observational study in the Ternopil region of Ukraine involving 926 subjects: 848 individuals in the post-COVID period (0–90 days after a negative SARS-CoV-2 PCR test) and 78 (8.4%) in a control group. Data on medical history, clinical manifestations, treatment modalities, and pathomorphological findings were collected. Patients were categorized into four groups based on COVID-19 severity: mild, moderate, severe, and critical.

Results: HP was present in 46.2% of patients, with a prevalence of 75.0% among fatal cases ($p < 0.001$). Diabetes mellitus (DM) was diagnosed in 17.6%. HP was not associated with increased susceptibility to SARS-CoV-2 infection. In-hospital mortality risk significantly correlated with age ($r = 0.306$, $p < 0.001$), HP ($r = 0.145$, $p = 0.001$), DM ($r = 0.144$, $p = 0.001$), combined HP and DM ($r = 0.159$, $p < 0.001$), and irregular antihypertensive treatment ($r = -0.118$, $p = 0.037$). However, regular use of ACE inhibitors or ARBs did not significantly affect prognosis. Multivariable logistic regression identified age and irregular antihypertensive treatment as independent predictors of in-hospital mortality.

Conclusion: HP was not associated with increased susceptibility to SARS-CoV-2 infection, based on similar prevalence rates in patients and controls, but was linked to worse outcomes when combined with other risk factors. Age and irregular antihypertensive treatment emerged as independent predictors of in-hospital mortality. These findings highlight the importance of regular blood pressure management in reducing the severity and improving the prognosis of COVID-19 in hypertensive patients.

Keywords: COVID-19, comorbidity, hypertension, diabetes mellitus, antihypertensive treatment, survival

Introduction

Since its emergence, COVID-19 has posed significant global health challenges. Research has consistently identified older age, male sex, and chronic comorbidities, such as diabetes mellitus (DM) and cardiovascular disease, as factors that increase disease severity and mortality.^{1–4} Conversely, vaccination, a healthy diet, and adequate nutrition have been shown to offer protective benefits.^{5,6} Hypertension (HP) is one of the most common comorbidities among hospitalized COVID-19 patients.⁷ Early in the pandemic, particular concern surrounded the potential impact of HP and its treatment, especially the effects of medications targeting the renin-angiotensin-aldosterone system (RAAS) on disease outcomes.⁸ These concerns arose from the fact that SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) receptors for host cell entry, and RAAS inhibitors were thought to increase ACE2 expression.⁹ However, subsequent studies found that neither ACEIs nor ARBs significantly

enhance ACE2 expression or viral replication, and some even suggested potential protective effects due to their anti-inflammatory properties.^{10–12} While HP has been widely associated with increased COVID-19 severity and mortality,⁷ the extent to which this relationship is independent of other risk factors remains debated.^{3,13} Major health authorities, including the World Health Organization (WHO)¹⁴ and the Centers for Disease Control (CDC),¹⁵ along with the national authorities,¹⁶ have issued differing interpretations of HP-related risks in COVID-19 patients, highlighting ongoing uncertainty. A consistent finding across studies, however, is that older adults and individuals with comorbidities experience the most severe complications of COVID-19.^{3,7} Moreover, treatment-related factors may complicate patient outcomes. For example, glucocorticoids, often used for patients with respiratory failure or low oxygen saturation, can impair control of blood glucose and blood pressure, potentially exacerbating both DM and HP.¹⁷

In addition, population and regional differences complicate interpretation, as variations in demographics, comorbidities, healthcare access, and treatment protocols can significantly influence outcomes and limit the generalizability of findings.^{18–21} Given these uncertainties and regional disparities, our study aimed to examine the demographic and clinical characteristics of post-COVID-19 patients in the Ternopil region of Ukraine. In particular, we focused on the role of hypertension, related comorbidities, and treatment adherence in influencing COVID-19 outcomes within this specific healthcare setting.

Materials and Methods

A retrospective observational study of 926 subjects in the Ternopil region was conducted. We recruited 848 persons in their post-COVID period (0–90 days after the last negative PCR test to SARS-CoV-2) and 78 [8.4%] subjects who served as a control group (Cg). The control group included contact individuals (relatives of patients or healthcare workers) who showed no clinical signs of the disease and were seronegative upon real-time reverse transcription polymerase chain reaction (RT-PCR) testing. Recruitment was done between July 15, 2020, and December 28, 2021, at primary medical care facilities of the region and via social media.

All patients were categorized based on COVID-19 severity according to national Ukrainian protocols¹⁶ and WHO recommendations²² into the following groups:

- Home Quarantined with Mild disease course (HQM, n=283),
- Hospitalized with Moderate course (HMO, n=329),
- Hospitalized oxygen-dependent patients with Severe symptoms and (HSV, n=202),
- Hospitalized Critical patients in ICU departments with mechanical ventilation (HCR, n=34).

Medical records, clinical manifestations, treatment modalities and consequences, and pathomorphological protocols were recorded and analyzed. Anthropometric data, sex features, risk factors for cardiovascular complications (obesity, smoking, hereditary factors), comorbidity, especially high blood pressure, and DM, adherence to treatment, complications and outcomes, morbidity, and survival rate were studied and evaluated.

In all cases, the diagnosis of COVID-19 was confirmed by RT-PCR tests; patients without laboratory-confirmed diagnoses were not involved in the study (exclusion criteria). The severity of the disease was diagnosed based on the national protocols and WHO recommendations for clinical signs and laboratory tests (out-of-hospital or hospitalized patients, respiratory indices, oxygen blood saturation, percentage of lung damage for computed tomography (CT) results, invasive or non-invasive oxygen ventilation, complications). HP and/or DM were diagnosed by the patient's general practitioner/family physician before the SARS-CoV-2 infection. The verification of the above mentioned diseases was performed in accordance with the guidelines of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) that were current at the time of initial diagnosis.^{23,24} Irregular (inconsistent) antihypertensive therapy was defined as the sporadic use of antihypertensive medications in response to specific situations, typically during periods of worsened symptoms or when blood pressure readings were significantly elevated, rather than as part of a regular, prescribed regimen.

Statistical Analysis

Statistical analysis was performed using SPSS 21.0 software (SPSS Inc., Chicago, IL, USA). Variables with normal distribution are presented as mean $\pm$ standard error (M $\pm$ SEM), while categorical variables are shown as percentages. Between-group comparisons for continuous variables were conducted using the independent Student's *t*-test or the Mann-Whitney *U*-test, as appropriate. Categorical variables were compared using Fisher's exact test.

Exploratory data analysis using Pearson correlation assessed the strength and direction of relationships between variables. Univariable and multivariable logistic regression was used to identify independent predictors of in-hospital mortality. Variables with $p \leq 0.05$ in univariable analysis were entered into the multivariable model and removed if $p > 0.10$.

For time-to-event data, survival analysis was performed using Kaplan–Meier curves, and group differences were evaluated with the Log rank test. Multivariable Cox proportional hazards modeling was then applied to identify predictors of survival, with results expressed as hazard ratios (HRs) and 95% confidence intervals (CIs).

Results

Cohort Characteristics

Among the 926 individuals involved, 325 were male (35.1%) and 601 were female (64.9%), with a total of 278 medical workers (30.0%) of either sex. Patients' ages ranged from 18 to 91 years, with a median age of 56 years.

The distribution of the study cohort ($n=848$) according to COVID-19 severity was as follows: HQM – 33.4%, HMO – 38.8%, HSV – 23.8%, and HCR – 4.0% (Figure 1). This distribution corresponds with the statistics of COVID-19 severity in the Ukrainian population as of April 2021.¹⁶

Sex Impact

A higher prevalence of females was observed among out-of-hospital patients compared to the cohort of hospitalized patients: 76% vs 57% ($p < 0.0001$). Among hospitalized patients, the proportion of males increased, with their numbers tending to rise in accordance with the severity of the illness, although this trend was not statistically significant (39.5% in the HMO group vs 47.5% in the HSV group, $p = 0.07$). However, among critically ill patients (HCR), the proportion of males and females was equal (50%).

Comorbidities

Hypertension (HP) was recorded in 427 patients (46.2%), with 11 patients (1.2%) being diagnosed with HP for the first time during COVID-19. The incidence rate of HP among fatal cases was 75.0% ($p < 0.001$), while in the control group, it

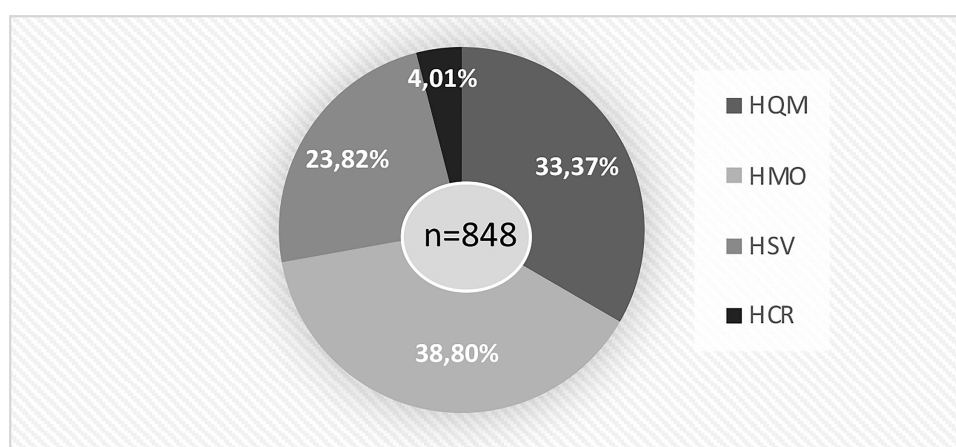


Figure 1 Distribution of the patients included in the study based on COVID-19 severity.

Abbreviations: HQM, Home Quarantined with Mild disease course; HMO, Hospitalized with Moderate course; HSV, Hospitalized oxygen-dependent patients with Severe symptoms; HCR, Hospitalized Critical patients in ICU departments with mechanical ventilation.

was 38.5%, which aligns with data from the STEPS National Registry. The average duration of HP history was 10.73 ± 0.57 years. Diabetes mellitus (DM) was recorded in 163 patients (17.6%), with 58 patients (6.3%) being diagnosed for the first time. During the course of COVID-19, signs of glucose intolerance were observed in 39 patients (4.2%).

Age and Comorbidities

Figure 2 illustrates the impact of age, concomitant HP, and DM on COVID-19 severity. Correlation analysis revealed that age ($r=0.485$, $p<0.0001$), comorbid HP ($r=0.471$, $p<0.0001$), diabetes mellitus (DM) ($r=0.346$, $p<0.0001$), duration of HP ($r=0.394$, $p<0.0001$), and HP complications ($r=0.261$, $p<0.0001$) significantly influenced disease severity and were associated with increased in-hospital mortality ($r=0.302$, $p<0.0001$). Comorbid HP was observed in 29.7% of out-of-hospital patients and in 55.5% of in-hospital patients ($p<0.001$). The proportion of patients with hypertension increased proportionally with the severity of COVID-19. Additionally, 474 individuals had a genetic predisposition to cardiovascular diseases (CVD) based on family history, with 193 individuals (40.7%) exhibiting a higher hereditary risk for CVD.

Among the 848 patients included in the study, 68 patients (8.08% of the entire cohort) died in the hospital, representing 12.04% of the hospitalized patients ($n=545$). The mean age of those who died was 69.54 ± 1.36 years, with 31 males and 37 females (45.6% and 54.4%, respectively, $p>0.05$). The mean age for males was 68.71 ± 2.05 years, while for females it was 70.20 ± 1.84 years.

A significant correlation between age and patient mortality was observed ($r=0.306$, $p<0.001$). Consequently, mortality rates were assessed across different age groups, categorized according to the WHO guidelines: young (≤ 45 years), middle-aged (46–59 years), elderly (60–74 years), senile (75–90 years), and long-livers (>90 years). The hospital mortality rate (Figure 3) was found to be three times higher in elderly patients and 11 times higher in senile patients compared to younger age groups ($p<0.001$). These findings highlight that individuals aged 60 and older are at significantly higher risk of mortality due to COVID-19, consistent with the results of most studies.^{8,12}

Among the COVID-19 patients who died in the hospital, 22 (32.25%) were treated with invasive ventilation, while only 12 patients (1.54%) among those discharged required the same intervention. The leading causes of death, as determined by autopsy, included acute respiratory failure and acute respiratory distress syndrome (ARDS) (59.09%), multiple organ dysfunction (28.79%), and cardio-respiratory insufficiency (12.12%). Autopsy findings also revealed pulmonary arterial thrombosis and/or thrombosis in segmental and subsegmental pulmonary arterial vessels in 13.24% of cases, coronary artery thrombosis in 2 patients, and stroke in 1 patient.

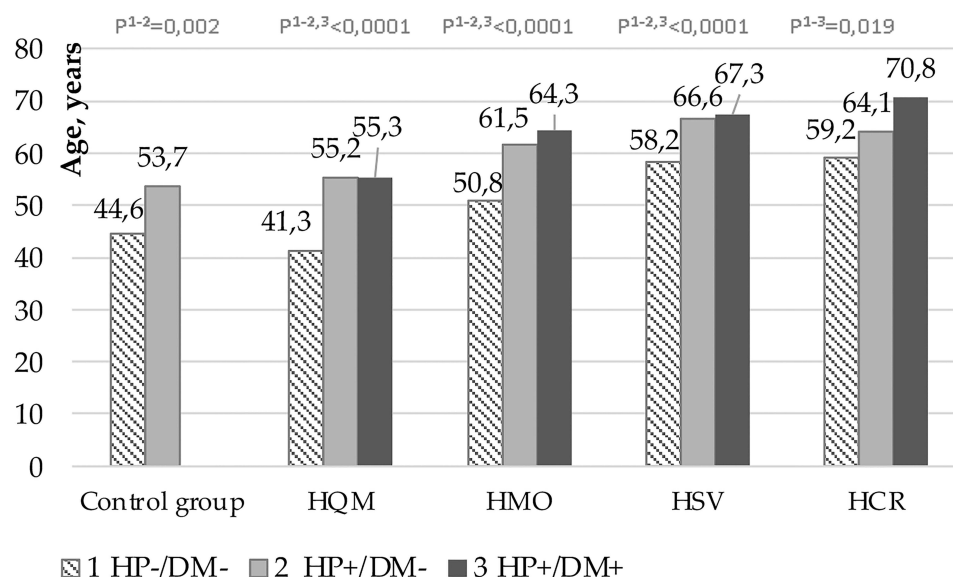


Figure 2 Age distribution in a cohort of patients based on COVID-19 severity and the presence of comorbidities. P-values are indicated with superscript indexes corresponding to the column numbers.

Abbreviations: HP, hypertension; DM, diabetes mellitus.

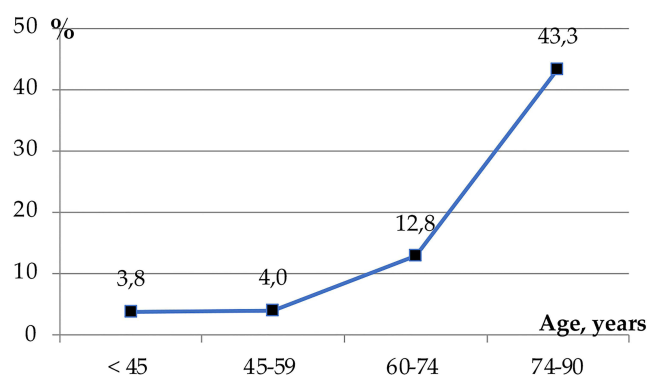


Figure 3 In-hospital mortality (%) among COVID-19 patients across different age groups.

A comparative analysis of the main characteristics of patients with “isolated” hypertension, with HP in combination with DM, as well as only with DM (without HP) and persons without HP and without DM (Table 1), was done.

In the studied cohort, the age of patients with COVID-19 and concomitant HP and/or DM was significantly higher than those without the mentioned illnesses. The oldest patients were those with concomitant diseases, who also had the highest body mass index (BMI), primarily due to individuals with DM.

Table 1 Clinical and Functional Characteristics of Patients with Covid-19 at Admission to Hospital, (M ± SEM)

Index	a COVID-19 and HP, n=250	b COVID-19 and HP +DM, n=85	c COVID-19 and DM, n=16	d COVID-19 without HP/DM, n=391	p-value
Age, years	60.92±0.67	65.75±0.88	59.13±3.01	46.27±0.68	$p^{a-b}<0.0001$; $p^{b-c}=0.049$; $p^{a,b,c-d}<0.0001$
Body mass index, kg/m ²	30.14±0.29	31.53±0.62	31.44±1.49	26.89±0.27	$p^{a-b}=0.039$; $p^{a,b,c-d}<0.0001$
Heart rate, per min	88.85±1.07	86.39±2.22	96.56±5.44	89.48±1.16	$p^{a-c}=0.029$; $p^{b-c}=0.030$; $p^{c-d}=0.045$
Systolic blood pressure, mmHg	134.63±1.41	128.47±2.64	117.22±5.53	120.00±1.21	$p^{a-b}=0.008$; $p^{a-c}=0.003$; $p^{a-d}<0.0001$; $p^{b-d}=0.004$
Diastolic blood pressure, mmHg	81.28±0.94	79.27±1.49	72.78±3.02	76.97±0.78	$p^{a-c}=0.012$; $p^{a-d}=0.001$
Respiratory rate, per min	22.47±0.43	22.61±0.36	21.67±0.33	21.38±0.29	$p^{a-d}=0.039$; $p^{b-d}=0.011$
Blood oxygen saturation (SpO ₂), %	87.68±0.73	84.67±1.29	85.33±2.65	90.85±0.49	$p^{a-b}=0.031$; $p^{a,b-d}<0.0001$; $p^{c-d}<0.013$
Computed tomography, area of damage, %	31.55±2.05	32.31±2.81	38.00±8.00	33.25±1.79	$p>0.05$
Aortic root diameter, cm	3.45±0.59	3.43±0.07	3.23±0.27	3.27±0.05	$p^{a-d}=0.024$; $p^{b-d}=0.05$
Left atrium, cm	4.07±0.11	4.28±0.08	4.03±0.10	3.72±0.07	$p^{a-d}=0.011$; $p^{b-d}<0.0001$
End diastolic diameter, cm	4.85±0.07	5.01±0.12	5.06±0.12	4.77±0.06	$p^{b-d}=0.0003$; $p^{c-d}=0.027$
Ejection fraction, %	59.27±1.07	57.05±1.60	63.33±0.67	62.66±0.60	$p^{a-d}=0.007$; $p^{b-d}=0.002$
Interventricular septal end diastole, cm	1.26±0.02	1.28±0.03	1.23±0.04	1.10±0.04	$p^{a,b-d}=0.002$
Posterior wall thickness, cm	1.20±0.02	1.20±0.02	1.17±0.03	1.02±0.02	$p^{a,b-d}<0.0001$; $p^{c-d}=0.043$
Right ventricle diameter, cm	2.41±0.07	2.51±0.06	2.27±0.14	2.25±0.03	$p^{a-d}=0.040$; $p^{b-d}=0.001$

(Continued)

Table 1 (Continued).

Index	a COVID-19 and HP, n=250	b COVID-19 and HP +DM, n=85	c COVID-19 and DM, n=16	d COVID-19 without HP/DM, n=391	p-value
E/A ratio	0.64±0.04	0.64±0.05	0.70±0.01	0.80±0.06	p ^{a-d} =0.033; p ^{b-d} =0.045
Systolic pulmonary artery pressure, mm Hg	26.59±2.34	25.88±2.06	28.67±8.41	21.08±1.18	p ^{a-d} =0.041; p ^{b-d} =0.037
COVID-19 diagnosis verification, days	5.58±0.42	4.80±0.38	8.33±1.60	4.64±0.39	p ^{a-c} =0.038; p ^{c-d} =0.018

Notes: P-values are indicated with superscript letters corresponding to the respective columns.

Initial heart rate was the highest in COVID-19 patients with DM. The main contributors could be significant intoxication and cardiac autonomic neuropathy (common in that pathology) - a frequent chronic complication of diabetes mellitus with potentially life-threatening outcomes. Also, the longest duration of COVID-19 diagnosis verification in that category of patients should be paid attention to (see Table 1). If common diagnosing lasts 4–5 days, usually, in case of “isolated” DM as comorbidity, COVID-19 was diagnosed at 7–9 days after the appearance of first symptoms. Systolic and diastolic blood pressure naturally were significantly higher in COVID patients with concomitant HP. The inferior numbers were observed in patients with concomitant DM, which points to disorders of autonomic regulation because of metabolic imbalance (it should be confirmed by laboratory tests) and also is a sign of the negative impact of viral infection on vessel tonus.

In COVID-19 patients with HP, especially with concomitant DM, suppression of the functional indices of the respiratory system was observed. This is manifested by a significant increase in respiratory rate at rest and a decrease in oxygen blood saturation compared to the cohort of COVID-19 patients without concomitant pathology.

Even though area of lung damage was not significantly different in studied groups we found weak correlation between the size of damaged area and COVID-19 severity ($r=238$, $p<0.001$), HP complications ($r=276$, $p=0.003$), presence of concomitant DM ($r=134$, $p=0.047$), cardiac arrhythmias ($r=156$, $p=0.022$) and myocardial impaired relaxation ($r=241$, $p=0.037$).

The echocardiographic evaluation identified a significant increase in aortic root diameters, left atrium (antero-posterior dimension), and wall thickness in patients with HP compared to those without concomitant pathology. In terms of other indices, the most significant negative impact on ventricle size was observed in patients with concomitant hypertension (HP) and diabetes mellitus (DM), likely due to hemodynamic overload from high blood pressure and metabolic disturbances associated with DM. Functional characteristics, particularly diastolic filling (E/A) and ejection fraction, were the lowest in patients with both hypertension and diabetes. Thus, the poorest cardio-respiratory indices were found in the group with concomitant HP and DM. Additionally, these patients were older and had a significantly higher incidence of obesity. The general characteristics of COVID-19 patients, along with treatment modalities and complications related to HP and DM, are presented in Table 2.

Almost every 4th COVID-19 patient was diagnosed with the complications of HP and around half of the patients with HP-controlled high blood pressure regularly with antihypertensive drugs. First-line drugs such as ACEIs/ARBs, diuretics, calcium channel blockers, and beta-blockers are the most used. Among patients with DM, two-thirds were taking oral hypoglycemic drugs.

COVID-19 in-hospital mortality risks significantly correlated with age ($r=0.306$, $p<0.001$), concomitant HP ($r=0.145$, $p=0.001$) or DM ($r=0.144$, $p=0.001$), their joint comorbidity ($r=0.159$, $p<0.001$) and previous regular antihypertensive treatment ($r=-0.118$, $p<0.037$).

Age showed the strongest correlation with in-hospital mortality. Fifty (73.53%) patients of those 68 who died in the hospital had HP and the average age of (71.12±1.32) years. Notably, only half of them (52.0%) controlled their blood pressure with medicines. The median age of patients who systematically took antihypertensive treatment was 74 years, those of them who did not and died because of COVID-19 – 66 years ($p=0.0003$). Partial correlation with excluding the age as a predictor still showed the correlation between fatal outcome and simultaneously comorbid DM and HP ($r=0.139$, $p=0.018$), and regular previous pharmacological treatment ($r=-0.165$, $p=0.005$), in particular with RAAS inhibitors ($r=-0.119$, $p=0.042$). Also, BMI

Table 2 The Most Common Complications of HP and Treatment Modalities of HP and DM in the Studied Cohort (Absolute Numbers, %)

Characteristics	n	n ₁	%
Hypertension complications:	427	103	24.1
History of transient ischemic attack		13	9
History of ischemic stroke		11	26
History of myocardial infarction			18
History of cardiac arrhythmias, including:			35
(Paroxysmal atrial fibrillation)			3.0
(Permanent atrial fibrillation)			2.6
Aorta ectasia /aneurysm			11
Others (eg, retinal hemorrhage)			4
Hypertension treatment:	427	283	66.3
Regular/systematic		71	16.6
Episodic		65	15.1
No treatment		8	1.9
Information unavailable			
Most commonly used pharmacological groups of Antihypertensive drugs:	427		
ACEIs regularly		142	33.25
ARBs regularly		92	21.54
ACEIs episodically		41	9.60
ARBs episodically		8	1.87
Diuretics regularly		163	38.17
Diuretics episodically		27	6.23
CCBs regularly		76	17.80
CCBs episodically		10	2.34
Beta-blockers regularly		118	27.63
Beta-blockers episodically		18	4.215
Diabetes mellitus treatment:	105		
Oral hypoglycemics regularly		74	70.48
Insulin preparations		18	17.14
Do not take anti-diabetic drugs		13	12.38

Notes: n – total available data. n₁ – absolute number of observations.

Abbreviations: ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCBs, calcium channel blockers.

correlated with in-hospital mortality rate ($r=0.117$, $p=0.046$). However, when we excluded the age from correlation analysis, the association of in-hospital mortality with HP was lost.

To analyze it deeper, we have compared the survival rates for different patient categories. Kaplan-Meier survival rate analysis demonstrates the higher in-hospital mortality rate in patients with comorbid HP ($\chi^2=11.39$, $p=0.001$) (Figure 4a), and in case of concomitant HP-DM survival curves begin to diverge in the first week of hospital stay ($\chi^2=15.83$, $p<0.001$) (Figure 4b). In both cases data are significantly different. A separate analysis of factors that impact the survival rate of isolated and joint comorbidity of HP and DM confirmed significantly worse outcomes in the case of the presence of both conditions.

A study on the impact of antihypertensive treatment on in-hospital mortality revealed a significant difference in outcomes between patients who regularly take antihypertensive medications and those who do not ($\chi^2=4.06$, $p=0.044$). Especially since Day 15 of hospital stay, cytokine storm course was milder in patients who regular and systematically controlled HP with medications before COVID-19 (Figure 5).

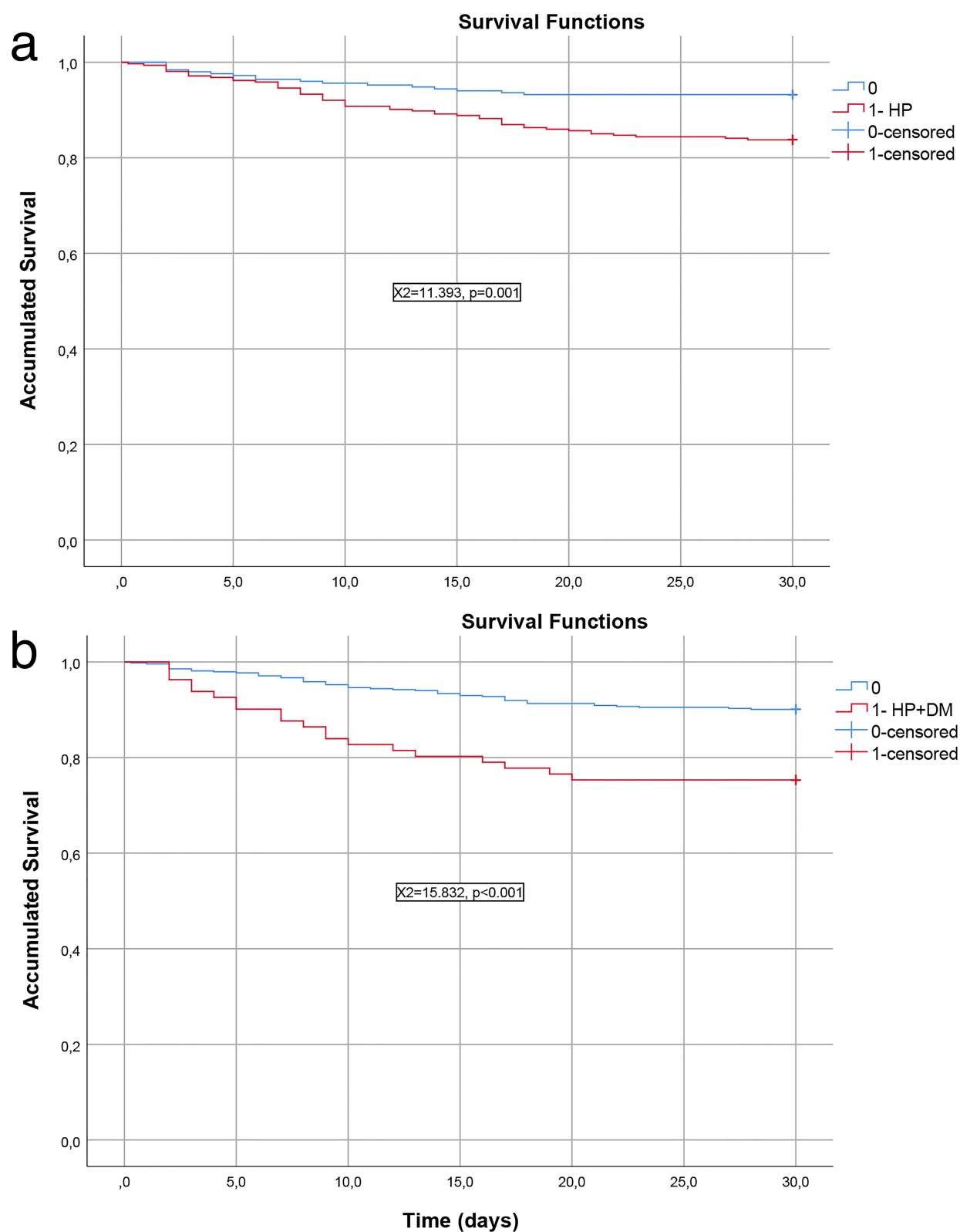


Figure 4 (a) Kaplan-Meier 30-day survival curves of hospitalized patients with COVID-19 and comorbid hypertension (HP); **(b)** Kaplan-Meier 30-day survival curves of hospitalized patients with COVID-19 with comorbid hypertension (HP) and diabetes mellitus (DM).

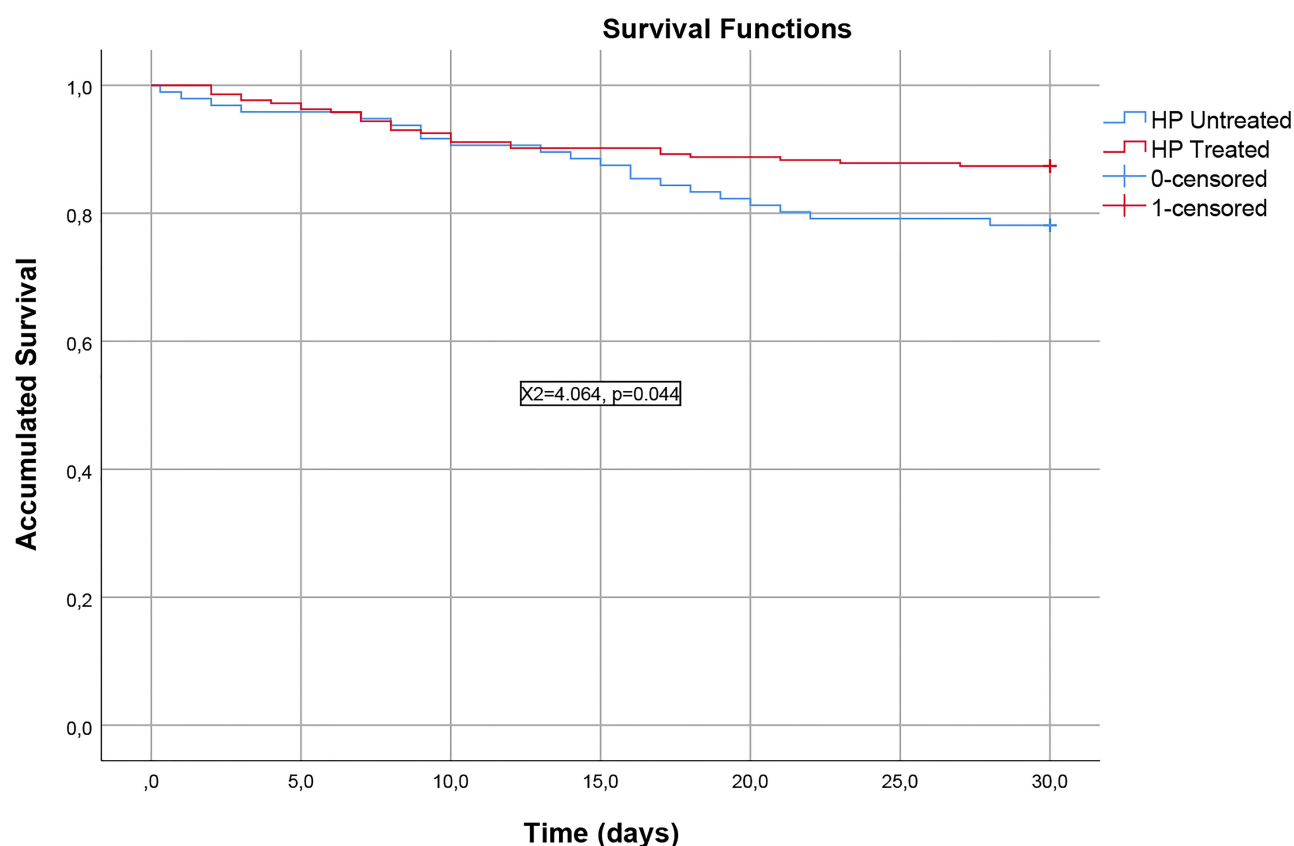


Figure 5 Kaplan-Meier 30-day survival curves for hospitalized COVID-19 patients with hypertension (HP) based on prior regular and systematic antihypertensive treatment.

However, systematic and regular use of ACEIs or ARBs did not have any influence on the outcome prognosis during the first 30 days after hospitalization due to COVID-19 ($\chi^2=2.434$, $p=0.119$). The data we obtained regarding the clinical significance of hypertension in patients with coronavirus infection was ambiguous. Therefore, for the final clarification of the prognostic value of individual factors that impact the COVID-19 patient's survival, regression analysis with the Cox proportional hazards model was applied. To identify independent mortality predictors, we used a multifactor model, which includes age, body mass index, HP, duration of existing HP, concomitant DM, previous pre-COVID regular high blood pressure control with drugs, previous treatment with RAAS regulators and calcium channel blockers (Table 3).

Table 3 Predictors of in-Hospital Mortality of Patients with COVID-19 for Data Regression Analysis (Cox Proportional Hazard Model)

Characteristics	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p	HR	95% CI	p
Age, years	1.086	1.060–1.112	0.001	1.11	1.030–1.202	0.007
BMI, kg/m ²	1.018	0.975–1.063	0.423	–	–	–
Hypertension	2.487	1.436–4.306	0.001	–	–	–
Duration of hypertension, years	1.051	0.993–1.111	0.084	–	–	–
Diabetes mellitus	2.485	1.486–4.158	0.001	–	–	–
Previous regular treatment of hypertension	0.562	0.317–0.993	0.047	3.51	1.061–1.637	0.040
Treatment with agents affecting RAAS	0.640	0.362–1.128	0.123	–	–	–
Treatment with calcium channel blockers	0.981	0.932–1.033	0.476	–	–	–

Abbreviations: BMI, body mass index; RAAS, renin-angiotensin-aldosterone system.

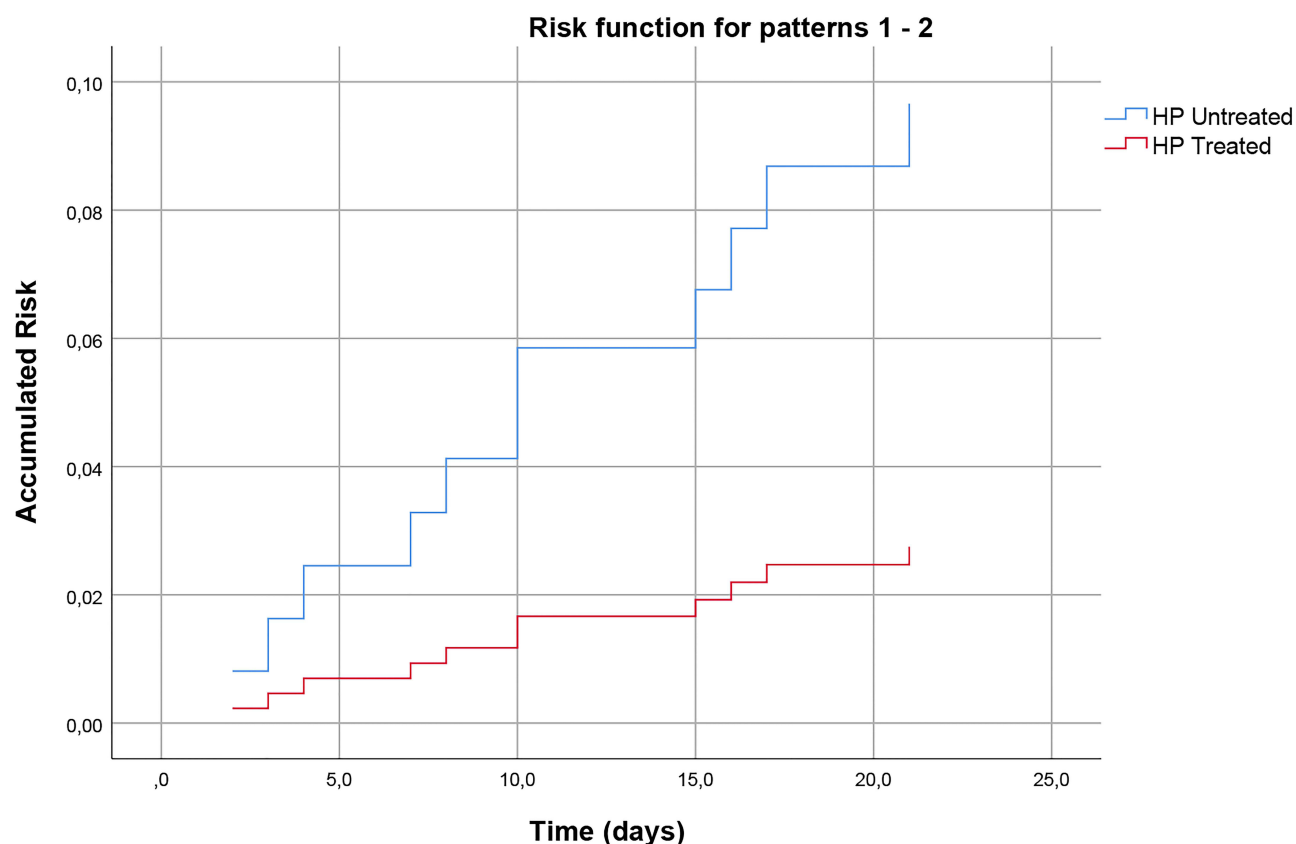


Figure 6 Risk of in-hospital mortality in patients with treated vs untreated hypertension (HP).

Multivariate logistic regression analysis identified the following factors as independent predictors of in-hospital mortality for patients with COVID-19 ($\chi^2=11.936$, $p<0.008$): patient age and absence of previous control of hypertension with medical agents. We observe a clear increase in the risk of an unfavorable prognosis in the absence of previous systematic antihypertensive therapy in patients with comorbid hypertension (Figure 6).

Discussion

Hypertension (HP) was the most prevalent comorbidity among the 848 patients with COVID-19 included in this study. Among those who died during hospitalization, two-thirds (50 of 68) had HP. Therefore, a central aim of our study was to evaluate whether HP increases the risk of contracting COVID-19. The incidence of HP in the control group of healthy contacts did not differ significantly, consistent with the epidemiological data from Ukraine, where approximately one-third (34.8%) of the adult population has elevated blood pressure, as reported by the WHO STEPS survey.²⁵ These findings align with studies from Wuhan and Europe, where HP and DM were among the most frequent comorbidities observed in COVID-19 patients.^{26,27} Subsequent meta-analyses and global surveillance studies confirm these trends, showing that HP remains one of the most common underlying conditions in COVID-19 hospitalizations.^{7,28,29} Thus, we conclude that HP is strongly associated with COVID-19, primarily due to their high prevalence.

Age was a significant predictor of poor outcomes in COVID-19 and correlated with most other risk factors, complications, and mortality. Other risk factors were often linked to age, and once adjusted for age, their prognostic significance diminished. Age played a crucial role in amplifying the impact of these factors. However, the role of hypertension in this context remained less clear. Statistical analysis showed that the incidence of HP was 1.9 times higher in hospitalized patients compared to outpatients ($p < 0.001$), with the proportion of patients with HP increasing in accordance with the severity of COVID-19. Furthermore, DM and high body mass index (BMI) were identified as aggravating factors that worsened the severity of the disease.

On one hand, the sufficient adherence to a systematic treatment regimen for hypertension (HP) can be considered a characteristic of our cohort, as 66.3% of patients were following regular antihypertensive treatment before the diagnosis of COVID-19. It is worth noting that, according to the aforementioned STEPS study,²⁵ only 34.8% of Ukrainians regularly take prescribed antihypertensive medications, and only 14.4% achieve target blood pressure levels. On the other hand, we recruited patients through the primary care physician's healthcare system and social media, resulting in a cohort of individuals who recognized the importance of qualified medical care and consultations. This could be one of the factors contributing to the high treatment adherence and compliance observed in our cohort.

A weak negative correlation was found between the previous regular use of antihypertensive medications and in-hospital mortality ($r=-0.118$, $p<0.037$), which remained even after excluding age from the correlation analysis. Additionally, partial correlation analysis revealed an inverse correlation with the prior use of RAAS blockers, consistent with some other studies. On one hand, an analysis of the Kaplan-Meier survival curve indicated that mortality was higher in patients with COVID-19 and comorbid hypertension (HP), particularly when associated with diabetes mellitus (DM). On the other hand, the survival rate was significantly higher in patients who had regularly controlled their high blood pressure with medication before contracting COVID-19. Thus, our study, along with the BRACE CORONA Trial, refutes the bias regarding the negative impact of ACE inhibitors (ACEIs) and angiotensin receptor blockers (ARBs).³⁰ However, we could not definitively confirm a direct positive impact of RAAS blockers on the mortality rate, which may be limited by the relatively small cohort size – an acknowledged limitation of our study. Other studies have reported similar finding.^{31,32}

Previous studies examining hypertension and antihypertensive use in COVID-19 reported no clear benefit of specific drug classes³³ or routine use of antihypertensive therapy in all patients.³⁴ For example, study from Iran³⁴ found no significant differences in key outcomes between hypertensive and normotensive patients, regardless of medication type. In contrast, our study focused on prior treatment adherence and found a weak but significant association between regular antihypertensive use before infection and reduced in-hospital mortality. This suggests that consistent blood pressure control may contribute to better outcomes.

Our study found that age (HR 1.11; 1.03–1.20 95% CI, $p=0.007$) and absence of previous regular antihypertensive treatment (HR 3.51; 1.06–1.64 95% CI, $p=0.040$) were the independent predictors of in-hospital mortality. Therefore, appropriate management, as well as increased treatment adherence and compliance in patients with hypertension, could be crucial due to the high incidence of high blood pressure.

Limitations

Our study has several limitations. First, it was conducted in a single region with a modest sample size, which may limit the generalizability of the findings. Second, recruitment methods may have introduced selection bias toward individuals with better access to care or higher health literacy. Third, treatment adherence was self-reported, which could introduce recall or reporting bias. Additionally, not all confounders could be fully accounted for, including socioeconomic factors and unmeasured comorbidities. Finally, the observational design does not allow for causal inference.

Future Directions

While COVID-19 is no longer considered a global health emergency and global vaccination efforts have reduced the acute burden of COVID-19,³⁵ its long-term impact, particularly among individuals with chronic comorbidities such as hypertension, remains clinically relevant. Further large-scale, multicenter studies are warranted to evaluate whether treatment adherence and specific antihypertensive regimens influence outcomes in the post-acute phase. Additionally, insights from this study may help strengthen preparedness strategies for managing patients with chronic conditions during future pandemics or public health emergencies.

Conclusions

This study found no significant difference in the prevalence of hypertension between patients with COVID-19 and healthy contacts, suggesting that hypertension may not increase the risk of contracting SARS-CoV-2. However, when combined with other risk factors such as age over 60 years, diabetes mellitus, and high body mass index, hypertension

significantly worsened the prognosis of COVID-19. Age was identified as an independent predictor of poor outcomes. Regular antihypertensive treatment appeared to mitigate the severity of COVID-19 in hypertensive patients.

Data and Materials Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics Statement

The study was approved by the Bioethics Committee (protocol No. 59 dated June 05, 2020) of the Ivan Horbachevsky Ternopil National Medical University. All patients gave informed consent for participation in the study. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and its subsequent amendments.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All the authors declare that they have no conflicts of interest in this work.

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