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COVID-19 AND ARTERIAL HYPERTENSION: WHETHER NORMAL BLOOD PRESSURE IS A SIGN OF A BENIGN COURSE OF COVID-19

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Key words: *COVID-19, hypertension, disease severity, blood pressure*
Ключові слова: *COVID-19, артеріальна гіпертензія, тяжкість захворювання, артеріальний тиск*

Abstract. COVID-19 and arterial hypertension: whether normal blood pressure is a sign of a benign course of COVID-19. Kuryata O.V., Frolova Ye.O., Stadnyk O.I., Semenov V.V. *SARS-CoV-2 virus, which causes coronavirus disease 2019 (COVID-19), apart from respiratory manifestations, is able to directly affect the cardiovascular system. Therefore, different from general population target values of blood pressure might be beneficial for the patients with COVID-19. The aim of this study was to investigate whether conventional blood pressure control was associated with the severity of COVID-19. From 260 patients that were hospitalised to the unit subdivision of stable patients of COVID-center between March, 2020, and December, 2020, 163 patients with confirmed infection with SARS-CoV-2 virus and hypertension were selected. The patients were distributed by hypertension control: blood pressure <140/90 mmHg (n=94) and blood pressure ≥140/90 mmHg (n=69). Routine instrumental and laboratory investigations were registered and analysed. The patients were diagnosed and treated according to national and European guidelines. The information about the control of blood pressure was taken from the patients' medical records. The group of patients with controlled hypertension had higher prevalence of females (p=0.03), 10 years higher median of age (p<0.01) and lower frequency of obesity (p=0.04). The patients with controlled hypertension had lower median of pulmonary injury (p=0.04) and lower frequency of SpO_2<92% (p=0.02). Glomerular filtration rate <60 ml/min and proteinuria were detected significantly more frequently in the patients with controlled hypertension (p=0.02). In the presented study blood pressure below 140/90 mmHg before the admission to the hospital was associated with a lower degree of pulmonary injury but with the higher frequency of nephropathy signs. Urine test and blood creatinine monitoring might be beneficial for the patients with COVID-19 and hypertension.*

Реферат. COVID-19 та артеріальна гіпертензія: чи є нормальний тиск ознакою доброякісного перебігу COVID-19. Курята О.В., Фролова Є.О., Стадник О.І., Семенов В.В. *Вірус SARS-CoV-2, який викликає коронавірусну хворобу 2019 (COVID-19), крім респіраторних проявів, здатен безпосередньо впливати на серцево-судинну систему. Тому для пацієнтів з COVID-19 може бути доцільним використання відмінних від загальнопопуляційних цільових значень артеріального тиску. Метою цього дослідження було дослідити асоціацію між традиційним контролем артеріального тиску та тяжкістю перебігу COVID-19. З 260 пацієнтів, які були госпіталізовані до відділення стабільних хворих COVID-центру в період з березня 2020 року до грудня 2020 року, було відібрано 163 пацієнти з підтвердженою інфекцією вірусом SARS-CoV-2 та артеріальною гіпертензією. Пацієнти були розподілені відповідно до контролю артеріальної гіпертензії: артеріальний тиск <140/90 мм рт. ст. (n=94) та артеріальний тиск ≥140/90 мм рт. ст. (n=69). Реєстрували та аналізували рутинні інструментальні та лабораторні дослідження. Пацієнтам встановлювали діагноз та проводили лікування відповідно до національних та європейських рекомендацій. Інформація про контроль артеріального тиску була взята з медичної документації пацієнтів. У групі пацієнтів з контрольованою артеріальною гіпертензією переважали особи жіночої статі (p=0,03), медіана віку була на 10 років вищою (p<0,01), а частота ожиріння – нижчою (p=0,04). Пацієнти з контрольованою артеріальною гіпертензією мали меншу медіану відсотків ураження легень (p=0,04) та меншу частоту SpO_2<92% (p=0,02). Швидкість клубочкової фільтрації <60 мл/хв та протеїнурія достовірно частіше виявлялися в пацієнтів з контрольованою артеріальною гіпертензією (p=0,02). У представленому дослідженні артеріальний тиск нижче 140/90 мм рт. ст. перед госпіталізацією асоціювався з меншим ступенем ураження легень, але з більшою частотою ознак нефропатії. Моніторинг сечі та креатиніну крові може бути корисним для пацієнтів з COVID-19 та артеріальною гіпертензією.*

The outbreak of coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, put healthcare systems worldwide under an unprecedented load [1]. During this pandemic, naturally, respiratory complications of the infection were

mainly in focus, dragging the attention away from other pathologies, including cardiovascular [2,3]. For instance, during the pandemic there was a drop in atrial fibrillation diagnosis [3] while cardiovascular mortality increased [2]. SARS-CoV-2 virus is capable of directly damaging the cardiovascular system [4]. Thus, individuals with cardiovascular pathology suffering from COVID-19 might require additional care in order to improve their outcomes.

Despite suggestions that hypertension (HTN) was associated with the worse prognosis of COVID-19 [1], currently there is no evidence that HTN per se is a risk factor of a poor outcome [5]. The telehealth technologies are widely introduced in management of stable patients [6, 7], including self-assessment by patients themselves. Similarly, self-isolated patients with COVID-19 and HTN should monitor their BP without attending a hospital [5]. Given the ability of SARS-CoV-2 virus to directly affect the cardiovascular system, different from general population target values of blood pressure (BP) might be beneficial for the patients with COVID-19.

The aim of this study is to investigate whether conventional BP control is associated with the severity of COVID-19.

MATERIALS AND METHODS OF RESEARCH

Between March, 2020, and December, 2020, 260 patients with confirmed infection with SARS-CoV-2 virus were hospitalised to the unit of stable patients of COVID-center, Mechnikov Dnipropetrovsk Regional Clinical Hospital, Dnipro, Ukraine. From those 163 patients with the diagnosis of HTN were selected. COVID-19 was confirmed using a nasopharyngeal polymerase chain reaction swab [8]. Pneumonia was diagnosed using chest computed tomography or chest X-ray investigation [8]. All the patients in the study had a non-severe course of COVID-19, did not require treatment in the intensive care unit and were discharged to outpatient healthcare facilities. The patients in the study received short-term oxygen support via cannula. The patients were diagnosed and treated according to national guidelines [8, 9]. The patients were distributed into two groups according to the control of HTN: BP<140/90 mmHg (n=94) and BP≥140/90 mmHg (n=69).

The diagnosis of HTN was confirmed from the medical records of the patient or if the patient had a history of treatment with antihypertensive drugs. Control of HTN was assessed according to 2018 European Society of Cardiology Guidelines on treatment of hypertension [10]. Discontinuation of antihypertensive drugs was not recommended to hospitalised patients. HTN was considered as controlled in patients with BP<140 mmHg before the admission to the hospital. The information about the control of BP was taken from the patients' medical records. Obesity was diagnosed in patients with body mass index above 25 kg/m^2[11].

Laboratory assessment included: clinical blood count; blood glucose, creatinine, albumin, bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, chloride, sodium, potassium, C-reactive protein (CRP), ferritin measurement; coagulation tests (activated partial thromboplastin time (APTT), international normalized ratio (INR) and fibrinogen); urine test [8, 9]. Glomerular filtration rate (GFR) was calculated using CKD-EPI equation [12]. Intake of non-steroid anti-inflammatory drugs (NSAIDs) before the admission to the hospital (acetylsalicylic acid, paracetamol or ibuprofen) was assessed.

The study was approved by the Ethical Committee of Dnipro State Medical University (protocol No. 9 from 24.05.2023) and was conducted in accordance with patients' written permission on the data collection and processing and in compliance with the Helsinki Declaration "Ethical principles for medical research involving human subjects" and "Universal Declaration on Bioethics and Human Rights (UNESCO)".

The data were processed and analysed using LibreOffice and R (version 4.2.1) software [13, 14]. The type of numeric data distribution was assessed using the Shapiro-Wilk test. As the majority of the numeric variables had non-parametric type of distribution, for their presentation median, 1st and 3rd quartiles (Me [1st;3rd quartile]) were used. Comparison of numeric variables between groups was performed using the U-Mann-Whitney test. Categorical data were presented as n (%) and were compared using Chi-squared test. Missing data were omitted from calculations. The level of p-value <0.05 was chosen for the confirmation of statistical hypotheses.

RESULTS AND DISCUSSION

Gender distribution of the patients in the study was almost equal (Table 1). 52.8% of the patients in the study were obese. Less than 25% of patients had massive COVID-19-related lung injury (>50%) or significant decrease of SpO_2 (<92%) at the moment of admission to the hospital. The group of patients with controlled HTN had higher prevalence of females (p=0.03), 10 years higher median of age (p<0.01) and lower frequency of obesity (p=0.04). The patients from both groups spent the same time in the hospital, but the patients with controlled HTN were hospitalised earlier (p=0.01). NSAIDs were used more frequently by the patients with uncontrolled HTN (p=0.02). The patients with controlled HTN had lower median of pulmonary injury (p=0.04) and lower frequency of SpO2<92% (p=0.02).

Table 1

Clinical and instrumental data of the patients with HTN subdivided by control of blood pressure

Parameter	HTN (n=163)	Uncontrolled HTN (BP≥140/90) (n=69)	Controlled HTN (BP<140/90) (n=94)	p-value
Females, n (%)	80 (49.1)	27 (39.1)	53 (56.4)	0.03
Males, n (%)	83 (50.9)	42 (60.9)	41 (43.6)	
Age, years	65.0 [57.5;73.0]	60.0 [53.0;69.0]	70.0 [59.0;74.0]	<0.01
Obese, n (%)	38 (52.8)	19 (67.9)	19 (43.2)	0.04
SBP, mmHg	130.0 [120.0;142.0]	150.0 [140.0;160.0]	120.0 [120.0;130.0]	<0.01
DBP, mmHg	80.0 [80.0; 89.0]	90.0 [80.0;100.0]	80.0 [80.0;80.0]	<0.01
Days of disease before hospitalisation	10.0 [7.0;11.0]	10.0 [8.5;11.0]	9.0 [6.0;11.0]	0.01
Days spent in hospital	10.0 [8.0;13.0]	10.0 [8.0;13.0]	10.0 [8.0;13.0]	0.37
NSAIDs usage, n (%)	184 (70.8)	67 (80.7)	117 (66.1)	0.02
Lung injury, %	18.0 [10.0;30.0]	30.0 [15.0;38.8]	15.0 [10.0;25.0]	0.04
Lung injury>50%, n (%)	16 (13.6)	5 (11.4)	11 (14.9)	0.59
SpO_2, %	95.0 [92.5;97.0]	95.0 [90.0;97.0]	95.0 [93.0;97.0]	0.47
SpO_2<92%, n (%)	41 (25.2)	24 (34.8)	17 (18.1)	0.02

Note: p-value corresponds to the comparison between the patients with uncontrolled and controlled HTN.

Median blood glucose of the patients was 6.6 [5.9;8.0] and exceeded the upper-normal threshold. Medians of ALT and AST were close to the upper-normal thresholds (Table 2). 31.8% of the patients had GFR lower than 60 ml/min and 33.8% of patients had proteinuria.

Table 2

Routine blood and urine tests subdivided by blood pressure control

Parameter	HTN (n=163)	Uncontrolled HTN (BP≥140/90) (n=69)	Controlled HTN (BP<140/90) (n=94)	p-value
Leukocytes, 10^{-9}/l	6.5 [4.5;9.6]	5.3 [4.5;8.8]	7.9 [4.6;9.6]	0.21
Erythrocytes, 10^{-12}/l	4.8 [4.3;5.1]	4.8 [4.4;5.1]	4.8 [4.1;5.1]	0.16
Hb, g/l	136.0 [124.0;152.0]	140.0 [124.0;150.0]	135.0 [124.0;152.0]	0.93
Anemia, n (%)	34 (22.1)	13 (18.8)	21 (24.7)	0.38
Platelets, 10^{-9}/l	227.0 [148.0;293.8]	248.0 [168.0;358.0]	218.0 [145.0;268.0]	0.01
Proteinuria, n (%)	45 (33.8)	13 (22.8)	32 (42.1)	0.02

Note: p-value corresponds to the comparison between the patients with uncontrolled and controlled HTN.

Medians of CRP, ferritin and fibrinogen were far above upper-normal limits. In the group with controlled HTN lower median of platelets (p=0.01), GFR (p<0.01), and chloride (p<0.01), and higher median of bilirubin (p=0.03), ALT (p=0.02) (Table 3) was detected. Despite the differences in the levels of chloride, bilirubin and ALT between groups, their levels were within normal ranges. Proteinuria was detected significantly more frequently in the patients with controlled HTN (p=0.02).

Table 3

Blood chemistry and electrolytes subdivided by blood pressure control

Parameter	HTN (n=163)	Uncontrolled HTN (BP≥140/90) (n=69)	Controlled HTN (BP<140/90) (n=94)	p-value
Glucose, mmol/l	6.6 [5.9;8.0]	6.6 [6.2;7.7]	6.5 [5.7;8.1]	0.13
Albumin, g/l	39.0 [36.0;41.6]	38.8 [36.3;41.6]	39.1 [36.0;40.4]	0.37
Bilirubin, mcmol/l	9.1 [6.1;10.3]	8.5 [5.5;10.0]	9.2 [6.3;10.9]	0.03
ALT, IU/l	27.1 [19.7;43.8]	23.2 [17.7;42.2]	32.7 [20.2;45.7]	0.02
AST, IU/l	31.7 [27.1;41.9]	30.6 [26.4;33.9]	32.3 [27.6;44.8]	0.09
Cholesterol, mmol/l	3.2 [2.8;3.4]	3.1 [2.8;3.4]	3.2 [3.2;4.2]	0.42
GFR, ml/min	66.8 [55.0;89.0]	82.0 [61.8;97.2]	62.0 [49.5;76.6]	<0.01
GFR<60 ml/min, n (%)	49 (31.8)	13 (20.3)	36 (40.0)	0.01
CRP, mg/dl	50.8 [28.1;95.5]	41.9 [33.5;75.1]	60.1 [8.3;126.5]	0.90
Ferritin, mcg/l	435.3 [347.6;733.1]	442.6 [316.2;733.1]	405.8 [349.6;721.0]	0.42
APTT, sec	27.5 [24.8;31.4]	29.0 [24.8;31.8]	25.5 [24.8;31.3]	0.18
INR	1.1 [1.0;1.1]	1.0 [1.0;1.2]	1.1 [1.0;1.1]	0.27
Fibrinogen, g//l	6.0 [4.9;6.7]	5.5 [5.0;6.4]	6.2 [4.9;6.7]	0.46
Chloride, mmol/l	98.7 [98.4;102.0]	102.0 [102.0;104.7]	98.4 [95.0;99.9]	<0.01
Sodium, mEq/l	139.0 [137.5;140.0]	139.0 [139.0;142.0]	138.0 [134.5;139.0]	0.09
Potassium, mmol/l	4.7 [4.6;5.1]	4.9 [4.6;5.3]	4.7 [4.4;5.0]	0.22

Note: p-value corresponds to the comparison between the patients with uncontrolled and controlled HTN.

In the presented study the patients with uncontrolled BP before the admission to the hospital had a slightly higher percent of pulmonary injury and percent of patients with decreased blood saturation, but also higher frequency of GFR<60 ml/min and proteinuria.

Uncontrolled BP deteriorates the course of COVID-19, probably via hypertension-mediated organ damage and vascular injury [1]. Results of our study partially confirm this idea. Despite being older and having a higher percent of patients with renal pathology, the patients with controlled BP had more benign pulmonary injury (Table 3). Females who suffer from non-severe forms of COVID-19 (like in the present study) have better prognosis of survival than males [15]. Higher frequency of females also may explain a more benign course of the disease in the group of the patients with controlled HTN. The patients with uncontrolled BP were more frequently diagnosed with obesity that could explain higher pulmonary injury percentage and lower saturation in the group [16].

In the present study the patients with controlled HTN had less severe course of COVID-19 in terms of percent of pulmonary injury and saturation, despite more advanced age and worse renal function. These findings reconfirm the importance of BP control in patients with COVID-19, as uncontrolled HTN may contribute to COVID-related vasculopathy and organ damage [1]. Nevertheless, a significant difference in sex and age distribution between groups was likely to influence the results of the study and will need further investigation.

Higher proportion of patients with proteinuria and GFR<60 ml/min in the group of patients with controlled BP is unexpected, as HTN is recognised as a common sign of nephropathy [17]. However, in case of COVID-19 it might be related to the direct renal damage by virus (coronavirus associated nephropathy – COVAN) [18,19]. It may be hypothesised that the normalisation of BP is developed via the loss of electrolytes by kidneys with the subsequent dehydration. This idea is indirectly confirmed by the slightly lower levels of chlorides (p<0.01), sodium (p=0.09) and potassium (non-significant) in the patients with controlled BP. Thus, it may be

recommended to monitor urine tests and blood creatinine in patients with COVID-19 and HTN, especially in case of controlled BP. This recommendation might be of a greater importance, given that the virus mutation might result in increased tropism to kidneys, which has already been observed in the study by Portoles et al. [20].

CONCLUSIONS

1. In the presented study blood pressure below 140/90 mmHg before the admission to the hospital was associated with a lower degree of pulmonary injury but with the higher frequency of nephropathy signs.
2. Urine test and blood creatinine monitoring might be beneficial for the patients with COVID-19 and hypertension.

Contributors:

Kuryata O.V. – conceptualization, methodology, data curation, writing – original draft, writing – review & editing;

Frolova Ye.O. – data curation, writing – review & editing;

Stadnyk O.I. – data curation, writing – review & editing;

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