Arterial Hypertension in Patients with COVID-19 - Neural Network Model

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ABSTRACT

Background: Angiotensin-converting enzyme 2 (ACE2) is not only an enzyme but also a functional receptor on cell surfaces through which Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2). The exact mechanism by which arterial hypertension (particularly regulated) could affect the presentation and outcome of Coronavirus disease-19 (COVID-19) has not been fully elucidated. Objective: The aim of this study was to analyze the parameters of patients with verified COVID-19 and existing arterial hypertension at the time of hospital admission and to develop neural network model. Methods: The research had a cross-sectional descriptive and analytical character, and included patients (n=634) who were hospitalized in the General Hospital “Prim. dr. Abdulah Nakas” and Sarajevo, Bosnia and Herzegovina, in the period from 01 Sep 2020 to 01 May 2021. From the hospital information system, which is used in everyday clinical work, laboratory parameters at admission were verified, along with demographic data, the comorbidities, while the outcome (recovery, death) was recorded thirty days after the admission. Results: Out of the total number, in 314 patients (200 males), arterial hypertension was verified, out of which, 56 (17.83%) patients died. Patients were divided into two groups, according to outcome, i.e., whether they survived COVID-19 infection or not. A significant difference in age (p = 0.00), erythrocyte count (p = 0.03), haemoglobin (p = 0.05), hematocrit (p = 0.03), platelets count (p = 0.00), leukocytes (p = 0.01), neutrophils (p = 0.00), lymphocytes (p = 0.00), monocytes (p = 0.00), basophils (p = 0.00), eosinophils (p = 0.00), C-reactive protein (p = 0.00) and D-dimer (p = 0.01) was noted. When patients who died and had hypertension were compared with those who died and did not have hypertension (n = 15), out of all the analyzed parameters, the only significant difference was established in the patient’s age (p = 0.00). In case when patients with hypertension who died were compared to patients with hypertension and diabetes mellitus who died no significant differences were found between features. Conclusion: Patients with hypertension and COVID-19 who died were older, had higher values of erythrocytes, hemoglobin, hematocrit, leukocytes, neutrophils, CRP and D-dimer, and lower values of platelets, lymphocytes, monocytes, basophils and eosinophils count at admission. Compared to deaths without hypertension, the only difference that was established was that patients with hypertension were older.

Keywords: Coronavirus, Blood Pressure, Mortality, Hypothesis Testing, Neural Network.

1. INTRODUCTION

Arterial hypertension (AH) is defined as measured values of systolic blood pressure ≥140 mmHg and/or values of diastolic blood pressure ≥90 mmHg in the office, in a sitting position (1).

Angiotensin-converting enzyme 2 (ACE2) has a fundamental role in local and systemic haemodynamics, as its main effect is to lower blood pressure, and regulate the angiotensin-converting enzyme (ACE) action by reducing the amount of angiotensin II and increasing angiotensin (2). Angiotensin-converting enzyme 2 (ACE2) is not only an enzyme but also a functional receptor on cell surfaces through which Severe acute respiratory syndrome coronavirus 2...
(SARS-CoV2) enters the host cells and is highly expressed in the heart, kidneys, and lungs and shed into the plasma. ACE2 is a key regulator of the renin–angiotensin–aldosterone system (2). The exact mechanism by which arterial hypertension (particularly regulated) could affect the presentation and outcome of Coronavirus disease-19 (COVID-19) has not been fully elucidated (3). Potential ways in which such a connection could be interpreted is imbalanced or impaired regulation of the renin-angiotensin-aldosterone axis and changes in the immune response that may be caused by arterial hypertension (2, 3). Also, patients with arterial hypertension may have an increased risk for malignant cardiac arrhythmias due to underlying undetected structural heart disease, especially in the context of more severe forms of infection and hypoxemia as triggers of malignant arrhythmia (3). In patients with unregulated hypertension, this risk should certainly be even higher (3). It is thought that due to its ability to bind to ACE2, the virus can induce myocardial injury through hypoxia, disrupt microvascular architecture, and increase the systemic inflammatory response (4). The question is what factors could have an effect on the outcome, in the earliest stage of acute infection with SARS COV-2, or whether they could help the doctor at the level of family medicine, based on the existence of comorbidities, decide which patient to refer to hospital, and try to avoid lethal outcome through controlled surveillance. The question is whether arterial hypotension represents significant comorbidity in patients with SARS-CoV2 infection.

2. OBJECTIVE

The aim of this study was to analyze the parameters of patients with verified COVID-19 and existing arterial hypertension at the time of hospital admission and to develop neural network model.

3. METHODS

Patients and study design

The research had cross-sectional, descriptive and analytical character, and included patients (n=634) who were hospitalized in the General Hospital “Prim. dr. Abdulah Nakas” in Sarajevo, Bosnia and Herzegovina, in the period from 01 Sep 2020 to 01 May 2021.

Methods

From the hospital information system, which is used in everyday clinical work, laboratory parameters at admission were verified, along with demographic data, the comorbidities, while the outcome (recovery, death) was recorded after thirty days of admission. Criteria for inclusion in the study were: patients who were real time polymerase chain reaction (PCR) tested positive for SARS-COV2 (verified COVID-19), who has peripheral saturation higher than 88%, older than 18 years, and patients who had documented values of complete blood cell, differential blood cell, C-reactive protein (CRP) and D dimer values on admission. Reference ranges for parameters were: erythrocytes 4.34 - 5.72 x10¹²/L males and 3.86 - 5.08 x10¹²/L females, leukocytes 3.4 - 9.7 x10⁹/L for males and females, haemoglobin 137 - 175 g/L males and 119-157 g/L females, hematocrit 0.41 - 0.53 % males and 0.35 - 0.47 % females, platelets 158-424 x10⁹/L for males and females, Neutrophil granulocytes 44-72%, lymphocytes 20-46 %, monocytes 4-8 %, basophil granulocytes 0-1 %, eosinophil granulocytes 2-4 %, CRP up to 5.0 mg/L, D-dimer up to 804 μg/L. The exclusion criteria were met in case if the patient had incomplete documentation. After analysis of data from the hospital database of all hospitalized patients, arterial hypertension was verified in 314 patients and they were included in the analysis.

Ethical approval was obtained from the Ethical Committee of General Hospital “Prim. dr. Abdulah Nakas”, Sarajevo, Bosnia and Herzegovina. Patients were assigned

| Comorbidity                      | Total number | Survivors | Death cases |
|----------------------------------|--------------|-----------|-------------|
| Hypertension                     | 314          | 258       | 56          |
| Diabetes mellitus                | 130          | 105       | 25          |
| Diabetes mellitus & Hypertension | 116          | 93        | 23          |

Table 1. Patients with hypertension and diabetes mellitus

| Feature                  | death cases (n=64) | survivors (n=258) |
|--------------------------|--------------------|-------------------|
| Age (years)              | 72.11              | 67.39             |
| Erythrocytes             | 4.58               | 4.39              |
| Hemoglobin               | 135.036            | 130.189           |
| Hematocrit               | 0.401              | 0.387             |
| Thrombocytes             | 212.94             | 303.97            |
| Leukocytes               | 10.5875            | 9.28              |
| Neutrophil granulocytes  | 88.21              | 78.09             |
| Lymphocytes              | 7.48               | 14.72             |
| Monocytes                | 3.9                | 6.38              |
| Basophil granulocytes    | 0.166              | 0.248             |
| Eosinophil granulocytes  | 0.239              | 0.548             |
| C-reactive protein       | 101.24             | 47.39             |
| D-dimer                  | 7396.38            | 4002.167          |

Table 2. Patients with hypertension who died versus patients with hypertension who survived

| Parameters                | death cases with hypertension; n=56 | death cases without hypertension; n=15 |
|---------------------------|-------------------------------------|---------------------------------------|
| Age                       | 72.11                               | 63.73                                 |
| Erythrocytes              | 4.58                                | 4.86                                  |
| Hemoglobin                | 135.036                             | 143.73                                |
| Hematocrit                | 0.401                               | 0.425                                 |
| Thrombocytes              | 212.94                              | 244.93                                |
| Leukocytes                | 10.5875                             | 12.926                                |
| Neutrophil granulocytes   | 88.21                               | 88.49                                 |
| Lymphocytes               | 7.48                                | 7.34                                  |
| Monocytes                 | 3.9                                 | 3.726                                 |
| Basophil granulocytes     | 0.166                               | 0.153                                 |
| Eosinophil granulocytes   | 0.2339                              | 0.286                                 |
| C-reactive protein        | 101.24                              | 83.82                                 |
| D-dimer                   | 7396.38                             | 12860                                 |

Table 3. Patients with hypertension who died versus patients without hypertension who died
into four different categories as follows: patients with hypertension and diabetes mellitus who died and patients with hypertension and diabetes mellitus who recovered, patients without hypertension who died and patients with hypertension and diabetes mellitus who died.

### Statistical analysis

Formal hypothesis test was performed, also known as significance test, to compare input features mean values of above-mentioned categories to see whether there was statistical evidence to reject or do not reject the null hypothesis and to make a correct decision. F-test was used to check if two variances of input features values were equal or not to make a decision whether to use test with equal or unequal variances. The null hypothesis, and alternative hypothesis, were defined and one-tail directional tests were used in this research. The level of significance for this research was chosen to be $\alpha=0.05$. Decision whether to reject or not to reject null hypothesis, was made comparing calculated p-value and level of significance $\alpha$.

### Neural network

Neural network model was developed for prediction of outcomes of COVID-19 hospitalized patients with hypertension, diabetes mellitus and patients with both of these comorbidities. Python 3.8 in Jupyter Notebook with Tensorflow 2.4.0 and Keras were used to develop neural network model. The dataset consisted of 328 samples, where one sample means one patient with all laboratory findings, demographics including hypertension and diabetes mellitus as comorbidities used as neural network inputs and the outcome of the hospital treatment used as neural network output. Neural network structure consists of 16 neurons in input layers, one hidden layer with 50 neurons and one neuron in output layer. In this model, sigmoid activation function was used with Adam optimizer, while data were normalized between 0 and 1. In this research confusion matrix was created and accuracy, precision, sensitivity and specificity were calculated.

| Parameters | death cases with hypertension (n=56) | death cases with hypertension and diabetes mellitus; (n=23) |
|------------|-----------------------------------|----------------------------------------------------------|
| Age        | 72.11                             | 72.87                                                   | 0.3732       |
| Erythrocytes | 4.58                              | 4.78                                                    | 0.1221       |
| Hemoglobin | 135.036                           | 136.65                                                  | 0.3789       |
| Hematocrit | 0.401                             | 0.409                                                   | 0.2892       |
| Thrombocytes | 212.94                           | 192.61                                                  | 0.1395       |
| Leukocytes | 10.5875                           | 10.49                                                   | 0.4645       |
| Neutrophil granulocytes | 88.21                           | 87.39                                                   | 0.288        |
| Lymphocytes | 7.48                              | 7.64                                                    | 0.4417       |
| Monocytes | 3.9                               | 4.6                                                     | 0.1021       |
| Basophil granulocytes | 0.166                           | 0.165                                                   | 0.4844       |
| Eosinophil granulocytes | 0.2339                          | 0.1957                                                  | 0.3840       |
| C-reactive protein | 101.24                          | 99.43                                                   | 0.4721       |
| D-dimer | 7396.38                           | 4133.35                                                 | 0.0686       |

### RESULTS

Out of the total number of 634 patients, the number of patients with verified arterial hypertension was 314 (200 males), and 320 patients didn’t have arterial hypertension. In patients who had arterial hypertension 258 of them survived and 56 of them died, while out of 320 patients who didn’t have hypertension 15 of them died. Out of 130 patients who had diabetes mellitus, 116 of them had arterial hypertension as well and 23 of them died (Table 1). A significant difference in age ($p=0.00$), erythrocyte values ($p=0.03$), hematocrit ($p=0.03$), platelet count ($p=0.00$), leukocytes ($p=0.01$), neutrophils ($p=0.00$), lymphocytes ($p=0.00$), monocytes ($p=0.00$), basophils ($p=0.00$), eosinophils ($p=0.00$), CRP ($p=0.00$) and D-dimer ($p=0.01$) was noted (Table 2). The patient’s age was the only parameter which showed a significant difference among patients with hypertension who recovered and who had a lethal outcome ($p=0.00288$) (Table 3). There was no significant difference among patients with hypertension who had lethal outcome, and patients with both hypertension and diabetes mellitus who had a lethal outcome (Table 4).

Confusion matrix is presented in Table 5. From Table 5 it can be seen that true positive (TP) value is 261 and true negative (TN) value is 31, which means that neural network predicted correctly the outcome for 292 out of 328 patients, which means that the prediction accuracy is high with the value of 89.02%. False negative (FN) value is 27, while false positive (FP) value is 9. Based on TP, TN, FN and FP values, besides accuracy, precision, sensitivity and specificity were calculated. Precision and sensitivity are with high values of 96.67% and 90.63% respectively, while specificity has value of 77.50%.

### DISCUSSION

Arterial hypertension presents a medical condition that significantly increases the risk of heart, brain, kidney, and other diseases, and it is estimated that 1.28 billion adults aged 30-79 worldwide have hypertension, with the majority (two-thirds) living in a low- and middle-income countries. (5). It is estimated that 46% of adults with hypertension are unaware of their condition (5). Less than half of adults (42%) with hypertension are diagnosed and treated (5). Approximately 1 in 5 adults (21%) with hypertension has regulated blood pressure values (5). All of the above ranked hypertension as the most common companion of COVID-19 infection.

Patients with hypertension and COVID-19 who died were older, had higher values of erythrocytes, haemoglobin, hematocrit, leukocytes, neutrophils, CRP and D-dimer, and lower values of platelets, lymphocytes, monocytes, basophils and eosinophils count at admission. Compared to deaths without hypertension, the only difference was that patients with hypertension were older. Analyzing diabetes mellitus as comorbidity with arterial hypertension, there was also no significant dif-
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treatment also in patients with COVID-19.

- **Patient’s Consent Form:** The authors certify that they have obtained all appropriate patient consent forms.
- **Author’s contribution:** E.B., F.K., A.G. and M.P. gave substantial contribution to the conception or design of the work and in the acquisition, analysis and interpretation of data for the work. A.M., A.P.A.B. and M.P. had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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