Retrospective evaluation of association between hypertension and clinical, and physical findings of covid-19 infected patients

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Abstract

Background

The sudden outbreak of coronavirus disease 2019 (covid-19), which originated from severe acute respiratory syndrome coronavirus 2 (SARS-COV2) infection, has recently become an international public health emergency. The aim of this study was to assess the clinical symptoms and physical findings in both hypertensive and non-hypertensive patients infected with covid-19.

Methods

Retrospective observational study with diagnosis of corona-induced pneumonia by laboratory-confirmed test was conducted on 280 consecutive unselected patients. The demographics, laboratory, and clinical findings data were extracted from the hospital registry database.

Results

Of our two hundred and eighty patients in the study, there were 70 men (47%) and the male-female ratio was 1.17:1 and 138 (50%) were older than 60 years (mean = 67.75), and also 50 in-hospital deaths occurred (mortality rate, 17%). totally 19(6.9%) were taking tobacco, opioid, and weed. There were no significant differences in the percentages of fever, cough, sputum production, gastrointestinal symptoms, muscle ache, and headache in the both hypertensive and non-hypertensive groups. The prevalence of underlying diseases was significantly higher in older patients in comparison with younger ones (p-value = 0 < 0.05), Clinical worsening was higher in patients with hypertension relative to patients with average blood pressure (P-value = 0 < 0.05).

Conclusion

The most common comorbidities in several reports was hypertension. People with high blood pressure are also slightly more likely to experience poor prognosis and even higher rate of mortality.in the other hand, hypertension may have associated with higher risk of severe or fatal COVID-19 disease.

Introduction

Coronavirus (COVID-19) was identified in Wuhan, China in December 2019 as an infectious disease with uncertain etiology characterized by acute pneumonia(1). the microorganism that cause this condition, has been established as a new beta-coronavirus RNA virus, called coronavirus 2 (SARS-CoV-2) severe acute respiratory syndrome(2). Coronavirus belongs to a family of viruses which can cause various symptoms such as pneumonia, fever, trouble breathing and inflammation of the lungs(3). These viruses are widespread worldwide in animals but very few examples have been reported to have impaction on

humans. The term 2019 novel coronavirus was used by the World Health Organization (WHO) on 29 December 2019 to attribute to a coronavirus that affected the lower respiratory tract in patients with pneumonia in Wuhan, China(4–6).

This infectious disease is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), (7) which enters cells through the angiotensin-converting enzyme 2 (ACE2) receptor and is therefore transmitted to humans(8). The role of this enzyme is to catalyze the conversion of angiotensin II to angiotensin 1–7, a peptide that contrasts with angiotensin II's pro-inflammatory, pro-oxidative, vasoconstrictive, and fibrotic properties (9).

Because of the interplay between SARS-CoV-2 and ACE2, it was proposed that hypertension may be involved in the pathogenesis of COVID-19 either by playing a direct role as a pre-existing clinical indicator of severity of disease or by leading to late worsening of disease with acute respiratory distress syndrome (ARDS), chronic inflammatory response syndrome (SARS) and/or multi-organ failure (MOF) (10).

There is currently no appropriate SARS-CoV-2 vaccine or antiviral medication available. Furthermore, the rate of case-fatality (i.e., COVID-19-related mortality) varies widely among epicenters and counties, also at world level. The detection of risk factors associated with disease severity and poor outcome among COVID-19 patients is urgently required to lower the overall mortality rate. COVID-19 patients with a comorbid illness could also have an elevated risk of worsening, and will therefore be referred to a specified unit for close observation in accordance with the screening and triage recommendations of the WHO (11).

While shown in other research, people with hypertension and diabetes had not been found to be more susceptible to 2019-nCoV infections. In people infected with the virus, the prevalence of hypertension and diabetes is about the same as in the general population, and even slightly lower (12). In most studies, scientists have investigated risk factors in several cases for assessing the prognosis and clinical course of hospitalized patients with covid-19 infection. Although, just in the fewer surveys, the differences in clinical characteristics of patients in the poor prognosis group analysis was done (13). Herein, we assessed the clinical symptoms and physical findings in both hypertensive and non-hypertensive patients infected with covid-19 (Fig. 1).

Method

Study design and participants:

A retrospective observational study of consecutive unselected patients admitted to Shahid beheshti Hospital, Kashan between January 2019 and November 2020 with a diagnosis of Corona-induced pneumonia was carried out. The study was approved by the Kashan Research Ethics Committee. Corona-induced pneumonia was diagnosed using the following criteria recommended by WHO interim guidance. In this case control survey of which collected data from 280 hospitalized male and female patients with Covid-19, under the coordination of the Kashan University of Medical Sciences for Research Committee

which mandated the reporting of clinical findings information from individual designated hospital admitted patients with Covid-19. Our sampling method in this study was simple random sampling. After careful medical folder review, we compiled the clinical data of laboratory-confirmed hospitalized cases from Shahid Beheshti hospital. The diagnosis of Covid-19 was made based on the clinical manifestation and para clinical findings according to WHO interim guidance. All clinical profiles were centrally provided by the respiratory and infectious disease specialist and also their interns were dispatched. Inclusion Criteria as determined were diagnosis of patients with respiratory symptoms who has been registered in the file based on clinical and laboratory symptoms and pulmonary CT scan by a coronavirus Pneumonia Infectious Diseases Specialist that has been admitted to Beheshti Hospital during a pandemic.

Case group were people with high blood pressure (recorded in their history sheet) who were diagnosed with covid-19 pneumonia at Beheshti Hospital in 2019-2020 and their information is fully recorded in the file. Control group were People with covid-19 pneumonia who had been admitted to Beheshti Hospital in 2019-2020 and their information has been fully recorded in the file, but they have no history of blood pressure at the time of admission and also hospitalization, and no antihypertensive drug was being used. Participants who did not meet the inclusion criteria were excluded from this study. This study was conducted with the Declaration of Helsinki and was approved by the Vice Chancellor for Research of Kashan University of Medical Sciences and obtaining a code of ethics (1399.054).

Study protocol

Covid-19 patients admitted to hospital with laboratory-confirmed diagnosis. After clinical cessation of symptoms, including fever, cough, and dyspnea, throat-swab specimens were collected for SARS-CoV-2 PCR re-examination every other day but only qualitative data were accessible.

For all patients admitted with corona-induced pneumonia, a proforma was completed on admission that included patient observations (blood pressure, pulse pressure, respiratory rate, and temperature), Routine blood examinations were complete blood count, coagulation profile, serum biochemical tests (including renal and liver function, creatine kinase, lactate dehydrogenase, and electrolytes), and myocardial enzymes. All observations were taken in the emergency department within 4 hours of arrival. On admission, patients were risk assessed using Pneumonia Severity Index score(14). All patients received standard antibiotic therapy in accordance to the NICE guideline (15).

After the ethic code was obtained, referring to the Beheshti Hospital Medical Records Unit, the files of patients with coronavirus-induced pneumonia were reviewed and the patients who had met the inclusion criteria to join the study were listed (i.e. those whose blood pressure was mentioned normal on the admission time in their history sheet, does not have history of previous hypertension and not taking antihypertensive drugs and also those high blood pressure or with history of taking antihypertensive drugs). The discharge criteria were absence of fever for at least 3 days, significant change in both chest CT lungs, clinical respiratory symptom remission, and two negative SARS-CoV-2 RNA throat-swab samples collected at least 24 hours apart.

Definitions:

Fever has been described as a minimum axillary temperature of 37·3 ° C. Classification of blood pressure into 4 categories: BP less than 120/80 mm Hg; considered normal. Those with Systolic pressure of less than 80 and 120-129 or diastolic; known as elevated. And when there was systolic pressure between130-139 or diastolic pressure between80-89; classified as stage 1 and systolic pressure at least 140 or diastolic pressure at least 90 mm Hg; considered stage 2. The 2016 Third International Consensus Classification for Sepsis and Septic Shock identified sepsis and septic shock (16).

Secondary infection was detected when patients had clinical symptoms or signs of pneumonia or bacteremia, and a positive culture of a new pathogen was collected from lower respiratory tract specimens (qualified sputum, endotracheal aspiration, or Broncho alveolar lavage fluid) or blood samples following admission (16).Ventilator-associated pneumonia was confirmed according to hospital-acquired and ventilator-associated pneumonia care recommendation(17). Acute kidney injury was diagnosed in accordance with the KDIGO guidelines for clinical practice (18) and acute respiratory distress syndrome (ARDS) was diagnosed in accordance with the Berlin Definition(19). Acute heart injury was detected if serum levels of cardiac biomarkers (e.g. elevated cardiac troponin I) were above the upper reference limit of the 99th percentile, or if new abnormalities were observed in electrocardiography and echocardiography;(16) The disease severity of COVID-19 was described in accordance with the Chinese COVID-19 management guideline (version 6.0)(20). Coagulopathy was characterized as a 3-second extension of pro thrombin time or a 5-second prolongation of activated partial thromboplastin time. Hypoproteinemia is characterized as a blood albumin of less than 25 g / L. Exposure history was described as exposure to people with reported SARS-CoV-2 infections or to the Wuhan seafood market.

S**tatistical analysis**

The statistical analysis was conducted using SPSS version 23. We used means and standard deviation for normal distribution variables and median and inter quartile range (IQR) for otherwise. Categorical variables were expressed as frequency (percentage). To compare the qualitative variables, Chi-Square test or Fisher Exact test and for quantitative variables, independent t-test were used.

Results

Demographic and epidemiological characteristics:

This case-control study enrolled 280 hospitalized patients with confirmed COVID-19, in Beheshti hospital from 2019 to 2020 in Kashan province. The median age was 59.38 years and 149(53%) were men. There were 50 in-hospital deaths (mortality rate, 17%). Among the 280 patients, there were 137 patients with hypertension (50.001%). The characteristics and clinical findings and outcomes of these patients are summarized in Tables concerning they were not using antihypertensive drugs (Table 1).

Table 1
Demographics and characteristics of COVID-19 patients

	Total patients (N = 280)			
Variable	**All cases N (%)**	**High blood pressure (%)**	**Non-high blood pressure (%)**	**p-value**
Age	276(100)	67.75 **± 14.96**	51.01 **± 19.22**	< 0.01
Gender	276(100)			0.27
Male	149(53)	70(47)	79(53)	
Female	127(47)	68(53.5)	59(46.5)	
Hospitalization-term	273(100)	5.65 **± 3.65**	6.25 **± 4.26**	
Lung involvement based on CT result	111(40.8)	53(39.3)	58(42.3)	0.60
Smoker	10(3.6)	7(5.1)	3(2.2)	0.19
Opioid	5(1.8)	1(0.7)	4(2.9)	0.17
Tobacco	4(1.5)	0(0)	4(2.9)	0.04
Underlying disease				
Ischemic heart disease	50(18.1)	39(28.3)	11(8)	< 0.01
Diabetes	81(29.3)	55(39.9)	26(18.8)	
Chronic kidney disease	15(5.4)	11(8)	4(2.9)	< 0.01
others	81(29.3)	53(38.4)	28(20.3)	0.06
				0.06
Outcome				
Death	48(17.4)	30(21.7)	18(13)	0.05

Patients with hypertension were older and had a greater prevalence of chronic diseases; they also had more severe manifestations of COVID-19, including higher pulse rate (Fig. 1). Hospitalization-term, and also were greater in-hospital mortality. The patients with hypertension were further analyzed and form the basis of this article. There were 70 men (47%) and the male-female ratio was 1.17:1 and 138 (50%) were older than 60 years (mean = 67.75), and a total of 19(6.9%) were taking tobacco, opioid, and weed. In-hospital mortality in this group was 21.8% (N = 30). There were no significant differences in the percentages of fever, cough, sputum production, gastrointestinal symptoms, muscle ache, and headache in the both groups (Table 2).

Table 2
Clinical characteristics of patients with COVID-19 in Shahid beheshti hospital, Kashan.

Total patients (N = 280)				
Characteristic	All cases (%)	High blood pressure	Non-high blood pressure	P-value
Fever	191(72.3)	96(72.7)	95(75)	0.89
Coughing	194(70.3)	97(70.3)	97(70.3)	1.00
Sore throat	29(10.5)	15(10.9)	14(10.1)	0.84
Headache	76(27.5)	34(24.6)	42(30.4)	0.32
Myalgia	148(53.6)	76(55.1)	72(52.2)	0.62
Dyspnea	183(66.5)	87(63.5)	96(69.6)	0.28
Sneezing	21(7.6)	10(7.2)	11(8)	0.82
Sputum	42(15.2)	21(15.2)	21(15.2)	1.00
Malesia	62(22.9)	37(27)	25(18.7)	0.10
Chilling	133(48.4)	67(48.6)	66(48.2)	0.95
Nausea and vomiting	91(33)	48(34.8)	43(31.2)	0.52
Diarrhea	28(10)	11(8)	16(11.6)	0.31

There were 137 patients with hypertension (50.001%). The characteristics and clinical outcomes of the patients with hypertension compared with those without hypertension are summarized in Table-2 in the Supplement. Patients with hypertension were older and had a greater prevalence of chronic diseases; they also had more severe manifestations of COVID-19, including higher pulse rate, hospitalization-term, and were greater in-hospital mortality. In brief, fever, cough, and dyspnea were the most common symptoms in both groups (Table 2).

We also analyzed the laboratory markers and also physical examination in both group, in table-3. Concerning infection-related markers, there was no significant difference in both ESR and SPO2% [1]between hypertensive and non-hypertensive COVID-19. (P-value = 0.078 and 0.232). The average body temperature of the group with high blood pressure was 37.462 and in rest of them was 37.671. On admission, more patients in the hypertensive group had an increased level of troponin (2545.86 vs 516.77) and a lower level of CPK (214.34 vs 314.26 in Mean). Furthermore, platelets level was higher in the hypertension group rather than the non-hypertension group (Mean: 187.06 vs 179.61).

There was no significant difference in both C reactive protein (CRP) and LDH between hypertensive and non-hypertensive patients with COVID-19 (p-value = 0.711 and 0.987) (Table 3). Illness severity was higher

in older patients. In other words, the prevalence of any coexisting medical condition was significantly higher in older patients compared to younger patients (p-value = 0 < 0.05), including the rate of hypertension. The rate of decreased respiratory, but not pulse respiratory, was significantly exceeded in patients with high blood pressure than in other group (p-value = 0.025). Clinical worsening was slightly higher in patients with hypertension relative to patients with average blood pressure. (P-value = 0 < 0.05) (Table 3).

Table 3

Physical examination and laboratory markers of patients with COVID-19.

	Total patients (N= 280)					
Variable	High blood pressure(N)	Non-high blood pressure(N)	Mean	SD	95% CI	P-value
Pulse rate	138	137	89.32	18.95	-4.95 , 5.53	0.91
Respiratory rate	130	131	20.02	11.86	-8.60 , -0.58	0.26
Temperature	138	137	37.46	0.81	-0.41 , 0.00	0.05
SPO2%[1]	132	127	89.63	9.42	-3.39 , 0.82	0.23
CRP[2]	119	124	43.32	36.34	-6.61 , 9.69	0.71
ESR[3]	123	119	42.11	32.58	-0.78 , 14.79	0.07
Leukocyte	136	135	6.64	3.23	-0.96 , 0.75	0.81
Lymphocyte	136	135	20.86	10.52	-2.77 , 2.30	0.85
Platelet	136	134	187.06	76.60	-10.18 , 25.07	0.40
LDH	94	90	755.44	432.17	-120.52 , 122.54	0.98
Troponin	89	82	2545.86	16899.25	-1740.01 , 1621.48	0.60
CPK	35	34	214.34	229.02	-316.35 , 116.50	0.45

[1] blood oxygen saturation levels

[2] *C-Reactive Protein*

[3] Erythrocyte sedimentation rate

Discussion

We reported here 280 hospitalized patients with clinical or laboratory-confirmed COVID-19. There were no significant clinical manifestation differences between the hypertensive and non-hypertensive group. The majority of patients presented with fever, cough, and dyspnea in this case control study. However, manifestations of the upper respiratory tract and gastrointestinal symptoms have been uncommon, indicating distinct viral tropism compared to severe acute respiratory coronavirus syndrome (SARS-CoV) and coronavirus syndrome of the Middle East (MERS-CoV)(21, 22). The common clinical manifestations of COVID-19 patients are fever, cough, and sputum.6 it may manifest as normal body temperature when the patient's immune response is low. Breath shortening or dyspnea indicates impaired lung function and loss of oxygen. Therefore, if the patient is observed to be in trouble breathing with no fever, the patient's health needs to be monitored for possible worsening (23).

Our findings show that male patients over the age of 65 and smoking may pose a higher risk of progressing to a serious or fatal condition and that comorbidities such as obesity, diabetes, cardiovascular disease or respiratory disease may also have a major impact on the prognosis of COVID-19.

Women are less vulnerable to viral infection than males, likely due to the protection of X chromosomes and sex hormones, which play an important role in both innate and adaptive immunity(24). At the same time, men thought to be associated with poor lifestyle behaviors such as smoking and underlying diseases. Therefore, most critical or fatal patients are male. As the body's immunity decreases with age, older patients are more likely to develop or even die of a critical illness. As a result, the patient is at higher risk of developing critical illness or death when the patient is male, over 65 years of age and smoking. Among those 280 patients in baseline isolation ward, 232 (82.6%) patients were discharged and 48 (17.4%) worsened. Those patients with poor prognosis were older male patients with more comorbidities, dyspnea, and lower counts of lymphocytes, and increased numbers of pulmonary lobes involvement from CT images of the chest. We have observed that patients with bad prognosis on admission often had elevated levels of CRP for further multivariate analysis of these risk factors, the major predictors of poor prognosis in COVID-19 patients were male sex, lymphopenia and obviously elevated CRP.

CRP is an acute-phase, downstream protein of the innate immune response(25). It is produced to activate the immune response, due to the increased synthesis of pro-inflammatory cytokines(26). Consequently, the serum CRP level has also been used as an inflammatory marker in the laboratory(25, 26). A range of studies suggested that CRP is a predictive factor for the progression of disease in patients diagnosed with MERS-CoV and H1N1(27, 28). They first stated in this analysis that CRP could also be the marker for COVID-19 progression.

When patients are combined with basic diseases such as diabetes and hypertension, the body is in a long-term state of discomfort and the immunity appears to be weak. In addition, the long-term history of diabetes and hypertension will damage the vascular structure, and the risk of developing into critical disease in infection is greater. Chronic heart disease patients are more likely to get infected because of their weakened heart function and low immunity. They are more likely to experience serious coronary problems when diagnosed with SARS-CoV-2, and to evolve into extreme diseases (23).

Coronavirus is a single-stranded, enveloped, non-segmented RNA virus(29). Six human coronaviruses have currently been identified. And the SARS-CoV-2 is identified as the seventh human coronavirus, isolated from the lower respiratory tract of pneumonia patients with unknown causes in Wuhan(30). SARS-CoV-2 attacks the alveolar epithelial cells through angiotensin-converting enzyme 2 (ACE2). ACE2 is the ACE of isozyme, expressed primarily in gastrointestinal, liver, test, lung and colon, and other organizations(31). ACE2's key function is to incise Ang II to produce Ang 1–7, which mediates the defensive effects of vasodilatation, anti-inflammatory and anti-proliferation, vascular smooth muscle contraction, cell proliferation, promotion of fibrosis and vascular inflammation(32–34). When SARS-CoV-2 binds to the ACE2 receptor on the surface of alveolar epithelial cells, mechanisms such as internalization, shedding, and viral replication down-regulate the expression of ACE2 in alveolar epithelial cells. Then the elevated accumulation of Ang II contributes to inflammatory response and exudation of neutrophils, macrophages and fibrins, resulting in loss of function of the pulmonary ventilation and difficulties in maintaining oxygenation(35). At the same time, viral infection triggers the imbalance between T-helper-1 and T-helper-2 responses which induces an inflammatory storm by increasing the levels of inflammatory factors such as interleukin-4, interleukin-10 and interleukin-6(36). Cytokines released by inflammatory storm in critical patients, inducing systemic immune dysfunction, which may be a major cause of multiple organ failure and even death (37).

previous studies have identified the prevalence of common comorbidities as rising the risk of COVID-19 patients (1). Additionally, some scholars believe that the presence of any coexisting disease was more common among patients with severe illness than among those with non-severe illness(2). It has been found that the most serious and lethal cases of COVID-19 occurred in the elderly or in patients with underlying comorbidity, in particular CVDs, diabetes mellitus, chronic lung and renal disease, hypertension, and cancer (2, 38–40). One Chinese meta-analysis involving 1,527 patients found that hypertension and cardiovascular disease accompanied by diabetes were the most prevalent cardiovascular metabolic comorbidities with COVID-19, consistent with our study. In their study, patients with diabetes or hypertension had a 2-fold increase in risk of serious illness or requiring intensive care (ICU) admission, whereas those with cardiovascular disease had a 3-fold increase(12). In a subset of 355 COVID-19 patients who died in Italy, the mean number of pre-existing underlying conditions was 2.7, and only 3 subjects had no comorbidity(41).

Our findings revealed the importance of the early detection of COVID-19 high risk patients, especially in hypertensive patients in primary hospitals.

having a control group was the strength point of our investigation. However, there are some limitation to the report. First, this was a single-center study with a small sample size. Second, that was a retrospective study, and the results need to be further verified by prospective studies. Third, we missed asymptomatic and mild cases managed at home, and hence it may have affected the outcome of the study.

Due to the rapidly evolving outbreak internationally, ongoing studies with the inclusion of more patients would be required to increase statistical power and support group analyzes stratified by specific comorbidities in particular, hypertension and association with death risk.

as explained, hypertension is one of the most common risk-associated comorbidities, but age co-founded this association. It's not clear if hypertension is an age-independent risk factor consistent with COVID-19 outcomes. It is necessary that hypertension stays tightly controlled as a precaution.

Conclusion

In conclusions, patients with previous hypertension may be at greater risk of progressing into the severe condition. Our results offer a new insight into both subsets of patient's clinical symptoms and physical findings, supporting the suggestion that hypertension plays a significant role in patients with comorbidities, but the clinical manifestations were the same in both groups. The similarities and differences between hypertensive and non-hypertensive patients in this report indicate that hypertensive patients with certain comorbidities, advanced age, smoking, hypoxia, declined %SPO2 and elevated rates of CRP and ESR are all highly correlated with disease severity and prognosis, which should be critically evaluated during diagnosis and care. Male sex, over 65 years of age, and even clinical symptoms such as fever, shortness of breath or dyspnea, and laboratory tests such as WBC, lymphocyte, platelet and LDH may indicate COVID-19 progression. Due to the high mortality rate in patients with coronavirus infection with underlying diseases, health care policies should lead to the diagnosis and better control of patients with underlying diseases, especially hypertension.

Declarations

Ethics approval and consent to participate

This study was approved by Ethical Committee of Kashan University of Medical Sciences. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments. Written informed consent was obtained from all participants or, if participants are under 16, from a parent and/or legal guardian.

Consent for publication

All study process was presented to patients and they were reassured about confidentiality of their records, they were requested to present their written consent of participation in the study.

Availability of data and material

The primary data for this study is available from the authors on direct request.

Competing interests

The authors declare no conflict of interest.

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Authors' contributions

FA, HR and MN were responsible for the study conception and design. AM, HP and FA performed data collection and MN. FA preparing the first draft of the manuscript. MN did the data analysis, HHK made critical revisions to the paper for important intellectual content and supervised the study. All authors read and approved the final manuscript.

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Figures

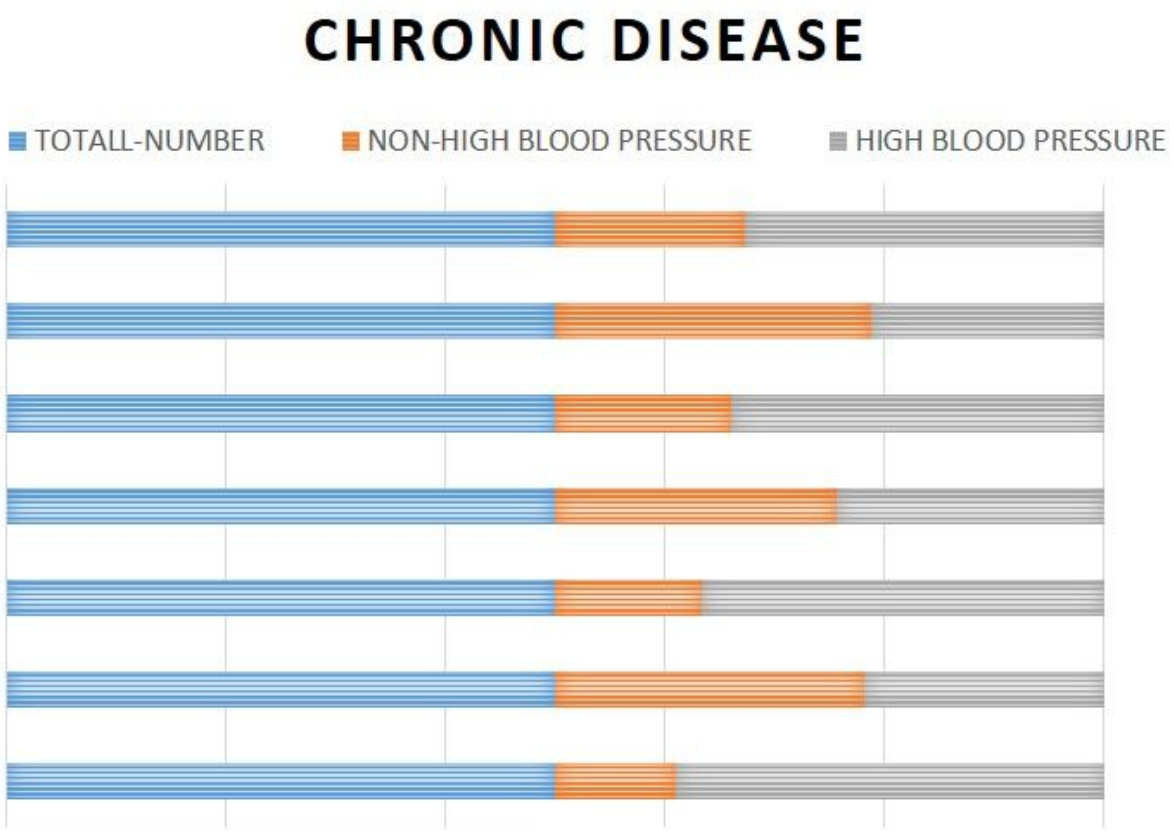

Figure 1

Underlying diseases in hypertensive and non-hypertensive covid-19 hospitalized patients