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INVESTIGATION OF CLINICAL PARAMETERS OF PATIENTS ADMITTED WITH COVID-19 PNEUMONIA AND MEDICATIONS USED TO TREAT THEIR CO - MORBIDITIES

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Abstract:
There has already been further research into the risk factors and molecular mechanisms underlying Covid-19's serious breathing involvement and reservations regarding nonsteroidal anti-inflammatory inhibitors (NSAIDs) and renin angiotensin-aldosterone (RAAS) have also arisen.
Objective: *The purpose of this study was to determine whether there were any associations between medications taken on a regular basis for comorbid diseases prior to the diagnosis of Covid-19 pneumonia and demographic or clinical characteristics at admission.*
Materials and Methods: *Between March 11th and April 15th, 2020, patients diagnosed with pneumonia in emergency, internal medicine, and cardiology outpatient clinics were recruited, and their clinical and demographic characteristics, including blood tests, oxygen saturations (SO2), and degree of lung infiltration on computed tomography, were analysed in relation to the medications they took on a regular basis.*
Results: *Angiotensin converting enzyme inhibitors (ACE inh.) or angiotensin receptor blockers (ARB) users were significantly older than the no-ACE inh./ARB group and had significantly lower SO2 levels on admission, whereas NSAID users with Covid-19 exhibited a significant female predominance and lower haemoglobin levels than the no-NSAID group. Additionally, PPI users had a significant female predominance, were older in age, and had lower haemoglobin levels. Finally, antiaggregant users who used Covid-19 had a lower SO2 level upon admission, and overall, cases involving regular drug use were significantly associated with older age.*
Conclusion: *There were significant associations between demographic and clinical characteristics at the time of admission for Covid-19 pneumonia and the use of major drug classes, including RAAS inhibitors, NSAIDs, and proton pump inhibitors.*
Key words: *Proton pump inhibitors, Non-steroidal anti-inflammatory drugs, Angiotensin receptor blockers, Angiotensin converting enzyme inhibitors, Covid-19.*

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INTRODUCTION:

Coronaviridae is a large family of viruses that can manifest themselves in a variety of ways, from the common cold to Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) (SARS). On December 31st, the World Health Organization's (WHO) regional office in China reported cases of pneumonia of unknown origin in Wuhan, the capital city of Hubei, which were confirmed to be a novel type of coronavirus not previously detected in humans. While the majority of patients initially presented with fever, others initially presented with chills, respiratory complaints, mild dry cough, fatigue, or diarrhoea. However, in severe cases, the disease progressed rapidly. Advanced stage disease was characterised by multiorgan dysfunction, persistent metabolic acidosis, and coagulation abnormalities, all of which were accompanied by lethal inflammatory storms. 1 Coronavirus 2 (CoV-2) infection of millions of people worldwide has sparked intense interest in the mechanisms by which the novel coronavirus causes acute respiratory distress syndrome (ARDS) and multiorgan dysfunction. Previously published research established that the SARS-CoV virus uses the angiotensin converting enzyme (ACE)-2 as its primary entry point into vascular endothelium and type-2 alveolar epithelial cells. 2,3 Several authors hypothesised that angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) might facilitate the spread of Covid-19 infection. 4 Similarly, some concerns have been raised about non-steroidal anti-inflammatory drugs (NSAIDs), specifically ibuprofen. 5 Numerous scientific societies have stated that human data is insufficient to support or refute these claims and concerns. Thus, we sought to examine possible associations between commonly used medications for chronic diseases and the clinical presentation of Covid-19 infections.

MATERIALS AND METHODS:

Between March 11th, 2020 and April 15th, 2020, we recruited patients diagnosed with COVID-19 pneumonia in our emergency, internal medicine, and cardiology outpatient clinics. Prior to conducting the study, it was approved by the local ethics committee, and all procedures were in accordance with the 1975 Helsinki Declaration, as revised in 2008. All demographic characteristics, admission complaints, computed tomography (CT) scans of the chest without intravenous contrast performed by our staff radiologist, and admission c-reactive protein (CRP) and complete blood count (CBC) values were retrospectively recorded. Their polymerase chain reaction (PCR) test results were derived from hospital records using public health covid-19 database notifications and a list of medications taken on a regular basis for more than 8 weeks prior to the diagnosis of COVID-19 pneumonia from the national pharmacy database. Other systemic diseases and significant medical conditions of patients were gleaned from medical histories obtained from appropriate physicians. Cases with at least one of the characteristic symptoms, such as cough, fever, or dyspnea, and characteristic CT findings, such as peripherally located ground glass infiltrations on thoracic CT scan (Figure 1), that are reported by the radiologist as having a high probability of COVID-19, and who are started on at least two of the three recommended first-line agents (azitromycine, hydroxychloroquine, or oseltamivir).

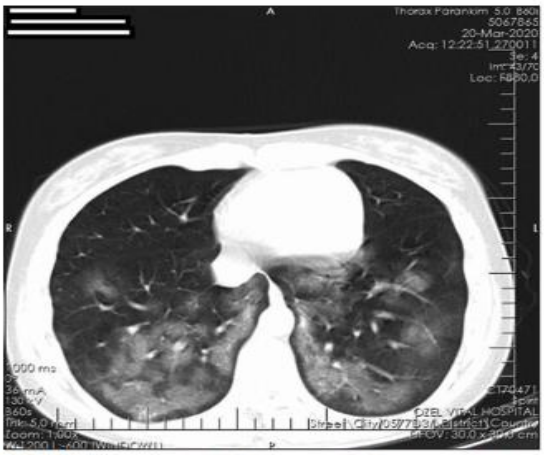

Figure 1: Typical ground-glass appearence on thoracic CT scan of a patients with confirmed Covid-19 pneumonia

According to the number of segments involved, the extent of infiltrations upon admission was roughly classified as mild to moderate and diffuse. 6 Mild to moderate infiltration of the lungs was defined as involvement of one to three segments, whereas involvement of more than three segments in the right and left lungs was defined as diffuse infiltration. On admission, monocyte, eosinophil, red blood cell (RBC), white blood cell (WBC), and platelet (PLT) counts were collected, as well as oxygen saturation (SO2), CRP, haemoglobin, and mean platelet volume (MPV) values. Additionally, the ratios of thrombocytes to lymphocytes and neutrophils to lymphocytes were calculated and added to the study data (Table 1). We identified common classes of medications that newly diagnosed COVID-19 patients took on a regular basis. The patients who received each group of medications were compared to those who did not receive them on the basis of demographic characteristics, the extent of infiltrations on CT scan,

SO2, CRP, haemoglobin, MPV, monocyte, eosinophil, RBC, WBC, and PLT, as well as thrombocyte/lymphocyte (PLT/LYM) and neutrophil/lymphocyte (NEU/LYM) ratios, which have been shown to predict prognosis 7 Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS 22.0) for Windows software. Means and standard deviations were used to express continuous variables, while percentages and 95% confidence intervals were used to express categorical variables (95 percent CIs). Where appropriate, Pearson Chi-square, Mann-Whitney U, or independent samples tests were used to examine potential associations between variables. Significant differences were defined as those with P values less than 0.05.

RESULTS:

Between March 11th and April 15th, 2020, 73 patients with suspected Covid-19 pneumonia were evaluated in outpatient emergency, internal medicine, and cardiology clinics. 18 of the patients investigated had other lower respiratory tract infections or Covid-19 upper respiratory tract involvement with pulmonary sequelae from previous infections, whereas one patient had insufficient medical records due to rejection of the diagnosis and treatment process. The study population consisted of 54 patients, 26 of whom were female (48.1%) and 28 of whom were male (51,9 percent). Their mean age was 51,214,71 years, ranging from 19 to 78. 16 of them had negative PCR results and no confirmatory tests were performed; however, they were deemed to be Covid-19 pneumonia cases because they all had peripheral pulmonary ground glass infiltrates and pneumonia symptoms, and a diagnosis of Covid-19 pneumonia could not be ruled out. The most frequently prescribed medication groups by newly diagnosed COVID-19 pneumonia patients were identified. There were 19 patients in the ACE inh/ARB group who were significantly older than those in the non-ACE inh/ARB group. Additionally, the median SO2 on admission was significantly lower in ACE inh./ARB users than in non-users. As shown in Table 1, a slightly greater proportion of patients receiving regular ACE inh/ARB had diffuse lung infiltration, but this difference was not statistically significant. Additionally, the BC count was lower and the NEU/LYM ratio was higher in ACE inh/ARB users, although the p values were not statistically significant. All other admission parameters were not statistically significant when ACE inh/ARB users were compared to non-users. On the other hand, females with Covid-19 pneumonia were significantly more likely to take regular NSAIDs (more than four pills per week). Additionally, the regular NSAID group's haemoglobin levels were significantly lower than the non-NSAID group's. However, diffuse lung involvement and SO2 levels upon admission were not associated with regular NSAID use. Platelet count and PLT/LYM ratio appear to be increased in NSAID users with Covid-19 pneumonia, although they did not reach statistical significance, as shown in Table 2. In our study population, mean age, CRP, and other haematological indices were not associated with regular NSAID intake. Female patients (68,8 percent, n=11) were again more prevalent than those in the non-PPI group (39,5 percent, n=15, p=0,049) in the analysis of PPI users with Covid-19 pneumonia. Additionally, they were significantly older than non-PPI users (62,910,1 versus 46,313,6 years, p=0,0001) and had significantly lower RBC (4,710,58 versus 5,030,41 x106, p=0,025) and haemoglobin levels (12,9 1,6 versus 14,11,3 gr/dL, p=0,0005). All other variables compared between the PPI and non-PPI groups were insignificant. For more than two months, 31 of the study population took at least one medication daily for chronic and systemic diseases such as hypertension, diabetes, coronary artery disease, and chronic gastritis, whereas 23 did not take any medication at all. The mean age of drug users was significantly greater than the mean age of non-users (58,3911,98 versus 41,5212,46 years, p=0,0001). Additionally, drug users had significantly lower eosinophil counts (23,7 versus 32,6 /micL, p=0,034) and SO2 values upon admission (median SO2; 97 and 98 percent, mean ranks 23,8 and 32,5, p=0,04). All other variables compared between drug users and non-users were insignificant. Antiaggregants (primarily acetylsalicylic acid and clopidogrel) and statins were routinely used in 11 (20,4%) and 8 (14,8%) of 54 Covid-19 pneumonia cases, respectively, whose mean ages were significantly higher than those in the no-antiaggregant and no-statin groups (59,312 versus 49,114 years, p=0,04 and 65,256,11 versus 48,76 Additionally, antiaggregant users with Covid-19 pneumonia had significantly lower SO2 values on admission (median SO2; 95% versus 97%, mean ranks; 16,8 and 30,2, p=0,010). Other variables were not statistically significant when compared between two groups for each entity. In 12 of 54 cases, OAD and/or insulin were routinely used. Covid-19 pneumonia cases (22%) with a significantly higher mean age than the non-OAD/insulin group (63,679,23 versus 47,6414,09 years, p=0,001). Other variables comparing two groups failed to demonstrate statistical significance. Finally, the degree of lung tissue involvement and SO2 levels at admission were analysed to determine if there were any possible correlations between these variables. Median SO2 on admission decreased slightly with diffuse lung segment involvement, but

not statistically significantly (SO2: 97 percent versus 98 percent, mean ranks 24,8 and 33,4, p=0,058).

Table 1: Distribution of demographic and clinical parameters on admission in ACE inh/ARB user and non-ACE inh/ARB user groups

Demographic and clinical parameters on admission	Regular ACE inh./ARB	No ACE inh./ ARB	P value
Gender (Female/Male)	10/9	16/19	0,627
Diffuse infiltration on CT	73,7%	65,7%	0,547
Median SO2 (%)	96% (mean rank=20,9)	98%(mean rank=31,1)	0,021[a]
Mean Age (years)	62,8±10,6	44,9±12,7	0,0001[a]
Monocyte count (mean)/micL	480±204,1	530,6±205,6	0,391
RBC x10^6	4,78±0,53	5,02±0,44	0,080
Hemoglobin (g/dL)	13,48±1,59	13,95±1,42	0,273
PLT/micL	198789±68484	215114±73275	0,419
WBC/micL	5889±2112	5782±2072	0,858
MPV fL	10,3±0,64	10,06±0,94	0,268
PLT/LYM	149,02±53,66	144,29±61,36	0,771
CRP	30,05	26,11	0,380
Eosinophil/micL	24,4	29,2	0,271
NEU/LYM	32,5	24,8	0,085

a: statistically significant (p<0,05)

Table 2: Distribution of demographic and clinical parameters on admission in NSAID user and non-NSAID user groups

Demographic and clinical parameters on admission	Regular NSAID	No NSAID	P value
Gender (Female/Male)	8/1	18/27	0,007[b]
Diffuse infiltration on CT	66,6% (n=6)	68,9% (n=31)	0,896
Median SO2 (%)	97% (mean rank=29,7)	97% (mean rank=27,1)	0,646
Mean Age (years)	52,9±10,8	50,9±15,5	0,71
Monocyte count (mean)/micL	514,4±198	512,4±208,1	0,979
RBC x10^6	4,84±0,65	4,95±0,45	0,524
Hemoglobin (g/dL)	12,34±1,72	14,07±1,28	0,001[b]
PLT/micL	250778±55545	201088±71837	0,06
WBC/micL	5297±1219	5925±2193	0,41
MPV fL	10,27±0,49	10,12±0,91	0,636
PLT/LYM	179,1±66,7	139,3±54,9	0,06
CRP	25,9	27,8	0,745
Eosinophil/micL	24,83	28,03	0,566
NEU/LYM	28,0	27,4	0,917

b: statistically significant (p<0,05)

There is growing concern that medical treatment for coexisting conditions, specifically the use of RAAS inhibitors for hypertension, may have contributed to the adverse events observed in Covid-19 pneumonia cases, as the SARSCov2 virus infects cells via ACE2 receptors. Earlier research indicates that different RAAS inhibitors may have varying effects on ACE2 levels. Whereas ARBs and mineralocorticoid receptor

antagonists increased ACE2 expression and function in a variety of experimental and clinical models,8,9 ACE inhibitors increased myocardial Ace2 mRNA levels but had no effect on ACE2 function in experimental models. 10 Additionally, regular administration of aliskiren (a direct renin inhibitor) was associated with decreased ACE2 expression in a model of diabetic nephropathy. 11 However, there is insufficient evidence to suggest that increased ACE2 expression predisposes to Covid-19 infection. Due to the small number of participants, we were unable to compare the vulnerability of ACE ihn. and ARB users to Covid-19 infections separately from that of non-users. Instead, we evaluated the demographic and initial clinical features of a population with Covid-19 pneumonia cases based on ACE ihn. or ARB intake. According to our findings, regular ACE inh./ARB use by Covid-19 pneumonia patients was not associated with significant differences in the majority of demographic and clinical parameters on admission between the ACE inh./ARB user and non-ACE inh./ARB user subgroups, with the exception of mean age on admission, which was significantly and unsurprisingly higher, and median SO2 on admission, which was significantly and unsurprisingly higher. As several studies have demonstrated, medical issues such as hypertension appear to correlate closely with advanced age12, which is emerging as a major predictor of Covid-19–related mortality13. Other diseases that frequently coexist with advanced age in Covid-19 infections include diabetes, coronary artery disease, and chronic kidney disease14, all of which are risk factors for a poor prognosis in addition to male sex. According to the National Health Commission of China's clinical classification of the COVID-19, a SO2 level of 93 percent at rest is one of the components indicating severe infection. Due to the novel coronavirus's ability to enter the host cell via the S protein on the viral surface binding to the ACE2 on the cell surface, nearly all endothelial and smooth muscle cells in organs expressing ACE2 become a battleground for the novel coronavirus and immune cells, interfering with essential functions such as gas exchange. 15 However, a small but significant decrease in SO2 on admission in our study population receiving ACE inh/ARB may be due to these agents' facilitating effect on Covid-19 for pulmonary involvement, as these patients did not have any other pulmonary disease at the time. It was also speculated in several publications during the outbreak's early months. 16 - 17 As current knowledge regarding the effect of RAAS inhibitors on viral binding to ACE2 receptors is insufficient to level a charge against a specific agent, additional analysis with various RAAS inhibitors in the context of SARS-CoV-2 infection is required. Additionally, the RBC count was significantly lower and the NEU/LYM ratio was significantly higher in ACE inh/ARB users. The lack of significance for these parameters may be explained by the small population of ACE inh/ARB users in our Covid-19 cases. Nonetheless, this change in blood cell composition was previously demonstrated in previous trials,18,19 indicating that the disease may have a pulmonary component. Its relationship to ACE inh./ARB is unknown. NSAIDs are widely used to treat chronic pain, particularly in the elderly. However, concerns have been raised that when NSAIDs are used in cases of acute COVID-19 infection, they may increase the risk of adverse events. One study on the molecular basis of NSAID effect discovered that ibuprofen augments ACE2 expression in diabetics and those treated with angiotensin II type-I receptor blockers. 17 Thus, it was suggested that increased ACE2 expression in these comorbid patients might facilitate COVID-19 infection. In another study, indomethacin was shown to have potent antiviral activity against canine coronavirus in vitro, significantly inhibiting virus replication and preventing virus-induced damage. 20 In our study, we identified NSAID prescriptions in the national pharmacy database of a social security institution that contained more than four pills per week for at least eight weeks prior to the diagnosis of Covid-19 pneumonia. Nine out of 54 cases met this criteria, with eight being females, a significant difference when compared to other Covid-19 cases without NSAID intake. Given that there is no evidence in the literature to support or refute this gender difference, it emerges as a novel finding that warrants further investigation. Additionally, because the symptomatic level of patients requiring outpatient care varies by individual, comorbidities or medications may not be the sole factor affecting the severity of disease upon admission. On the other hand, radiological interpretations of computed tomography are expert reports issued by our staff radiologists and may be subject to diagnostic bias because the study design did not include blinded data collection.

In conclusion, demographic characteristics and medications taken on a routine basis prior to diagnosis may have an effect on the presentation of Covid-19 pneumonia.

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