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Clinical Features in Patients with Acute Pulmonary Edema with Confirmed Coronavirus Disease 2019 (COVID-19): Comparison with Those without Acute Pulmonary Edema

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Abstract

Background: Although poor clinical outcomes have been reported for Coronavirus Disease 2019 (COVID-19), comprehensive data regarding Acute Pulmonary Edema (APE) concomitant with patients with COVID-19 are scarce. This study investigated the clinical features and outcomes of APE in patients with COVID-19.

Methods: Of 50 patients enrolled from a COVID-19 registry database, 5 patients presented with APE (APE group) and 45 did not (Non-APE [NAPE] group).

Results: Most clinical presentations and in-hospital courses were different between the groups. The APE group was older (P=0.001) and had higher prevalence of underlying diabetes (P=0.005), hypertension (P=0.005), coronary artery disease (P=0.001), stroke/transient ischemic attack (P=0.001) and chronic renal failure (P=0.002). The APE group had significantly higher prevalence of sputum (P=0.002), higher body temperature (P=0.004) and shock (P=0.002). The APE group had significantly higher prevalence of ST depression (P=0.023) and T-wave inversion (P=0.045). The APE group had significantly higher levels of high sensitivity-C Reactive Protein (hs-CRP) (P=0.007), Erythrocyte Sedimentation Rate (ESR) (P=0.001) and procalciton in (P=0.001). The APE group had significantly higher prevalence of bilateral involvement (P=0.002) and multi-lobal involvement (P=0.001) of Ground Glass Opacities (GGO). The APE group required more frequent use of inotropics (P=0.002), ventilator (P=0.001), Angiotensin-converting enzyme inhibitors (P=0.001), diuretics (P=0.001), and antibiotics (P=0.001). The APE group had significantly higher in-hospital mortality (P=0.002).

Conclusion: Our study demonstrated that the APE group had higher in-hospital mortality than the NAPE group. A meticulous diagnostic and therapeutic approach should be considered for elderly patients with COVID-19 having diabetes, hypertension, coronary artery disease, chronic renal failure, stroke, and ST depression and T-wave inversion, bilateral, multi-lobal involvement of GGO and high levels of ESR, hs-CRP and procalcitonin at the time of admission.

Keywords: Coronavirus Disease 2019 (COVID-19); Cardiovascular complications; Acute pulmonary edema; Acute heart failure

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Introduction

Since an ongoing outbreak of pneumonia associated with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was reported in Wuhan, Hubei province, China in December 2019, the disease caused by this novel coronavirus (Coronavirus Disease 2019, COVID-19) has resulted in considerable morbidity and mortality in vulnerable populations worldwide [1-4]. Although some reports suggested the links between COVID-19 and cardiac injury, the data describing cardiovascular complications of COVID-19 are limited [5-7]. Moreover, a limited amount of literature exists about the role of COVID-19 as a trigger of in-hospital morbidity and mortality in these patients concomitant with Acute Pulmonary Edema (APE) [5-7].

The aim of this study was to determine the clinical characteristics, laboratory parameters, and radiographic and Electrocardiographic (ECG) findings for adults with COVID-19 and assess the differences in these parameters between adult patients who had concomitant Acute Pulmonary Edema (APE group) and those who did not (Non-APE [NAPE] group), and to assess the in-hospital courses and mortality in the two groups.

Materials and Methods

Study design and subjects

Study data were obtained from the Coronavirus Disease 2019 registry database at the Seongnam Citizens Medical Center Medical Center (SCMC) (one of the largest hospitals affiliated to the Korea Covid-19 Task Force team). We approached 50 consecutive patients >18 years of age who were admitted to our hospital, a 509-bed referral center, for confirmed COVID-19 infection between 1st January and 31st April, 2020. Real-Time Reverse-Transcription-Polymerase-Chain-Reaction (RT-PCR) assay has been used for diagnosis of COVID-19. Fifty patients were divided into two subgroups according the presentation of APE at admission: Five (10%) patients presented with APE group and 45 did not (NAPE group). In the APE group, shock occurred in one patient at admission, and death in one during index hospitalization.

The medical records of patients with confirmed COVID-19 were retrospectively reviewed, including demographic information, clinical manifestations, radiographic and laboratory and ECG findings. In all patients, ECGs, radiographic and laboratory studies were performed on the first hospital day.

APE was defined as the presence of a radiographic report of pulmonary alveolar/interstitial congestion at initial chest roentgenogram and/or Computed Tomogram (CT) with at least two of the following physical signs: Pulmonary rales, elevated central venous pressure, and a third heart sound [8]. The gold standards for the diagnoses of APE determined by two cardiologists who independently reviewed all medical records. Shock was defined as a systolic blood pressure <90 mmHg f or ≥ 30 min that was not responsive to fluid administration alone, accompanied by evidence of tissue hypo-perfusion in the setting of clinically adequate or elevated LV filling pressure [9]. Diabetes mellitus was defined as a serum glucose level >126 mg/dl, a history of diabetes mellitus, or current use of anti-diabetic medications. Hypertension was defined as repeated measurements of a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg, or previous anti-hypertensive medication treatment. Current smoking was defined as having smoked cigarettes <1 year before admission.

The protocol was approved by the Institutional Review Board of the Seongnam Citizens Medical Center. The recommendations of the revised version of the Declaration of Helsinki were met.

Radiographic data

Chest roentgenograms and/or CTs were read initially by two radiologists who were masked with respect to the status of the patient's illness. Three second radiologists reviewed the radiographic findings to determine the clinical significance of the findings. All patients underwent baseline-digital anteroposterior chest roentgenograms at full inspiration using a mobile chest radiograph machine (GM 85, Samsung Healthcare; DRX-Revolution Mobile X-ray System, Seoul, Korea) and CT using a multi-detector CT scanner with 128 channels. Two attending radiologists (with 30 and 40 years of experience in chest imaging, respectively) reviewed the chest radiographs and CT images by consensus on a picture archiving and communication system (PACS, GE Healthcare). The readers assessed the presence, location, and density of parenchymal abnormalities on chest radiographs and the CT images, and graded the abnormalities using the following 4 patterns: 1) normal; 2) focal Ground Glass Opacities (GGO) involving no more than one segment or one lobe; 3) multifocal GGO; and 4) diffuse GGO. After the initial assessment of the chest radiographs, we checked whether the abnormalities on chest radiographs corresponded to abnormalities on chest CT images.

CT protocol: All CT examinations were performed using a multi-detector CT scanner with 128 channels (Somatom Definition edge, Siemens Healthineers, Erlangen, Germany). The detailed parameters for CT acquisition were as follows: Tube voltage, 100 kVp; tube current, low-dose (reference mAs, 30) with automatic exposure control; slice thickness, 1.0 mm; reconstruction interval, 3.0 mm; and a sharp reconstruction kernel. CT images were obtained with the patient in the supine position at full inspiration and without contrast medium.

ECG

ECGs were read initially by two cardiologists who were masked with respect to the status of the patient's illness. Two second cardiologists reviewed the ECGs to determine the clinical significance of the findings.

Laboratory data including procalcitonin

Blood samples were obtained from the antecubital vein into tubes containing lithium heparin, and then centrifuged. The blood samples were stored at -70°C until further analysis. Procalcitonin levels were measured using cobas e801 analyzer (Roche Diagnostics) and an Elecsys BRAHMS PCT kit (Roche Dignostics). The laboratory technicians were blinded to the patient identities and characteristics.

Statistical analysis

Statistical analysis was performed using SPSS Pc+24.0 Software. Data for continuous variables are expressed as the mean ± SD. A Student's t-test was used to compare continuous variables, and a chi-square test was used to compare the categorical variables. Age, body temperature, systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, corrected QT interval, white blood count, hemoglobin, high sensitivity-C Reactive Protein (hs-CRP), Erythrocyte Sedimentation Rate (ESR), sodium, potassium, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) Blood Urea Nitrogen (BUN), Creatinine, Creatine Phosphokinase (CPK), Lactate Dehydrogenase (LDH), procalcitonin levels, and hospital stay are given in terms of the median and Inter Quartile Range (IQR), and the Mann-Whitney non-parametric U test was used to analyze differences in these parameters between the two groups because of wide standard deviation. Differences were considered statistically significant when p-values were <0.05.

Results

Clinical characteristics

The clinical characteristics and initial presentations of the APE and NAPE groups are compared in Table 1. There were no significant differences in gender, body surface area, and the prevalence of current smoker status and underlying liver cirrhosis, bronchial asthma and malignancy between the two groups. The APE group had significantly higher prevalence of diabetes mellitus (40% *vs.* 4%, p=0.005),

Table 1: The comparison of clinical characteristics between COVID-19 patients with and without APE.

	Total (n=50)	APE group (n=5)	NAPE group (n=45)	p
Age (years)†	35.0 (27.5–54.5)	66.0 (60.5–79.0)	34.0 (26.0–50.0)	0.001*
Female gender, n (%)	27 (54)	1 (20)	26 (58)	0.108
Body surface area (m^2)	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.2	0.579
Hypertension, n (%)	8 (16)	3 (60)	5 (11)	0.005*
Diabetes mellitus, n (%)	4 (8)	2 (40)	2 (4)	0.005*
Current smoker, n (%)	7 (14)	1 (20)	6 (13)	0.684
Underlying diseases				
Coronary artery disease, n (%)	3 (6)	2 (40)	1 (2)	0.001*
Stroke/Transient ischemic attack, n (%)	2 (4)	2 (40)	0 (0)	0.001*
Liver cirrhosis, n (%)	2 (4)	0 (0)	2 (4)	0.630
Chronic renal failure, n (%)	1 (2)	1 (20)	0 (0)	0.002*
Malignancy, n (%)	2 (4)	1 (20)	1 (2)	0.054
Bronchial asthma, n (%)	1 (2)	0 (0)	1 (2)	0.736
Clinical presentation				
Febrile sensation, n (%)	25 (50)	4 (80)	21 (47)	0.157
Myalgia, n (%)	20 (41)	1 (25)	19 (42)	0.502
Cough, n (%)	13 (26)	3 (60)	10 (22)	0.068
Sputum, n (%)	7 (14)	3 (60)	4 (9)	0.002*
Nasal discharge, n (%)	6 (12)	0 (0)	6 (13)	0.384
Sore throat, n (%)	12 (24)	1 (20)	11 (24)	0.825
Chest pain/discomfort, n (%)	1 (2)	0 (0)	1 (2)	0.736
Dyspnea, n (%)	2 (4)	1 (20)	1 (2)	0.054
Palpitation, n (%)	1 (2)	0 (0)	1 (2)	0.736
Initial vital signs				
Body temperature (°C)†	36.0 (36.0–36.6)	36.9 (36.5–38.1)	36.0 (36.0–36.0)	0.004*
Heart rate (beats/min)†	71 (65–79)	70 (60–80)	71 (66–79)	0.778
Respiratory rate (rates/min)†	18 (18–20)	20 (18–22)	18 (18–20)	0.150
SBP (mmHg)†	112 (102–121)	109 (83–144)	112 (102–121)	0.925
DBP (mmHg)†	72 (66–79)	76 (52–84)	71 (66–79)	0.469
Shock, n (%)	1 (2)	1 (20)	0 (0)	0.002*

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure
†Presented as median (inter-quartile range), *Significant finding

hypertension (60% *vs*. 11%, p=0.005), coronary heart disease (40% *vs*. 2%, p=0.001), stroke and transient ischemic attack (40% *vs*. 0%, p=0.001), and chronic renal failure (20% *vs*. 0%, p=0.002). Most initial presentations of the APE and NAPE groups were similar between the two groups. However, there was a significantly higher incidence in the APE group than the NAPE group of sputum (60% *vs*. 9%, p=0.021) and shock (20% *vs*. 0%, p=0.002). There were no significant differences in systolic and diastolic blood pressures, respiratory and heart rate. However, there was a significantly higher levels in the APE group than the NAPE group of body temperature (median, 36.9°C *vs*. 36.0°C, p=0.004) at admission.

Laboratory and ECG findings

The laboratory and ECG findings for the APE and NAPE groups are compared in Table 2. There were no significant differences in corrected QT interval and the prevalence of ST elevation, Q-wave, life-threatening arrhythmias such as third-degree atrioventricular block, ventricular tachycardia, ventricular fibrillation, and cardiac arrest. However, the APE group had significantly prevalence of ST depression (40% *vs*. 2%, p=0.023) and T wave inversion (40% *vs*. 4%, p=0.045) than the NAPE group.

The APE group had significantly higher blood levels of hs-CRP (median, 4.4 mg/dL *vs*. 1.44 mg/dL, p=0.007) and ESR (median, 76 mm/hr *vs*. 24 mm/hr, p=0.001) than the NAPE group. In addition, the APE group had significantly higher levels of BUN (median, 4754.0 pg/ml *vs*. 480.0 pg/ml, p=0.012), creatinine (median, 4754.0 pg/ml *vs*. 480.0 pg/ml, p=0.012), and procalcitonin (median, 4754.0 pg/ml *vs*. 480.0 pg/ml, p=0.012) than the NAPE group, whereas, the NAPE group had significantly higher levels of hemoglobin (median, 4754.0 pg/ml *vs*. 480.0 pg/ml, p=0.012) and AST (median, 4754.0 pg/ml *vs*. 480.0 pg/ml, p=0.012). There were no significant differences in the white blood count, sodium, potassium, CPK, and LDH levels between the two groups.

Radiographic findings

Sixteen (32%) of 50 patients showed radiographic abnormalities (focal Ground Glass Opacities (GGO) involving no more than one segment or one lobe in 4 (8%) patients; multifocal GGO in 3

Table 2: The comparison of initial electrocardiographic and laboratory findings between COVID -19 patients with and without APE.

	Total (n=50)	APE group (n=5)	NAPE group (n=45)	p
Electrocardiographic findings				
Life-threatening arrhythmia, n (%)	0 (0)	0 (0)	0 (0)	-
Corrected QT interval (ms)†	428 (420–449)	452 (406–509)	428 (420–445)	0.454
ST-segment elevation, n (%)	0 (0)	0 (0)	0 (0)	-
ST-segment depression, n (%)	3 (6)	2 (40)	1 (2)	0.023*
Q-wave, n (%)	0 (0)	0 (0)	0 (0)	-
T-wave inversion, n (%)	4 (8)	2 (40)	2 (4)	0.045*
Laboratory findings				
White blood count (× $10^3/\mu L$)†	5105 (4490 - 5885)	4170 (2510 - 9815)	5150 (4600–5910)	0.311
Hemoglobin (g/dL)†	13.8 (13.1 - 14.8)	10.9 (7.3 - 13.8)	13.9 (13.3–14.9)	0.018*
hs-CRP (mg/dL)†	1.9 (0.03 - 10.22)	4.4 (0.96 - 10.22)	1.44 (0.03–8.65)	0.007*
ESR (mm/hr)†	25 (13.5 - 52.3)	76 (57 - 96)	24 (11–42)	0.001*
Sodium (mmol/L)†	139 (137 - 141)	139 (134 - 145)	139 (137–141)	0.660
Potassium (mmol/L)†	4.1 (3.9 - 4.2)	3.8 (3.6 - 4.1)	4.1 (3.9–4.2)	0.075
AST (U/L)†	22 (17 - 30)	50 (21 - 70)	21 (17–28)	0.039*
ALT (U/L)†	20 (14 - 41)	25 (15 - 42)	20 (14–42)	0.730
BUN (mg/dL)†	11.8 (9.9 - 15.8)	26.2 (16.8 - 45.6)	11.7 (9.5–14.1)	0.002*
Creatinine (mg/dL)†	0.76 (0.66 - 0.94)	1.66 (0.89 - 6.87)	0.75 (0.65–0.87)	0.009*
Peak CPK (ng/ml)†	80 (61–124)	279.0 (106.0–412.0)	76 (59–117)	0.150
LDH (U/L)†	182 (160 - 218)	3.5 (1.3 - 11.1)	180 (159–217)	0.114
Procalcitonin (ng/ml)†	0.030 (0.020–0.053)	0.270 (0.110–19.885)	0.030 (0.020–0.050)	0.001*

Life-Threatening Arrhythmia: Third-Degree Atrioventricular block, Ventricular Tachycardia, Ventricular Fibrillation, Cardiac Arrest
†Presented as median (inter-quartile range), * Significant finding

Table 3: The comparison of initial radiographic findings between COVID-19 patients with and without APE.

	Total (n=50)	APE group (n=5)	NAPE group (n=45)	p
Normal	34 (68)	0 (0)	34 (76)	
Focal involvement, n (%)	4 (8)	1 (20)	3 (6.5)	
Multifocal involvement, n (%)	3 (6)	0 (0)	3 (6.5)	
Diffuse involvement, n (%)	9 (18)	4 (80)	5 (11)	0.001*
Bilateral involvement, n (%)	7 (14)	3 (60)	4 (9)	0.001*

GGO: Ground Glass Opacity on lung fields
*Significant finding

(6%) patients; diffuse GGO in 9 (18%) patients each). Seven of 50 patients showed bilateral involvement of GGO. The APE group had significantly higher prevalence of diffuse (80% *vs*. 11%, p=0.001) and/or bilateral (60% *vs*. 9%, p=0.002) involvement of GGO than the NAPE group Table 3.

Clinical course and treatment

The clinical courses and treatment for the APE and NAPE groups are compared in Table 4. There was no significant difference in prevalence of use of hydroxychloroquine between two groups. The APE group had significantly higher prevalence of use of inotropics (20% *vs*. 0%, p=0.002), use of ventilator (40% *vs*. 0%, p=0.001), use of angiotensin converting enzyme inhibitor/angiotensin receptor blocker (60% *vs*. 7%, p=0.001), use of diuretics (40% *vs*. 2%, p=0.001), and use of antibiotics such as azithromycin (80% *vs*. 2%, p=0.001) than the NAPE group. In addition, The APE group had significantly higher in-hospital mortality (20% *vs*. 0%, p=0.002) than the NAPE group. During hospitalization, one of 50 patients (2%) died of septic shock.

Discussion

There were three main findings of this study. First, the APE group had a higher prevalence of the elderly, underlying diabetes, hypertension, coronary artery disease, chronic renal failure, stroke, and ST depression and T-wave inversion on ECG, bilateral and/or multi-lobal involvement of GGO and higher levels of ESR, hs-CRP and procalcitonin at the time of admission than the NAHF group, despite the similarity of other clinical features. Second, the APE group may have higher in-hospital mortality than the NAPE group. Third, A meticulous diagnostic and therapeutic approach should be considered for elderly patients with COVID-19 having diabetes, hypertension, coronary artery disease, chronic renal failure, stroke, and ST depression and T-wave inversion, bilateral and/or multi-lobal involvement of GGO and high levels of ESR, hs-CRP and procalcitonin at the time of admission.

Overall, the clinical features of COVID-19 were similar to published studies in other areas of the world [1-4,10-13]. In consistent with previous studies [10-12], in our study, female was 27

Table 4: The comparison of clinical courses and management between COVID-19 patients with and without APE.

	Total (n=50)	APE group (n=5)	NAPE group (n=45)	p
Use of inotropics, n (%)	1 (2)	1 (20)	0 (0)	0.002*
Use of ventilator, n (%)	2 (4)	2 (40)	0 (0)	0.001*
Use of IABP/ECMO, n (%)	0 (0)	0 (0)	0 (0)	-
Use of ACEI or ARB, n (%)	6 (12)	3 (60)	3 (7)	0.001*
Use of diuretic, n (%)	3 (6)	2 (40)	1 (2)	0.001*
Use of antibiotic, n (%)	5 (10)	4 (80)	1 (2)	0.001*
Use of Hydroxychloroquine, n (%)	8 (16)	1 (13)	7 (88)	0.797
In-hospital mortality, n(%)	1 (2)	1 (20)	0 (0)	0.002*

IABP: Intraaortic Balloon Pump; ECMO: Extracorporeal Membrane Oxygenation; ACEI: Angiotensin Converting Enzyme Inhibitor; ARB: Angiotensin Receptor Blocker
*Significant finding

(54%) of 50 enrolled patients and there was no significant difference in gender between the APE group and the NAPE group. Although data of gender preponderance in patient with COVID-19 show equal numbers of cases between men and women so far, there seem to be sex differences in mortality and vulnerability to the disease [10-13]. Emerging evidence suggests that more men than women are dying, potentially due to sex-based immunological or gendered differences, such as patterns and prevalence of smoking [10-13]. However, current data of gender preponderance are incomplete, cautioning against early assumptions because data from China suggest that more than 90% of health-care workers in Hubei province are women [10-13].

Similar to previous studies [10-13], our data showed the most prevalent clinical symptom was febrile sensation, followed by myalgia, cough and sore throat. The most prevalent co morbidities were hypertension and diabetes, followed by coronary artery disease.

A notable finding was that the APE group had a significantly higher prevalence of underlying diseases than the NAPE group. The possible explanation of this preponderance in the APE group is that underlying diseases such as older age, presence of diabetes, hypertension, coronary artery disease, chronic renal failure, stroke/transient ischemic attack, may affect immune competence of patients with COVID-19. The previous findings showing older adults and people of any age who have serious underlying medical conditions might be at higher risk for severe illness from COVID-19 [14-16], in addition to the results of our study, points to a role for the underlying diseases in producing or exacerbating severe symptoms and signs.

In our study, the APE group had significantly higher procalcitonin levels than the NAPE group. The levels of procalcitonin level can be markedly elevated during the acute phase in most septic conditions [17-19] as well as acute heart failure [20-22], and higher procalcitonin levels in patients with COVID-19 concomitant with APE might reflect the greater extent of affected and/or injured myocardium compared with those without APE. Our data have not demonstrated that elevated procalcitonin levels were independent predictors of APE in contrast with recent studies [20-22]. This discrepancy with our data may be due to differences in scale of study population and heterogeneity in the condition between sepsis/inflammation and acute heart failure with pulmonary edema.

In the present study, the APE group had significantly higher CRP and ESR levels than the NAPE group. In COVID-19, the infiltration of the myocardium by inflammatory cells such as activated macrophages, may be considered to be a mechanism of myocardial injury [23,24]. Consistent with our data, recent studies reported that elevated ESR and CRP levels were found in patients with COVID-19 [25,26]. We supposed that higher ESR, hs-CRP, and procalcitonin levels might predict APE occurrence and could be used as a biomarker for predicting clinical course during index hospitalization in such patients.

Presently, the APE group had significantly higher prevalence of cardiac injury markers on ECG, such as ST segment depression and T wave inversion, than the NAPE group. The hypothesis is that the extent of the affected/injured myocardium could be smaller in patients with the NAPE group compared with APE group. These findings may indicate that the APE group had a greater extent of affected/injured myocardium and that in addition to these ECG markers, cardiac markers like brain natriuretic peptide, CK-MB and troponin-I may reflect this extent of affected myocardium.

In our study, the APE group had significantly higher prevalence of bilateral and/or diffuse GGO involvement than the NAPE group. These findings may indicate that greater extent of lung parenchymal inflammation and/or injury in the APE group had affected a greater extent of myocardium.

Recent studies reported that coronaviruses with single-stranded RNA, about 120 nanometers in diameter, enter host cells by harnessing the action of the angiotensin converting enzyme, ACE-2, which is expressed in the membranes of many cells in the body, including lung alveolar epithelial cells [27-29]. Reducing the activity of ACE-2 in cell membranes could theoretically reduce the ability of coronaviruses to penetrate cells. ACE-1 inhibitors, currently used to treat hypertension and heart failure, do not inhibit ACE-2 [27-29]. In experimental animals, ACE-1 inhibitors and ARBs both increase the activity of cardiac ACE-2 because the presence of an increased amount of angiotensin I, due to inhibition of ACE-1, might tend to up regulate ACE-2 [30]. To our knowledge, studies that show an effect of ACE inhibitors or ARBs on ACE- 2 expression or activity in lung are lacking. In addition, effects of rennin–angiotensin system inhibition on the COVID-19 are highly controversial. Interestingly, in our study, the APE group had a significantly higher proportion of patients who have used ACEI/ARB to treat hypertension before admission than the NAPE group. These findings are in concordance with the aforementioned reports [27-30]. However, we do not know whether the supposed benefits of ACE-1 inhibitors or ARBs during an episode of infection with coronaviruses outweigh the potential harms. It seems likely that it would be unwise to use either conventional ACE-1 inhibitors or ARBs to treat COVID-19 and patients who are already taking ACE-1 inhibitors or ARBs have generally been advised to continue taking their medicines [29,31].

In our study, older age, presence of diabetes, hypertension,

coronary artery disease, chronic renal failure, stroke/transient ischemic attack and ST depression and T-wave inversion on ECG, bilateral and/or diffuse GGO involvement and higher levels of ESR, hs-CRP and procalcitonin at the time of admission may affect the development of APE in patients with COVID-19. Despite the inherent limitation of a retrospective analysis, our study suggests that risk stratification using these factors may allow physicians to identify patients with COVID-19 at high risk for APE for initial diagnosis and management.

Presently, the overall mortality was relatively lower than in previous studies (3.4% worldwide, 4.9% in Wuhan, 3.1% in Hubei province) [32,33]. This discrepancy with our data may be due to differences in scale of study population and strength of meticulous diagnostic and therapeutic approach of COVID-19 under territorial health departments and state.

Study Limitations

There are some limitations that should be considered in our study. First, this is a retrospective analysis. The use of a retrospective medical record review may have contributed to information bias even though data of all patients from admission to discharge are standardized because COVID-19 has been strictly controlled under territorial health departments and state. Second, because the small number of case patients may not represent the full COVID-19 clinical spectrum, our study may have been underpowered to compare the differences between the two groups and these comparisons should be interpreted with caution. However, this is one of the largest studies in Republic of Korea to date to compare clinical characteristics, laboratory, radiographic and echo cardio graphic findings between the subgroups in detail published. Third, we did not perform systemic investigations of all patients, such as echocardiogram, cardiac enzyme such as troponin-T or I, brain natriuretic peptide levels, or pathology because of high cost and high risk of contagion. Finally, we could not investigate asymptomatic cardiac involvement in adult patients with COVID-19 because of a retrospective design.

Conclusion

Our study demonstrated that the APE group had higher in-hospital mortality than the NAPE group. A meticulous diagnostic and therapeutic approach should be considered for elderly patients with COVID-19 having diabetes, hypertension, coronary artery disease, chronic renal failure, stroke/transient ischemic attack and ST depression and T-wave inversion on ECG, bilateral and/or diffuse GGO involvement on chest roentgenograms and higher levels of ESR, hs-CRP and procalcitonin at the time of admission.

References

1. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020:395(10223):497-506.
2. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: A descriptive study. Lancet. 2020;395(10223):507-13.
3. Hui DS, I Azhar E, Madani TA, Dorsten C, Zumla A, Petersen E, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - The latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020;91:264-66.
4. Chang, Lin M, Wei L. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020.
5. Li JW, Han TW, Woodward M, Anderson CS, Zhou H, Chen YD, et al. The impact of 2019 novel coronavirus on heart injury: A systemic review and Meta-analysis. Prog Cardiovasc Dis. 2020;S0033-0620(20)30080-3.
6. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular implications of fatal outcomes of patients with Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020.
7. Ammirati E, Wang DW. SARS-CoV-2 inflames the heart. The importance of awareness of myocardial injury in COVID-19 patients. Int J Cardiol. 2020;311:122-123.
8. Llorens P, Javaloyes P, Masip J, Gil V, Puente PH, Sanchez FJ, et al. Prognostic value of chest radiographs in patients with acute heart failure: The Radiology in Acute Heart Failure (RAD-ICA) study. Emergencias. 2019;31(5):318-326.
9. Seymour CW, Rosengart MR. Septic shock: Advances in diagnosis and treatment. JAMA. 2015;314(7):708-17.
10. Richardson S, Hirsch JS, Narasimhan M. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA. 2020.
11. Tian S, Hu N, Lou J, Chen K, Kang X, Xiang Z, et al. Characteristics of COVID-19 infection in Beijing. J Infect. 2020;80(4):401-6.
12. Chen T, Wu D, Chen H. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: Retrospective study. BMJ. 2020.
13. Fu L, Wang B, Yuan T, Chen X, Fitzpatrick T, Li P, et al. Clinical characteristics of Coronavirus Disease 2019 (COVID-19) in China: A systematic review and meta-analysis. J Infect. 2020;8(6):656-65.
14. Zheng Y, Xu H, Yang M, Zeng Y, Chen H, Liu R, et al. Epidemiological characteristics and clinical features of 32 critical and 67 noncritical cases of COVID-19 in Chengdu. J Clin Virol. 2020;127:104366.
15. Li X, Xu S, Yu M, Wang K, Tao Y, Zhou Y, et al. Risk factors for severity and mortality in adult COVID-19 inpatients in Wuhan. J Allergy Clin Immunol. 2020.
16. Li X, Wang L, Yan S, Yang F, Xiang L, Zhu J, et al. Clinical characteristics of 25 death cases with COVID-19: A retrospective review of medical records in a single medical center, Wuhan, China. Int J Infect Dis. 2020;94:128-32.
17. Prkno A, Wacker C, Brunkhorst FM, Schlattmann P. Procalcitonin-guided therapy in intensive care unit patients with severe sepsis and septic shock--a systematic review and meta-analysis. Crit Care. 2013;17(6):R291.
18. de Jong E, van Oers JA, Beishuizen A, Vos P, Vermeijden WJ, Hass LE, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: A randomised, controlled, open-label trial. Lancet Infect Dis. 2016;16(7):819-27.
19. Wirz Y, Meier MA, Bouadma L, Luyt CE, Wolff M, Chastre J, et al. Effect of procalcitonin-guided antibiotic treatment on clinical outcomes in intensive care unit patients with infection and sepsis patients: A patient-level meta-analysis of randomized trials. Crit Care. 2018;22(1):191.
20. Möckel M, Searle J, Maisel A. The role of procalcitonin in acute heart failure patients. ESC Heart Fail. 2017;4(3):203-208.
21. Möckel M, Slagman A, Vollert JO, Ebmeyer S, Wiemer JC, Searle J, et al. Rationale and design of the IMPACT EU-trial: Improve management of heart failure with procalcitonin biomarkers in cardiology (BIC)-18. Biomarkers. 2018;23(1):97-103.
22. Cvetinovic N, Isakovic AM, Lainscak M, Dungen HD, Nikolic NM, Loncar G. Procalcitonin in heart failure: Hic Et Nunc. Biomark Med. 2017;11(10):893-903.
23. Tersalvi G, Vicenzi M, Calabretta D, Biasco L, Pedrazzini G, Winterton D. Elevated troponin in patients with Coronavirus Disease 2019 (COVID-19): Possible mechanisms. J Card Fail. 2020.
24. Zhu H, Rhee JW, Cheng P, Waliany S, Chang A, Witteles RM, et al.

Cardiovascular complications in patients with COVID-19: Consequences of viral toxicities and host immune response. Curr Cardiol Rep. 2020;22(5):32.

25. Tan C, Huang Y, Shi F, Tan K, Ma Q, Chen Y, et al. C-reactive protein correlates with computed tomographic findings and predicts severe COVID-19 early. J Med Virol. 2020.

26. Li LQ, Huang T, Wang YQ, Wang ZP, Liang Y, Huang TB, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol. 2020.

27. Vaduganathan M, Vardeny O, Michel T, McMurray JJ, Pfeffer MA, Solomon SD. Renin-Angiotensin-aldosterone system inhibitors in patients with Covid-19. N Engl J Med. 2020;382(17):1653-9.

28. Zhang P, Zhu L, Cai J, Lei F, Qin J, Xie J, et al. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. Circ Res. 2020;126(12):1671-81.

29. Guo J, Huang Z, Lin L, Lv J. Coronavirus Disease 2019 (COVID-19) and cardiovascular disease: A viewpoint on the potential influence of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers on onset and severity of severe acute respiratory syndrome coronavirus 2 infection. J Am Heart Assoc. 2020;9(7):e016219.

30. Ferreira AJ, Shenoy V, Qi Y, Fraga –Silva RA, Santos RA, Katovich MJ, et al. Angiotensin-converting enzyme 2 activation protects against hypertension-induced cardiac fibrosis involving extracellular signal-regulated kinases. Exp Physiol. 2011;96(3):287-94.

31. Sommerstein R, Kochen MM, Messerli FH, Grain C. Coronavirus Disease 2019 (COVID-19): Do angiotensin-converting enzyme inhibitors/angiotensin receptor blockers have a biphasic effect? J Am Heart Assoc. 2020;9(7):e016509.

32. Report of the WHO-China joint mission on Coronavirus Disease 2019 (COVID-19) - World Health Organization. 2020.

33. WHO Director-General's opening remarks at the media briefing on COVID-19 - 3 March 2020 - World Health Organization. 2020.