Clinical impact of blood pressure variability in patients with COVID-19 and hypertension

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Objective This study aimed to investigate the relationship between blood pressure variability (BPV) and clinical outcomes in patients with coronavirus disease 2019 (COVID-19) and hypertension.

Methods A total of 136 patients hospitalized with COVID-19 were enrolled in this study. Patients were grouped according to the presence of hypertension and BPV. Mean arterial pressure (MAP) measured at 8 a.m. and 8 p.m. was analyzed, and BPV was calculated as the coefficient of variation of MAP (MAPCV). High BPV was defined as MAPCV values above the median. We compared MAPCV (11.4 ± 4.8 vs. 8.9 ± 3.2; P = 0.002), and higher MAPCV (HR 1.617, 95% CI, 1.281–2.040, P < 0.001) were significantly associated with in-hospital mortality. In Cox regression analysis, advanced age [≥80 years, hazard ratio (HR) 10.4, 95% confidence interval (CI) 2.264–47.772, P = 0.003] and higher MAPCV (HR 1.617, 95% CI, 1.281–2.040, P < 0.001) were significantly associated with in-hospital mortality.

Conclusion High BPV in COVID-19 patients with hypertension is significantly associated with in-hospital mortality. Advanced age and systemic inflammation are proportional to high BPV. Additional attention is needed for COVID-19 patients with hypertension and high BPV.

Keywords: blood pressure variability, coronavirus disease 2019, SARS-CoV-2, hypertension

Introduction

In December 2019, pneumonia caused by an unknown pathogen broke out in Wuhan City, the capital of Hubei Province, China. In January 2020, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the pathogen underlying the disease [1]. As of 15 November 2020, the number of confirmed cases of coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has surpassed 53.7 million cases globally, resulting in 1.3 million deaths [2].

The clinical and epidemiological features of COVID-19 have been repeatedly reported, and one of the most common comorbidities among COVID-19 patients is hypertension [3–5]. Some studies have shown that hypertension is a risk factor for worse outcomes in patients with COVID-19 [6, 7]. In other studies, hypertension was no longer an independent risk factor for outcomes of COVID-19 patients after multivariate analysis, despite being identified as a risk factor by univariate analysis [3, 8]. Taken together, the prevalence of hypertension seems to be high among patients with COVID-19, but the available evidence so far is not solid enough to support the conclusion that hypertension is a real independent risk factor for clinical outcome in COVID-19 patients.

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It has recently been suggested that the occurrence of cardiovascular complications may be related not only to the severity of blood pressure (BP) values but also to the degree of BP fluctuation. In fact, blood pressure variability (BPV) has been identified in various studies as a predictor of cardiovascular complications and organ damage marker in the general population as well as among hypertensive patients [9,10]. However, the risk associated with BPV in COVID-19 patients with hypertension has been less investigated.

In this study, we aimed to clarify the impact of BPV on the outcomes of COVID-19 patients with hypertension.

Methods

Study design and participants

This single-center, retrospective, observational study was performed at Yeungnam University Medical Center in Daegu, Republic of Korea. We analyzed adults (≥18 years old) with COVID-19 who were diagnosed according to the interim guidance of the WHO [11], and who were hospitalized in our hospital from 14 February 2020, to 08 April 2020. The electronic medical records of the patients were reviewed by two physicians (JH Nam and JI Park). Patient data during hospitalization, including demographics, comorbidities, laboratory findings, treatments and outcomes were collected and analyzed. The identification of patients with hypertension was based on a clearly documented medical history of hypertension with antihypertensive drugs or a systolic BP ≥ 140 mmHg or a diastolic BP ≥ 90 mmHg as the criteria [12]. This study was approved by the Institutional Review Board (IRB) of Yeungnam University Medical Center (YUMC 2020-04-080) and conformed to ethical guidelines of the 1975 Declaration of Helsinki. The IRB waived the need for informed consent from patients owing to the retrospective nature of the study and the absence of patients’ identification in the data presented.

Definitions

Acute respiratory distress syndrome was defined according to the Berlin Definition [13]. Sepsis and septic shock were defined according to the WHO interim guideline [11]. The acute cardiac injury was considered to occur when the level of creatine kinase-MB (CK-MB) was above the 99th percentile of the upper reference limit or when the level of N-terminal pro-B type natriuretic peptide (NT-proBNP) was ≥300 pg/mL [14,15]. Acute renal injury was defined as an increase in the serum creatinine level of >0.3 mg/dL within 48 h or 1.5 times the baseline level within 7 days and decreased urine output of <0.6 mL/kg/h for 6 h [16].

Blood pressure monitoring and assessment of blood pressure variability

Serial BP recordings during hospitalization were obtained from the electronic medical records. Noninvasive BP recordings were obtained twice a day (8 a.m. and 8 p.m.) using an automated oscillometric device (UA-767JP, A&D Company, Kitamoto-shi, Saitama, Japan). In the ICU, BP was recorded every hour with invasive BP monitoring via peripheral arterial lines. The invasive arterial catheter used was a BD Angiocath Plus 22G (Becton Dickinson Medical, Singapore) in the right or left radial artery. Invasive arterial BP was recorded with the invasive pressure device (TruWave, Edwards Lifesciences Corp., Irvine, California, USA) connected to the monitor (Bedside Monitor BSM-3763, NIHON KOHDEN, Tokyo, Japan). Invasive BP measurements at 8 a.m. and 8 p.m. were selected, which is the same timing as that of the noninvasive BP measurement.

BP profiles were described using parameters for mean arterial pressure (MAP): mean (MAPmean), SD (MAPSD) and coefficient of variation (equal to (SD × 100)/mean, MAPCV) values for MAP were measured and calculated for each individual. In our study, MAP CV was considered the parameter of BPV. BPV was classified as high BPV when the values of MAP CV were above the median and low BPV when the values were below the median.

Statistical analysis

Categorical variables are shown as frequencies or percentages, and continuous variables as mean ± SD or median. Categorical variables were compared using the χ2 test, Fisher’s exact test or linear by linear association. Continuous variables were compared using Student’s t test or Kruskal–Wallis test. The Pearson correlation was used to evaluate the relationship of MAP CV with age and levels of C-reactive protein (CRP), CK-MB, NT-proBNP and creatinine. Survival was estimated using the Kaplan–Meier method. Cox proportional hazard regression analysis was applied to determine the potential risk factors associated with in-hospital mortality. Variables that were considered clinically relevant or that showed a univariate relationship with in-hospital mortality (P < 0.05) were included in the multivariate regression analysis, and the results are reported as hazard ratios (HR) and 95% confidence interval (CI). All statistical analyses were performed using IBM SPSS version 20.0 (IBM Co., Armonk, New York, USA). A two-sided P value <0.05 was considered statistically significant.

Results

Clinical characteristics and outcomes of COVID-19 patients with or without hypertension

A flowchart of the data screening procedure is shown in Fig. 1. A total of 136 patients were enrolled for final analysis. Of the 136 patients, 51 (37.5%) had a medical history of hypertension. The clinical characteristics and outcomes of the COVID-19 patients with and without hypertension are reported in Table 1. When compared with patients without hypertension, patients with hypertension were older (70 ± 12 vs. 53 ± 17 years, P < 0.001), more likely to have a prior history of diabetes mellitus (17 [33.3%] vs. 9 [10.6%]), P = 0.001) or chronic kidney disease (CKD; 5 [9.8%] vs. 0, P = 0.007). The CRP level was significantly higher in hypertensive patients than in nonhypertensive patients (9.429 ± 9.170 vs. 5.270 ± 8.205 mg/dL, P = 0.009). Patients with hypertension exhibited higher levels of
NT-proBNP (2149.9 ± 7252.5 vs. 189.9 ± 466.3 pg/mL, \(P = 0.077\)) and creatinine (1.83 ± 4.05 vs. 0.80 ± 0.24, \(P = 0.076\)) than those without hypertension. Compared with the patients without hypertension, those with hypertension had higher MAP \(_{\text{mean}}\) (95 ± 8 vs. 88 ± 13 mmHg, \(P = 0.001\)), MAP \(_{\text{SD}}\) (11 ± 4 vs. 8 ± 3 mmHg, \(P < 0.001\)), and MAP \(_{\text{CV}}\) (11 ± 5 vs. 9 ± 3, \(P = 0.002\)) during hospitalization. Hypertensive patients developed more frequent complications, including sepsis (21 [41.2%] vs. 17 [20.0%], \(P = 0.008\)), ARDS (17 [33.3%] vs. 13 [15.3%], \(P = 0.014\)), and shock (15 [29.4%] vs. 7 [8.2%], \(P = 0.001\)) compared with non-hypertensive patients. Among the 136 COVID-19 patients included in the analysis, 15 (11.0%) died during hospitalization. More hypertensive patients died compared to non-hypertensive patients (10 [19.6%] vs. 5 [5.9%], \(P = 0.013\)).

**Clinical characteristics and outcomes of COVID-19 patients grouped according to hypertension and blood pressure variability**

The clinical characteristics and outcomes of the COVID-19 patients subgrouped according to the presence of hypertension and high BPV are reported in Table 2. Age, diabetes mellitus, CKD, levels of CRP, CK-MB, NT-proBNP, creatinine and in-hospital mortality increased from patients with low BPV to nonhypertensive patients with high BPV and hypertensive patients with high BPV (\(P < 0.001\) for age, \(P < 0.001\) for diabetes mellitus, \(P < 0.003\) for CKD, \(P < 0.001\) for CRP, \(P = 0.006\) for CK-MB, \(P < 0.001\) for NT-proBNP, \(P < 0.001\) for creatinine and \(P < 0.001\) for in-hospital mortality). Antihypertensive treatments on admission were generally comparable between hypertensive patients with and without high BPV (32 [88.9%] vs. 14 [93.3%], \(P = 1\)).

**Associations between blood pressure variability and age, marker of inflammation, markers of acute cardiac injury, acute renal injury**

The associations of MAP \(_{\text{CV}}\) with age and levels of CRP, CK-MB, NT-proBNP and creatinine were analyzed in all patients (Fig. 2 and Supplementary Fig. 1, Supplemental digital content, http://links.lww.com/BPMJ/A137). Age and CRP levels were positively correlated with MAP \(_{\text{CV}}\) (\(r = 0.402\) and \(P < 0.001\) for age, \(r = 0.519\) and \(P < 0.001\) for CRP, respectively; Fig. 2a,b). MAP \(_{\text{CV}}\) was correlated with the levels of CK-MB, NT-proBNP and creatinine (\(r = 0.319\) and \(P = 0.012\) for CK-MB, \(r = 0.285\) and \(P = 0.002\) for NT-proBNP, \(r = 0.500\) and \(P < 0.001\) for creatinine, respectively; Supplementary Fig. 1a,b,c, Supplemental digital content, http://links.lww.com/BPMJ/A137).

**Prognosis of COVID-19 patients grouped according to hypertension and blood pressure variability**

The Kaplan–Meier curves showed that patients with hypertension were more likely to die than patients without hypertension, and patients with high BPV were more likely to die than those with low BPV (\(P = 0.02\) and \(P < 0.001\), respectively; Fig. 3a,b). The in-hospital mortality rates showed a gradual increase: patients with low BPV showed the lowest rates, followed by nonhypertensive patients with high BPV and hypertensive patients with high BPV, who had the highest rates (\(P < 0.001\); Fig. 3c).

To further explore the potential risk factors for in-hospital mortality, we performed a Cox proportional hazard regression analysis (Table 3). After adjusting for
| Demographics, laboratory findings, blood pressure profiles, treatments and outcomes of COVID-19 patients with and without hypertension |
|---------------------------------------------------------------|
| **All (n = 136)** | **Hypertension (−) (n = 85)** | **Hypertension (+) (n = 51)** | **P value** |
| Demographics | | | |
| Age, year | 60 ± 17 | 53 ± 17 | 70 ± 12 | <0.001 |
| <70 | 95 (69.9%) | 72 (84.7%) | 23 (45.1%) | <0.001 |
| 70–79 | 26 (19.1%) | 9 (10.6%) | 17 (33.3%) | |
| ≥ 80 | 15 (11.0%) | 4 (4.6%) | 11 (21.6%) | |
| Sex, men | 64 (47.1%) | 34 (40.0%) | 30 (58.8%) | 0.033 |
| BP on admission | | | | 0.027 |
| SBP, mmHg | 129 ± 20 | 126 ± 18 | 134 ± 21 | 0.453 |
| DBP, mmHg | 80 ± 14 | 81 ± 11 | 79 ± 18 | 0.532 |
| MAP, mmHg | 94 ± 14 | 98 ± 13 | 97 ± 16 | 0.001 |
| Comorbidities | | | | 0.001 |
| Diabetes mellitus | 26 (19.1%) | 9 (10.6%) | 17 (33.3%) | |
| CVA | 5 (3.7%) | 1 (1.2%) | 4 (7.8%) | 0.006 |
| CKD | 5 (3.7%) | 0 | 5 (9.8%) | 0.007 |
| IHD | 11 (8.1%) | 5 (5.9%) | 6 (11.8%) | 0.33 |
| Heart failure | 10 (7.4%) | 6 (7.1%) | 4 (7.8%) | 1 |
| Antihypertensive drugs on admission | | | | |
| ACEis/ARBs | 33 (64.7%) | – | 33 (64.7%) | – |
| Beta blockers | 12 (23.5%) | – | 12 (23.5%) | – |
| CCBs | 23 (45.1%) | – | 23 (45.1%) | – |
| Diuretics | 11 (21.6%) | – | 11 (21.6%) | – |
| Any of drugs above | 46 (90.2%) | – | 46 (90.2%) | – |
| Symptoms on admission | | | | 0.763 |
| Fever | 39 (28.7%) | 28 (32.9%) | 11 (21.6%) | |
| Cough | 37 (27.2%) | 28 (32.9%) | 9 (17.6%) | |
| Dyspnea | 28 (21.3%) | 12 (14.1%) | 17 (33.3%) | 1 |
| Myalgia | 18 (13.2%) | 9 (10.6%) | 9 (17.6%) | |
| Diarrhea | 2 (1.5%) | 0 | 2 (3.9%) | |
| Others | 11 (8.1%) | 8 (9.4%) | 3 (5.9%) | |
| Duration from symptom onset to admission, day | 7.9 ± 7.3 | 8.4 ± 7.8 | 7.3 ± 6.5 | 0.436 |
| Laboratory findings | | | | 0.001 |
| WBC, per μL | 6.79 ± 3.45 | 6.33 ± 2.87 | 7.55 ± 4.17 | |
| Hemoglobin, g/dL | 12.6 ± 1.6 | 13.1 ± 1.4 | 12.4 ± 1.8 | 0.045 |
| Platelets, per μL | 237 ± 103 | 244 ± 112 | 225 ± 86 | 0.312 |
| CRP, mg/dL | 6.817 ± 7.771 | 5.270 ± 8.205 | 4.292 ± 9.170 | 0.009 |
| Procalcitonin, ng/dL | 0.292 ± 1.118 | 0.298 ± 1.374 | 0.253 ± 0.374 | 0.829 |
| Creatinine, mg/dL | 4.1 ± 5.7 | 4.186 ± 5.614 | 4.186 ± 5.497 | 0.121 |
| CK-MB, ng/mL | 4.6 ± 6.6 | 3.8 ± 4.4 | 5.2 ± 7.8 | 0.191 |
| NT-proBNP, pg/mL | 9438.8 ± 45838.8 | 189.9 ± 466.3 | 21498.9 ± 72525.5 | 0.077 |
| Acute renal injury | 31 (22.8%) | 12 (14.1%) | 19 (37.3%) | 0.002 |
| Acute cardiac injury | 32 (23.5%) | 9 (11.8%) | 23 (46.9%) | <0.001 |
| BP profiles during hospitalization | | | | 0.001 |
| MAPmean, mmHg | 91 ± 12 | 879 ± 13.1 | 95.1 ± 8.1 | |
| MAP25, mmHg | 8.9 ± 3.6 | 8.0 ± 3.1 | 10.6 ± 3.9 | <0.001 |
| MAP95, mmHg | 9.8 ± 4.0 | 8.9 ± 3.2 | 11.4 ± 4.8 | 0.002 |
| Treatments | | | | 0.375 |
| Antibiotics | 135 (99.3%) | 85 (100%) | 50 (98.0%) | |
| Lopinavir/Ritonavir | 126 (92.6%) | 79 (92.9%) | 47 (92.2%) | |
| Hydroxychloroquine | 125 (91.9%) | 76 (92.9%) | 49 (96.1%) | 0.298 |
| Guilecortocoid | 42 (30.9%) | 21 (24.7%) | 21 (41.2%) | 0.044 |
| Intravenous immunoglobulin | 0 (0.0%) | 0 | 0 | 0.556 |
| Mechanical ventilation | 15 (11.0%) | 7 (8.3%) | 8 (15.7%) | 0.188 |
| Vasoressor use | 17 (12.5%) | 7 (8.2%) | 10 (19.6%) | 0.052 |
| RRT | 4 (2.9%) | 2 (2.4%) | 2 (3.9%) | 0.631 |
| ECMO | 7 (5.1%) | 4 (4.7%) | 3 (5.9%) | 0.013 |
| Outcomes | | | | 0.008 |
| Sepsis | 38 (27.9%) | 17 (20.0%) | 21 (41.2%) | |
| ARDS | 30 (22.1%) | 13 (15.3%) | 17 (33.3%) | 0.014 |
| Shock | 22 (16.2%) | 7 (8.2%) | 15 (28.4%) | 0.001 |
| ICU admission | 18 (13.2%) | 8 (9.4%) | 10 (19.6%) | 0.089 |
| In-hospital mortality | 15 (11.0%) | 5 (5.9%) | 10 (19.6%) | 0.013 |

Values are presented as number (%) or mean ± SD.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARDS, acute respiratory distress syndrome; BP, blood pressure; BPV, blood pressure variability; CCB, calcium channel blocker; CKD, chronic kidney disease; CK-MB, creatinine kinase-MB; CRP, C-reactive protein; CV, coefficient of variation; CVA, cerebrovascular accident; DBP, diastolic blood pressure; ECMO, extracorporeal membrane oxygenation; IHD, ischemic heart disease; MAP, mean arterial pressure; NT-proBNP, N-terminal pro-B type natriuretic peptide; RRT, renal replacement therapy; SBP, systolic blood pressure; WBC, white blood cell.
Table 2  Demographics, laboratory findings, treatments, and outcomes of COVID-19 patients grouped according to hypertension and BPV

| Hypertension (-), Low^a BPV (n = 53) | Hypertension (+), Low^a BPV (n = 15) | Hypertension (-), High^b BPV (n = 32) | Hypertension (+), High^b BPV (n = 36) | P value |
|---------------------------------------|---------------------------------------|---------------------------------------|---------------------------------------|---------|
| Demographics                          |                                       |                                       |                                       |         |
| Age, year                             | 48 ± 17                               | 61 ± 10                               | 62 ± 13                               | 73 ± 11  | <0.001 |
| <70                                   | 50 (94.3%)                            | 12 (80.0%)                            | 22 (68.8%)                            | 11 (30.6%) | <0.001 |
| 70–79                                 | 1 (1.9%)                              | 2 (13.3%)                             | 8 (25.0%)                             | 15 (41.7%) |         |
| ≥ 80                                  | 2 (3.8%)                              | 6 (40.0%)                             | 19 (59.4%)                            | 22 (61.1%) | 0.001  |
| Sex, men                              | 15 (28.3%)                            | 8 (53.3%)                             | 19 (59.4%)                            | 22 (61.1%) |         |
| BP on admission                       |                                       |                                       |                                       |         |
| SBP, mmHg                             | 124 ± 18                              | 140 ± 17                              | 130 ± 18                              | 131 ± 22  | 0.014  |
| DBP, mmHg                             | 80 ± 11                               | 80 ± 24                               | 81 ± 13                               | 78 ± 15   | 0.55   |
| MAP, mmHg                             | 95 ± 12                               | 100 ± 15                              | 97 ± 14                               | 96 ± 16   | 0.473  |
| Comorbidities                         |                                       |                                       |                                       |         |
| Diabetes mellitus                     | 3 (5.7%)                              | 4 (26.7%)                             | 6 (18.8%)                             | 13 (36.1%) | 0.001  |
| CVA                                   | 0                                     | 2 (13.3%)                             | 1 (3.1%)                              | 2 (5.6%)  | 0.253  |
| CKD                                   | 0                                     | 0                                     | 0                                     | 5 (13.9%) | 0.003  |
| IHD                                   | 0                                     | 5 (15.6%)                             | 6 (16.7%)                             | 6 (16.7%) | 0.001  |
| Heart failure                         | 1 (1.9%)                              | 0                                     | 5 (15.6%)                             | 4 (11.1%) | 0.03   |
| Antihypertensive drugs on admission   |                                       |                                       |                                       |         |
| ACEi/ARBs                             | –                                     | 9 (60.0%)                             | –                                     | 24 (66.7%) | 0.65   |
| Beta blockers                         | –                                     | 2 (13.3%)                             | –                                     | 10 (27.8%) | 0.47   |
| CCBs                                  | –                                     | 7 (46.7%)                             | –                                     | 16 (44.4%) | 0.884  |
| Diuretics                             | –                                     | 2 (13.3%)                             | –                                     | 9 (25.0%) | 0.472  |
| Any of drugs above                    | –                                     | 14 (93.3%)                            | –                                     | 32 (89.9%) | 1      |
| Symptoms on admission                 |                                       |                                       |                                       |         |
| Fever                                 | 15 (28.3%)                            | 6 (40.0%)                             | 13 (40.6%)                            | 5 (13.9%) | 0.76   |
| Cough                                 | 22 (41.5%)                            | 4 (26.7%)                             | 6 (18.8%)                             | 5 (13.9%) |         |
| Dyspnea                               | 7 (13.2%)                             | 2 (13.3%)                             | 5 (15.6%)                             | 15 (41.7%) |         |
| Myalgia                               | 4 (7.5%)                              | 2 (13.3%)                             | 5 (15.6%)                             | 7 (19.4%) |         |
| Diarrhea                              | –                                     | 5 (8.3%)                              | –                                     | 3 (8.3%)  |         |
| Acute respiratory distress syndrome   | 10.4 ± 9.0                            | 9.2 ± 4.6                             | 5.3 ± 4.0                             | 6.3 ± 7.1 | 0.009  |
| Laboratory Findings                   |                                       |                                       |                                       |         |
| WBC, per μL                           | 5649 ± 1824                           | 5996 ± 2310                           | 7467 ± 3812                           | 8202 ± 4603 | 0.005  |
| Hemoglobin, g/dL                      | 13.1 ± 1.3                            | 13.5 ± 1.2                            | 13.2 ± 1.6                            | 11.9 ± 1.8 | 0.001  |
| Platelets, per μL                     | 249 ± 98                              | 242 ± 86                              | 235 ± 133                             | 218 ± 86  | 0.588  |
| CRP, mg/dL                            | 2.354 ± 5.013                         | 2.332 ± 3.947                         | 10.227 ± 10.101                       | 12.654 ± 9.076 | <0.001 |
| Procalcitonin, ng/dL                  | 0.039 ± 0.043                         | 0.065 ± 0.043                         | 0.171 ± 0.277                         | 0.340 ± 0.420 | <0.001 |
| Creatinine, mg/dL                     | 0.73 ± 0.17                           | 0.81 ± 0.24                           | 0.92 ± 0.30                           | 2.26 ± 4.77 | <0.001 |
| CK-MB, ng/mL                          | 1.0 ± 0.2                             | 1.5 ± 1.2                             | 5.1 ± 4.8                             | 5.9 ± 8.3  | 0.006  |
| NT-proBNP, pg/mL                      | 92.0 ± 125.7                          | 159.3 ± 194.3                         | 353.2 ± 722.9                         | 2968.6 ± 8503.3 | <0.001 |
| Antibiotics                           | 53 (100%)                             | 15 (100%)                             | 32 (100%)                             | 35 (97.2%) | 0.191  |
| Lopinavir/ Ritonavir                   | 49 (92.5%)                            | 15 (100%)                             | 30 (93.8%)                            | 32 (88.9%) | 0.553  |
| Hydroxychloroquine                    | 45 (84.9%)                            | 14 (93.3%)                            | 31 (96.9%)                            | 35 (97.2%) | 0.021  |
| Glucocorticoid                        | 6 (11.3%)                             | 2 (13.3%)                             | 15 (46.9%)                            | 19 (52.8%) | <0.001 |
| Invasive BP monitoring                | 0                                     | 1 (6.7%)                              | 7 (21.9%)                             | 8 (22.2%)  | <0.001 |

Values are presented as number (%) or mean ± SD.

The term 'low' refers to values below the median.

The term 'high' to values above the median.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARDS, acute respiratory distress syndrome; BP, blood pressure; BPV, blood pressure variability; CCB, calcium channel blocker; CVD: chronic kidney disease; CK-MB, creatinine kinase-MB; CRP, C-reactive protein; CV, coefficient of variation; CVA, cerebrovascular accident; DBP, diastolic blood pressure; ECMO, extracorporeal membrane oxygenation; IHD, ischemic heart disease; MAP, mean arterial pressure; NT-proBNP, N-terminal pro-B type natriuretic peptide; RRT, renal replacement therapy; SBP, systolic blood pressure; WBC, white blood cell.
confounding factors, advanced age (≥80 years, HR 10.4, 95% CI 2.264–47.772, \( P = 0.003 \)) and higher MAPCV (HR 1.617, 95% CI 1.281–2.040, \( P < 0.001 \)) were significantly associated with in-hospital mortality.

**Discussion**

The major findings of this study are that high BP fluctuation (i.e. BPV) was significantly associated with in-hospital mortality. Moreover, this high BPV had a proportional relationship with advanced age, high levels of inflammatory markers such as CRP, and worse clinical outcomes, including cardiac and renal injury.

Several reports have demonstrated that the prevalence of hypertension is high among patients with COVID-19 [3–5]. For example, Zhou et al. reported that comorbidities were present in nearly half of COVID-19 patients, with hypertension being the most common comorbidity (58 of 191 (30.4%); 56 years of median age) [3]. However, a Chinese hypertension survey showed that 44.6% of the population aged 55–64 years had hypertension [17]. Our study showed that 51 of 136 (37.5%, 60 years of mean age) COVID-19 patients had a medical history of hypertension. According to a report from the Korea Centers for Disease Control and Prevention, the prevalence in the Korean general population aged 60–69 years was 46.0% [18]. The actual prevalence of hypertension in COVID-19 patients may not be higher, considering the prevalence of hypertension among the same age group in the general population.

Patients with COVID-19 and hypertension have been reported to have an increased risk of adverse outcomes. Zhou et al. [3] found that hypertension had an HR of 3.05 for in-hospital mortality in 191 COVID-19 patients. However, hypertension was not included as a potential risk factor in the multivariate analysis. In another study by Simonnet et al. [8], hypertension was not found to be an independent risk factor for outcomes of COVID-19 patients after multivariate analysis, despite being identified as a risk factor by univariate analysis. The Centers for Disease Control and Prevention also informed that adults with any age with hypertension might be at an increased risk for severe illness from COVID-19 [19]. Our study revealed that COVID-19 patients with hypertension tended to show higher mortality than those without hypertension. However, multivariate Cox regression analysis showed that after adjusting for confounders, including age and other comorbidities, hypertension did not have a significant correlation with in-hospital mortality. This result may be because older individuals often have multiple comorbidities, such as hypertension, diabetes mellitus or CKD, and are therefore vulnerable to infection. At this point, it is unclear whether hypertension or a high mean BP value only are indeed independent risk factors for developing a severe disease in patients with COVID-19.

It is known that not only mean BP values but also BP fluctuations (i.e. BPV) may be related to cardiovascular events [9,10]. There are several factors that can affect and increase BPV [9]. One of these factors is advanced age. It is suggested that advanced age is associated with progressive stiffening of major arteries, and reduced arterial compliance increases both BPV and the risk of cardiovascular events [20,21]. In our study, BPV significantly increased with aging. Systemic inflammation is also a plausible
factor that leads to high BPV [22]. Systemic inflammation following an infection, especially sepsis, increases inflammatory mediators that elicit diffuse vasodilation or transient suppression of myocardial function, and these changes can contribute to BP fluctuation. Impairment of myocardial function in severe COVID-19 patients has also been reported [23]. Altered vasomotor tone or impairment of myocardial function caused by systemic

Kaplan–Meier survival curves for mortality during hospitalization. (a) Patients with or without hypertension, (b) patients with high BPV or low BPV, (c) nonhypertensive patients with low BPV, hypertensive patients with low BPV, nonhypertensive patients with high BPV or hypertensive patients with high BPV. *The term 'low' refers to values below the median and the term 'high' to values above the median. BPV, blood pressure variability; CV, coefficient of variation; MAP, mean arterial pressure.
Table 3  Cox regression analysis on the potential risk factors associated with mortality in patients with COVID-19

| Variable                    | Univariate analysis | Multivariate analysis |
|-----------------------------|---------------------|-----------------------|
| Age, year                   |                     |                       |
| <70                         | Reference           |                       |
| 70−79                       | 4.392 (1.166−16.539) | 0.029                 |
| ≥80                         | 10.85 (3.045−39.381) | <0.001                |
| Sex, men                    | 1.492 (0.529−4.219)  | 0.451                 |
| Diabetes mellitus           | 2.964 (1.054−8.334)  | 0.039                 |
| Hypertension                | 3.317 (1.130−9.741)  | 0.029                 |
| CVA                         | 6.012 (1.660−21.778) | 0.006                 |
| CKD                         | 7.088 (1.997−25.158) | 0.002                 |
| CRP, mg/dL                  | 1.099 (1.049−1.152)  | <0.001                |
| Acute cardiac injury        | 5.55 (1.872−16.454)  | 0.002                 |
| Acute renal injury          | 10.516 (3.346−33.045)| <0.001                |
| MAP, mmHg                   | 1.425 (1.276−1.592)  | <0.001                |
| Vasopressor use             | 7.876 (2.837−21.884) | <0.001                |
| Body temperature ≥38°C      | 2.6 (0.925−7.309)    | 0.07                  |
| Heart rate ≥100 bpm         | 3.444 (0.773−15.336) | 0.105                 |

CI, confidence Interval; CKD, chronic kidney disease; CRP, C-reactive protein; CV, coefficient of variation; CVA, cerebrovascular accident; HR, hazard ratio; MAP, mean arterial pressure.

inflammation may explain our finding that inflammatory markers were positively correlated with BPV in COVID-19 patients.

BPV is associated with target organ damage and rate of cardiovascular events in both the general population and in patients with hypertension, independent of mean BP [9,10,24]. The pathophysiological mechanisms of BPV and cardiac injury caused by COVID-19 are not well defined. An increase in the markers of cardiac injury may be due to an increased oxygen demand by the myocardium or an inflammatory process caused by an exaggerated cytokine response by type 1 and 2 helper T cells, which could cause a reduction in coronary blood flow, decrease in oxygen supply, instability of the atherosclerotic plaque and microthrombogenesis [25]. It could be hypothesized that episodes of myocardial ischemia in COVID-19 patients could provoke sympathetic, angiotensin or other reactive responses that mediate systemic vasconstriction and affect BP, thus more closely linking cardiovascular events and BPV [21]. Our analysis was also consistent with this hypothesis by showing significantly high BPV in patients with cardiac injury compared with those without. The clinical significance of BPV for acute renal injury may be related to hemodynamic alterations caused by systemic inflammation. As described above, viral and bacterial infections are known to cause excessive release of inflammatory cytokines that lead to microvascular dysfunction, increased vascular permeability and tissue damage, along with hypoperfusion, which affects kidney microcirculation [26]. This pathophysiological mechanism may result in BP fluctuation.

Our study has several limitations. First, the sample size of this study was relatively small and the subgroups were not evenly distributed. Also, the number of invasive or noninvasive BP monitoring was not uniform among the subgroups and this could be a source of bias in our study. A larger cohort study is needed to support our conclusion. Second, serial BP measurements during hospitalization were obtained only twice a day (at 8 a.m. and 8 p.m.) owing to the limitations imposed in the isolation ward and the urgency of containing the COVID-19 epidemic. Increasing the time interval between BP measurements will result in less BP measurements, which can consequently increase BPV. Third, we could perform an echocardiographic exam in only 8 (5.9%) patients during hospitalization due to the complex vendor and transducer sterilization procedures and the difficulty acquiring echocardiographic images while wearing level-D personal protective equipment. Therefore, it is difficult to report the echocardiographic findings of our COVID-19 patients. Fourth, the decision to perform laboratory tests was left to the discretion of each physician in clinical practice; thus, some data, such as troponin I, as a marker of acute cardiac injury, were not adequately acquired. Fifth, although it is suggested that increased sympathetic discharge may exert detrimental effects on COVID-19 patients [27], we could not properly evaluate the relationship between autonomic dysfunction and BPV. However, we performed a Cox regression analysis by including the heart rate over 100 beats per minute, vasopressor use or body temperature over 38°C as confounding factors to adjust for the effects of autonomic dysfunction on BP. Sixth, we could not clarify whether the influence of ACEi/ARBs on COVID-19 is harmful, as only 33 COVID-19 patients with hypertension taking ACEi/ARBs were enrolled. However, in our subanalysis, the rate of in-hospital mortality was not different between hypertensive patients taking ACEi/ARBs and those not taking ACEi/ARBs [7 of 33 (21.2%) vs. 3 of 18 (16.7%), P = 1]. Seventh, as this study was retrospective, even though the association between BPV and outcome was significant and persisted after multivariate adjustments,
our findings cannot establish a causal link between BPV and outcome.

In conclusion, COVID-19 patients with hypertension and high BP fluctuation had worse clinical outcomes than those without hypertension. Advanced age and severe systemic inflammation may be a potential mechanism for BPV. Further studies are needed to identify a causal link between BPV and clinical outcome will be needed.

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Conflicts of interest
There are no conflicts of interest.

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