Prognostic utility of pulmonary artery and ascending aorta diameters derived from computed tomography in COVID-19 patients

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Abstract
Aim: Chest computed tomography (CT) imaging plays a diagnostic and prognostic role in Coronavirus disease 2019 (COVID-19) patients. This study aimed to investigate and compare predictive capacity of main pulmonary artery diameter (MPA), ascending aorta diameter (AAo), and MPA-to-AAo ratio to determine in-hospital mortality in COVID-19 patients.

Materials and methods: This retrospective study included 255 hospitalized severe or critical COVID-19 patients. MPA was measured at the level of pulmonary artery bifurcation perpendicular to the direction of the vessel through transverse axial images and AAo was measured by using the same CT slice at its maximal diameter. MPA-to-AAo ratio was calculated by division of MPA to AAo.

Results: Multivariate logistic regression model yielded MPA ≥29.15 mm (OR: 4.95, 95% CI: 2.01–12.2, p = 0.001), MPA (OR: 1.28, 95% CI: 1.13–1.46, p < 0.001), AAo (OR: .90, 95% CI: .81–.99, p = 0.040), and MPA-to-AAo ratio ≥.82 (OR: 4.67, 95% CI: 1.86–11.7, p = 0.001) as independent predictors of in-hospital mortality. Time-dependent multivariate Cox-proportion regression model demonstrated MPA ≥29.15 mm (HR: 1.96, 95% CI: 1.03–3.90, p = 0.047) and MPA (HR: 1.08, 95% CI: 1.01–1.17, p = 0.048) as independent predictors of in-hospital mortality, whereas AAo and MPA-to-AAo ratio did not reach statistical significance.

Conclusion: Pulmonary artery enlargement strongly predicts in-hospital mortality in hospitalized COVID-19 patients. MPA, which can be calculated easily from chest CT imaging, can be beneficial in the prognostication of these patients.

Keywords
ascending aorta, computed tomography, COVID-19, pulmonary artery
INTRODUCTION

A new infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and named as the Coronavirus disease 2019 (COVID-19) has become a threatening health crisis, since December 2019. Because the infection spread globally in a very short time, COVID-19 was characterized as a pandemic in March 2020. COVID-19 primarily affects the lungs and respiratory system. Besides, it has detrimental effects on vascular endothelium by impairing its functional and structural integrity.1,2

Chest computed tomography (CT) imaging plays a diagnostic and prognostic role in COVID-19 patients, and therefore, it is widely used in both diagnosed and suspected COVID-19 patients in order to examine the lungs and for risk stratification.3 Indices derived from chest CT such as main pulmonary artery diameter (MPA), ascending aorta diameter (AAo), and MPA-to-AAo ratio were shown to be useful parameters for predicting clinical outcomes in various lung diseases4,5 and COVID-19.6,7 For instance, increased MPA-to-AAo ratio was associated with the severity of lung involvement6 and enlarged MPA was associated with death in COVID-19 patients.7 This study aimed to investigate and compare predictive capacity of MPA, AAo, and MPA-to-AAo ratio to determine in-hospital outcomes in a relatively large COVID-19 patient population.

METHODS

2.1 Study design and patient population

The study was designed in a retrospective fashion and included consecutive 277 hospitalized COVID-19 patients at a tertiary hospital between April 2020 and September 2020. Adult patients diagnosed as COVID-19 by real-time reverse transcriptase polymerase chain reaction (RT-PCR) test and examined with non-contrast CT imaging were included in the study. Patients < 18 years old, patients without CT imaging, pregnant patients, and non-hospitalized patients were not included. In addition, history of primary pulmonary arterial hypertension, chronic thromboembolism, interstitial lung disease, and severe chronic obstructive pulmonary disease were defined as exclusion criteria. Patients with missing data were also excluded from the study. Twenty-two patients had at least one exclusion criterion and these patients were not included in statistical analyses. Primary endpoint of the study was defined as in-hospital mortality and the remaining 255 patients were categorized according to their survival status during their hospitalization period. Secondary outcome measures were defined as percentage of patients requiring intensive care unit (ICU) stay, invasive mechanical ventilation, and length of hospitalization.

All of the procedures applied in this study were in line with the Declaration of Helsinki and written informed consent was obtained from study participants. The local ethics committee of the hospital approved the study protocol. Clinical data of patients, length and type of hospital stay, and discharge status were obtained from hospital registry database.

2.2 Clinical follow-up

Decision for hospitalization and service or ICU stay was made by an infectious disease specialist blinded to study protocol. Hospitalized patients were at severe or critical condition according to clinical classification proposed by National Institutes of Health COVID-19 Treatment Guidelines.8 Peripheral venous blood samples including total complete blood count test, biochemical parameters, liver and renal function tests, ferritin, C-reactive protein (CRP), high sensitive troponin-I (hs-TnI) were obtained from a large antecubital vein at the time of hospital admission and studied at the biochemistry laboratory of the hospital immediately. Basal characteristics of the patients including clinical status, comorbidities, laboratory parameters, and chest CT findings were recorded on a chart by the physicians on a daily basis. Decision for discharge from hospital or transfer to ICU or service was also made by these physicians and they were also blinded to study protocol. Medical treatments of the patients included antiviral agents, antibiotic therapy, hydroxychloroquine, corticosteroids, tocilizumab, and enoxaparin in an individual basis. Criteria for discharge from hospital were defined as absence of fever for at least three consecutive days, clinical improvement of symptoms and two negative RT-PCR test results obtained at least 24-hour intervals.

2.3 Chest CT imaging and analysis

Chest CT examination was performed within the first 24 hour after admission to the hospital using a 128-slice multidetector CT scanner (GE, Revolution Evo, USA) in supine position and during end-inspiration without the administration of iodinated contrast agents. A dedicated room was prepared for CT imaging of COVID-19 patients. After each CT examination, passive air ventilation was performed for at least 30 minutes and machine surfaces were disinfected with ethanol and didecylmethylammonium chloride (DDAC). All CT images were evaluated in axial, sagittal, and coronal planes by two expert radiologists with 4 and 10 years of experience who were blinded to data of the study protocol. Clinical data of patients, length and type of hospital stay, and discharge status were obtained from hospital registry database.

Presence of unilateral or bilateral ground glass opacity, patchy infiltration, pleural effusion, and fibrotic changes were assessed. MPA was measured at the level of pulmonary artery bifurcation perpendicular to the direction of the vessel through transverse axial images and AAo was measured by using the same CT slice at its maximal diameter (Figure 1). Afterwards, MPA-to-AAo ratio was calculated by division of MPA to AAo.9
2.4 Statistical analysis

Statistical analyses were conducted via the IBM SPSS Statistics for Macintosh, Version 24.0 (IBM Corp., Armonk, NY, USA). One-sample Kolmogorov-Smirnov test was used to evaluate the distribution of numerical variables. Student-t test was applied to numerical data which conforms to normal distribution and results were presented as mean and standard deviation. On the other hand, Mann-Whitney-U test was applied for abnormally distributed variables and the results were given as median with inter-quartile range values. Chi-square and Fisher Exact tests were used for categorical variables where appropriate. Receiver operating characteristic (ROC) curve analyses were conducted in order to determine and compare the optimal cut-off values of MPA, AAo, and MPA-to-AAo ratio that predict in-hospital mortality. The area under the ROC curve (AUC) was reported with 95% confidence interval (CI) in addition to sensitivity, specificity, and positive likelihood ratio (PLR). According to these cut-off values, cumulative survival rates were calculated by the Kaplan-Meier method and compared between two groups using the log-rank test.

Predictors of in-hospital mortality were assessed through multivariate binary logistic regression and time-dependent multivariate Cox-proportion regression analyses. Length of hospitalization was considered as time to outcome as days in Cox regression analysis performed through enter method. Increased MPA as a categorical variable, MPA as a continuous variable, AAo as a continuous variable and increased MPA-to-AAo ratio as a categorical variable were investigated in four separate multivariate binary logistic and Cox regression models. All of these models were adjusted for clinical and laboratory variables (age, coronary artery disease, chronic obstructive pulmonary disease, CRP levels, and any abnormal CT lung parenchyma findings). The multicollinearity assessment was performed by correlation r coefficient value. Independent variables with correlation r coefficient above .7 were considered to comprise multicollinearity and were not evaluated in the same model. The results of regression analysis were reported with odds ratio (OR), hazard ratio (HR) and 95% CI. A two-tailed p value lower than 0.05 was considered to be statistically significant.

3 RESULTS

3.1 Baseline characteristics and clinical status

After the application of exclusion criteria, the remaining 255 patients were categorized according to their survival status namely survivor (n = 199) and non-survivor (n = 56). The mean age of the overall study cohort was 55±19 years and 52% of the patients were male. Hypertension was the most common comorbidity with a percentage of 37%. Myalgia or fatigue, cough, dyspnea, and fever were the most frequent admission symptoms, respectively.
TABLE 1  Baseline demographic and clinical features of the with COVID-19 patients according to in-hospital mortality status

| Baseline features                                      | All (n = 255) | Survivor (n = 199) | Non-survivor (n = 56) | p value |
|--------------------------------------------------------|---------------|--------------------|-----------------------|---------|
| Age (years)                                            | 55±19         | 50±17              | 75±10                 | <0.001  |
| Gender (male)                                          | 132 (52%)     | 102 (51%)          | 30 (54%)              | 0.759   |
| Diabetes mellitus                                      | 65 (26%)      | 45 (23%)           | 20 (36%)              | 0.047   |
| Hypertension                                           | 95 (37%)      | 69 (35%)           | 26 (46%)              | 0.108   |
| Coronary artery disease                                | 36 (14%)      | 20 (10%)           | 16 (29%)              | <0.001  |
| Chronic obstructive pulmonary disease                  | 25 (10%)      | 14 (7%)            | 11 (20%)              | 0.005   |

Presenting symptoms

| Fever (Temperature ≥37.3°C)                            | 113 (45%)     | 94 (48%)           | 19 (35%)              | 0.088   |
| Cough                                                  | 144 (57%)     | 120 (61%)          | 24 (44%)              | 0.025   |
| Sputum                                                 | 36 (14%)      | 28 (14%)           | 8 (14%)               | 0.940   |
| Sore throat                                            | 80 (32%)      | 71 (36%)           | 9 (16%)               | 0.006   |
| Dyspnea                                                | 141 (56%)     | 95 (48%)           | 46 (84%)              | <0.001  |
| Headache                                               | 55 (22%)      | 41 (21%)           | 14 (25%)              | 0.450   |
| Myalgia or fatigue                                     | 188 (74%)     | 147 (74%)          | 41 (74%)              | 0.964   |
| Diarrhea                                               | 13 (5%)       | 11 (6%)            | 2 (4%)                | 0.568   |
| Nause or vomiting                                      | 30 (12%)      | 23 (12%)           | 7 (13%)               | 0.822   |
| Rhinorrhea                                             | 21 (8%)       | 19 (10%)           | 2 (4%)                | 0.156   |
| Anosmia or loss of taste                               | 22 (9%)       | 21 (11%)           | 1 (2%)                | 0.041   |

Vital signs at presentation

| Highest Temperature (°C)                               | 37.1±.8       | 37.2±.8            | 37.0±.7               | 0.127   |
| Respiratory rate (breaths per min)                     | 18 (16-23)    | 18 (16-22)         | 23 (18-28)            | <0.001  |
| Respiratory rate >24 (breaths per min)                 | 51 (20%)      | 27 (14%)           | 24 (44%)              | <0.001  |
| Oxygen saturation (%)                                   | 95 (91-97)    | 96 (94-98)         | 90 (81-93)            | <0.001  |
| Systolic blood pressure (mm Hg)                        | 122±13        | 123±11             | 118±18                | 0.059   |

In-hospital treatment

| Antiviral agents                                       | 136 (54%)     | 94 (48%)           | 42 (76%)              | <0.001  |
| Antibiotic agents                                      | 186 (73%)     | 136 (69%)          | 50 (91%)              | <0.001  |
| Hydroxychloroquine                                     | 162 (64%)     | 145 (73%)          | 17 (31%)              | <0.001  |
| Corticosteroids                                        | 37 (15%)      | 15 (8%)            | 22 (40%)              | <0.001  |
| Anticoagulation                                        | 154 (61%)     | 108 (54%)          | 46 (84%)              | <0.001  |
| Tocilizumab                                            | 2 (1%)        | 2 (1%)             | 0 (0%)                | 1.00    |
| Interleukin-1 receptor antagonist                      | 3 (1%)        | 3 (2%)             | 0 (0%)                | 1.00    |

In-hospital other outcomes

| Intensive care unit admission                          | 98 (38%)      | 42 (21%)           | 56 (100%)             | <0.001  |
| Invasive mechanical ventilation                       | 59 (23%)      | 4 (2%)             | 55 (98%)              | <0.001  |
| Length of hospitalization, days                       | 12 (8-17)     | 11 (8-15)          | 12 (7-26)             | 0.319   |

Data are mean (SD), median (IQR) and number (%). p values were determined by student t-test, Mann-Whitney U test, Chi-square test or Fisher’s Exact test, as appropriate. Abbreviations: IQR, interquartile range; SD, standard deviation.

Non-survivor patients were more likely to be older and suffer from diabetes mellitus, coronary artery disease and chronic obstructive pulmonary disease when compared to survivor group patients. There was no difference between patient groups regarding gender and hypertension. When it comes to admission symptoms, dyspnea was significantly higher in non-survivor group, whereas fever, cough, sore throat, and anosmia or loss of taste were more prevalent in survivor group patients. There was no difference in vital signs at admission with respect to highest temperature and systolic blood pressure. However, respiratory parameters including respiratory rate and oxygen saturation were significantly impaired in non-survivors (Table 1).
TABLE 2  Laboratory and radiographic features of the with COVID-19 patients according to in-hospital mortality status

| Laboratory parameters | All (n = 255) | Survivor (n = 199) | Non-survivor (n = 56) | p value |
|-----------------------|--------------|------------------|----------------------|--------|
| Glucose (mg/dl)       | 103 (92-134) | 99 (90-119)      | 133 (107-205)        | <0.001 |
| Creatinin (mg/dl)     | .85 (.68-1.07)| .79 (.65-1.0)    | 1.1 (.91-1.46)       | <0.001 |
| Sodium (mEq/L)        | 139 (136-141)| 139 (137-141)    | 136 (133-141)        | 0.005  |
| Aspartate amino transferase (U/L) | 26 (18-44) | 25 (17-36)       | 44 (23-83)           | <0.001 |
| Albumin (g/dl)        | 4.2±.6       | 4.4±5            | 3.6±.5               | <0.001 |
| Ferritin (µg/L)       | 193 (57-450) | 140 (44-309)     | 464 (189-893)        | <0.001 |
| C-reactive protein (mg/L) | 15 (4-89)   | 8.8 (2.6-32)     | 135 (63-187)         | <0.001 |
| hs-Troponin I (ng/L)  | 4 (2-14)     | 3 (1.8-8)        | 27 (13-267)          | <0.001 |
| White blood cells (×10⁹/L) | 6.79±3.51   | 6.13±2.95        | 9.13±4.28           | <0.001 |
| Neutrophils (×10⁹/L)  | 3.73 (2.83-5.73)| 3.44 (2.66-4.8) | 7.32 (4.35-9.36)    | <0.001 |
| Lymphocytes (×10⁹/L)  | 1.29±.89     | 1.36±.93         | 1.03±.64            | 0.003  |
| Platelets (×10⁹/L)    | 233±80       | 230±73           | 244±99              | 0.318  |
| Hemoglobin (g/L)      | 13.5±1.8     | 13.8±1.6         | 12.6±2.1            | 0.001  |

CT parameters

| Clear                  | 32 (13%) | 31 (16%) | 1 (2%) | <0.001 |
| Unilateral ground-glass opacities | 56 (22%) | 50 (26%) | 6 (11%) | 0.022  |
| Bilateral ground-glass opacities    | 142 (56%) | 100 (50%) | 42 (76%) | 0.001  |
| Patchy infiltration            | 30 (12%) | 25 (13%) | 5 (9%) | 0.473  |
| Pleural effusion              | 18 (7%) | 7 (4%) | 11 (20%) | <0.001 |
| Fibrotic changes              | 51 (20%) | 32 (16%) | 19 (34%) | 0.003  |
| Main pulmonary artery diameter (mm) | 26.3±4.4  | 24.9±3.8 | 30.8±3.3 | <0.001 |
| Ascending aorta diameter (mm)  | 32.9±5.2 | 32.2±5.1 | 35.3±4.8 | <0.001 |
| MPA/AAo ratio                 | .80±.12   | .78±.10 | .88±.14 | <0.001 |

Data are mean (SD), median (IQR) and number (%).

p values were determined by student t-test, Mann-Whitney U test, Chi-square test or Fisher’s Exact test, as appropriate.

Abbreviations: CT, computed tomography; IQR, interquartile range; MPA/AAo ratio, Main pulmonary artery diameter to ascending aortic diameter ratio; SD, standard deviation.

3.2 | Treatment and secondary outcomes

Patients treated with antiviral agents, antibiotic therapy, corticosteroids, anticoagulant therapy were more frequent in non-survivor group, whereas the percentage of patients treated with hydroxychloroquine was higher in survived group.

During follow-up, the rate of patients that needed ICU stay and invasive mechanical ventilation were 38% and 23%, respectively, in the whole study group and the median length of hospitalization period was 12.0 days (IQR 8.0-17.0). The percentage of patients that required ICU stay and invasive mechanical ventilation significantly differed (p < 0.001 for both) but length of hospitalization was similar between survivor and non-survivor groups (p = 0.31) (Table 1).

3.3 | Laboratory parameters and chest CT imaging

Glucose, creatinine, aspartate amino transferase, ferritin, CRP, hs-Tnl, white blood cell, and neutrophil levels were significantly higher in non-survivor group. On the other hand, sodium, albumin levels, lymphocyte count, and hemoglobin levels were significantly lower in non-survivor group patients. Platelet count was comparable between groups.

CT scanning was normal in 13% of the patients and significantly differed between groups. The percentage of patients with bilateral ground glass opacity, pleural effusion, and fibrotic changes were significantly higher in non-survivor group, whereas unilateral ground-glass opacity was significantly higher in survivor group. Patchy infiltration was comparable between groups. MPA, AAo, and MPA-to-AAo ratio calculations were significantly higher in non-survivor group compared to survivor group (p < 0.001 for all) (Table 2).

ROC curve analyses for MPA, AAo, and MPA-to-AAo ratio to predict in-hospital mortality yielded an AUC .866 (95% CI: .816–.915, p < 0.001) with a PLR of 4.66 for MPA, AUC .666 (95% CI: .589–.743, p < 0.001) with a PLR of 1.85 for AAo and AUC .713 (95% CI: .639–.787, p < .001) with a PLR of 1.94 for MPA-to-AAo ratio. The cut-off value of MPA (29.15 mm) was associated with 75% sensitivity and 84% specificity. The cut-off value of AAo (34 mm) was associated with 60% sensitivity and 67% specificity. The cut-off value of MPA-to-AAo ratio (.82) was associated with 61% sensitivity and 69% specificity (Figure 2 and Table 3).
### TABLE 3
Optimal cutoff value of each CT-based main pulmonary artery diameter, ascending aortic diameter and MPA/AAo ratio measurements predicting for in-hospital mortality

| Variables                | Sensitivity | Specificity | PLR   | AUC (95% CI)       | p value |
|--------------------------|-------------|-------------|-------|--------------------|---------|
| MPA ≥ 29.15 mm           | 75%         | 84%         | 4.66  | .866 (.816–.915)   | <0.001  |
| AAo ≥ 34 mm              | 60%         | 67%         | 1.85  | .666 (.589–.743)   | <0.001  |
| MPA/AAo Ratio ≥ .82      | 61%         | 69%         | 1.94  | .713 (.639–.787)   | <0.001  |

**Abbreviations**: AAo, Ascending aortic diameter; AUC, Area under the curve; CI, Confidence interval; CT, computerized tomography; MPA, Main pulmonary artery diameter; PLR, Positive Likelihood Ratio.

### FIGURE 2
Receiver operating characteristic (ROC) curve analyses were conducted in order to determine and compare the optimal cut-off values of main pulmonary artery diameter (MPA), ascending aorta diameter (AAo) and MPA-to-AAo ratio that predict in-hospital mortality.

### 3.4 Survival status and predictors of in-hospital mortality

Cumulative survival rates were calculated as 43% and 92% for MPA ≥29.15 mm and MPA < 29.15 mm, respectively (p < 0.001), 66% and 86% for AAo ≥34 mm and AAo < 34 mm, respectively (p = 0.33), and 65% and 86% for MPA-to-AAo ratio ≥.82 and MPA-to-AAo ratio <.82, respectively (p = 0.04) (Figure 3–5).

Multivariate binary logistic regression model yielded MPA ≥29.15 mm (OR: 4.95, 95% CI: 2.01–12.2, p = 0.001), MPA (OR: 1.28, 95% CI: 1.13–1.46, p < 0.001), AAo (OR: .90, 95% CI: .81–.99, p = 0.040) and MPA-to-AAo ratio ≥.82 (OR: 4.67, 95% CI: 1.86–11.7, p = 0.001) as independent predictors of in-hospital mortality.

Time-dependent multivariate Cox-proportion regression model demonstrated MPA ≥29.15 mm (HR: 1.96, 95% CI: 1.03–3.90, p = 0.047) and MPA (HR: 1.08, 95% CI: 1.01–1.17, p = 0.048) as independent predictors of in-hospital mortality, whereas AAo and

### FIGURE 3
Cumulative survival rates according to cut-off values of main pulmonary artery diameter (MPA) calculated and compared by the Kaplan-Meier method and log-rank test.

### FIGURE 4
Cumulative survival rates according to cut-off values of main pulmonary artery (MPA) to ascending aorta diameter (AAo) ratio calculated and compared by the Kaplan-Meier method and log-rank test.
FIGURE 5  Cumulative survival rates according to cut-off values of ascending aorta diameter (AAo) calculated and compared by the Kaplan-Meier method and log-rank test

MPA-to-AAo ratio did not reach statistical significance ($p = 0.18$ and $p = 0.13$, respectively) (Table 4).

4  |  DISCUSSION

Besides being a primary lung disease, COVID-19 is an infectious pathology that also disrupts the endothelial system by activating numerous inflammatory and prothrombotic cascades. Acute lung injury and respiratory distress syndrome is the most severe form of the disease and associated with impairments in pulmonary vasculature functioning. Therefore, alterations in pulmonary hemodynamics and vascular anatomy and development of pulmonary hypertension (PH) might provide prognostic clues in COVID-19 patients. Evidence coming from various patient populations underlines that enlargement of pulmonary arteries, which can be calculated easily by CT scanning, is a parameter that helps to predict adverse outcomes.\textsuperscript{9,10} In parallel, in our study which comprises a relatively large patient population, we found that pulmonary artery enlargement predicts in-hospital mortality in COVID-19 patients. MPA both as a continuous and categorical variable predicted in-hospital mortality in various regression models.

Mortality rates in severe COVID-19 patients hospitalized in intensive care units may vary depending on various factors. In the early stages of the pandemic, mortality rates of up to 65% have been reported.\textsuperscript{11} Mortality rates may vary due to factors such as regional experiences, different treatment strategies between countries and health care systems. In addition, these mortality rates, which were higher in the early stages of the pandemic, have decreased gradually, thanks to the increasing experience and health care support and have decreased to approximately 20% nowadays.\textsuperscript{11} In our study, mortality rate of COVID-19 patients hospitalized in the intensive care unit was 21.9% consistent with the current data.

Chest CT scanning is widely used for diagnostic and prognostic purposes in COVID-19 patients. Ground glass opacity, pulmonary consolidation, crazy paving pattern, air bronchogram and airway changes, pulmonary vascular enlargement, reticular pattern and linear opacification, pleural effusion and pulmonary thromboembolism are the main chest CT findings of COVID-19.\textsuperscript{3} In our study, 87% of the patients had one or more pathological findings in CT examination and bilateral ground glass opacity, pleural effusion and fibrotic changes were more prevalent in non-survivors. Recent studies reported a frequency of pulmonary vascular enlargement between 45.2% and 89.2% in COVID-19 patients.\textsuperscript{3} Similarly, Matsushita et al. demonstrated increased MAP with unaltered AAo in patients with acute exacerbation of interstitial pneumonia.\textsuperscript{12} In our study, MPA was significantly higher in non-survivors. Furthermore, AAo and MPA-to-AAo ratio levels were increased at a significant level.

Pulmonary artery size obtained from chest CT scanning is occasionally calculated for evaluating PH in clinical practice but there are no well-defined and standardized reference values both for normal and abnormal conditions. For instance, in a previous study comprising a relatively healthy population, mean MPA was $26.1 \pm 2.4$ mm and $22.9 \pm 1.9$ mm for men and women, respectively.\textsuperscript{13} Framingham Heart Study revealed normal reference values of MPA as $24.7 \pm 2.7$ mm and MPA-to-AAo ratio as $0.8 \pm 0.09$ in the healthy population. These values were $25.1 \pm 2.8$ mm and $0.77 \pm 0.09$, respectively, in the entire

| TABLE 4  | Prediction of in-hospital mortality in patients with COVID-19 by multivariate binary logistic regression and time-dependent multivariate Cox-proportion regression analyses |
|-----------|---------------------------------------------------------------|
| | Logistic regression analyses\textsuperscript{a} | Cox regression analyses\textsuperscript{a} |
| Variables | OR (95% CI) | $p$ value | HR (95% CI) | $p$ value |
| Main pulmonary artery diameter, $\geq 29.15$ mm | 4.95 (2.01–12.2) | 0.001 | 1.96 (1.01–3.90) | 0.047 |
| Main pulmonary artery diameter, per mm | 1.28 (1.13–1.46) | $<0.001$ | 1.08 (1.01–1.17) | 0.048 |
| Ascending aortic diameter, per mm | 0.90 (0.81–0.99) | 0.040 | 0.95 (0.89–1.02) | 0.181 |
| MPA/AAo ratio, $\geq 0.82$ | 4.67 (1.86–11.7) | 0.001 | 1.59 (0.87–2.93) | 0.132 |

\textit{Abbreviations}: AAo, Ascending aorta diameter; HR, hazard ratio; MPA, main pulmonary artery diameter; OR, odds ratio.
\textsuperscript{a}Adjusted for age, coronary artery disease, chronic obstructive pulmonary disease, C-reactive protein levels and any abnormal CT lung parenchyma findings.
study cohort. When it comes to PH, MPA $\geq 37.7$ mm was an independent predictor of 5-year all-cause mortality in connective tissue disease related PH according to a recent study published by Li and colleagues. However, Zylkowska et al. demonstrated that MPA $\geq 48$ mm is an independent predictor of unexpected death and all-cause mortality in PH patients. The same discrepancy is also valid for AAo and MPA-to-AAo ratio calculations. For example, most studies consider MPA-to-AAo ratio cut-off $1.0$ or greater while evaluating adverse events but this cut-off may not indicate PH in some circumstances. Nevertheless, it should be mentioned that such discrepancies might originate from diversities in study designs such as outcomes, imaging techniques, etiology, and patient characteristics including age, gender, body size, ethnicity, and lifestyle. Hence, we decided to perform ROC curve analyses in order to determine the optimal thresholds of MPA, AAo, and MPA-to-AAo ratio that predict in-hospital mortality in our study cohort. ROC curve analyses yielded cut-off values $29.15$ mm, $34$ mm, and $.82$ for MPA, AAo, and MPA-to-AAo ratio, respectively, and time dependent survival analyses were performed according to these cut-off values.

The association between CT derived parameters and clinical outcomes in COVID-19 patients was investigated in recent studies. Eslami et al. found that MPA-to-AAo ratio $> 1$ was linked with extensive lung involvement and nonsignificant increase in odds of death in 87 hospitalized COVID-19 patients. Besides, increased cardiothoracic ratio was a strong predictor of mortality. According to a study published by Spagnolo et al. that included 45 COVID-19 patients with their previous chest CT scans demonstrated that MPA-to-AAo ratio increases after SARS-CoV-2 infection and significantly correlates with the extent of pneumonia. Furthermore, enlarged pulmonary artery diameter is associated with death in COVID-19 patients. Our study included 255 patients which was relatively larger than these two studies and our patient cohort included relatively younger and non-fragile patients compared to study of Spagnolo and colleagues. When it comes to our study, MPA was associated with in-hospital mortality according to cut-off values described above. MPA both as a continuous and categorical variable was an independent predictor of mortality both in logistic and time dependent Cox regression analyses. MPA-to-AAo ratio and AAo remained as an independent predictor of mortality in logistic regression model but not in Cox regression model. It is known that ageing influences aortic diameters more extensively than pulmonary artery diameters. This might partially explain why MPA is more powerful predictor of mortality compared to MPA-to-AAo ratio in our study cohort. Because COVID-19 is a primary lung disease, it is not surprising that AAo was not linked with mortality both in survival and regression analyses.

It is reasonable to question pathophysiological aspects of pulmonary artery enlargement in SARS-CoV-2 infection. Pulmonary parenchymal damage related fibrosis and subsequent hypoxic process can lead PH in chronic period. Activation of various inflammation and immune system related cascades can result with endothelial dysfunction and prothrombotic processes subsequently causing pulmonary vascular disease. Nevertheless, correlation between inflammatory markers such as CRP and neutrophil-to-lymphocyte ratio and MPA was shown in COVID-19 pneumonia patients. At this point, it should be emphasized that our results do not provide pathophysiological insights for pulmonary artery enlargement in COVID-19. Besides, we cannot directly conclude that pulmonary artery enlargement occurred secondary to SARS-CoV-2 infection in the light of these results. The contribution of right ventricular systolic dysfunction in the pathogenesis should also be underlined. For instance, D’Alto et al. demonstrated depressed right ventricular functions with mild increase in pulmonary artery pressures in COVID-19 patients.

4.1 | Study limitations

There are several limitations of this study that need to be mentioned. This was a single center, retrospective, and non-randomized study. Our study cohort included hospitalized severe or critical patients with chest CT imaging and for this reason these results cannot be generalized to all COVID-19 patients. In addition, MPA and AAo calculations were performed through non-contrast CT imaging and without electrocardiography gating. Our study lacks data from transthoracic echocardiography and right heart catheterization that could make us to yield more firm conclusions about hemodynamic status and pulmonary artery enlargement. Furthermore, we lacked data of previous CT scanning which hindered us to suggest that pulmonary artery enlargement occurred subsequent to SARS-CoV-2 infection. Besides, follow-up CT scanning could give more beneficial results.

5 | CONCLUSION

Pulmonary artery enlargement strongly predicts in-hospital mortality in hospitalized COVID-19 patients. MPA, which can be calculated easily from chest CT imaging, can be beneficial in the prognostication of these patients.

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CONFLICT OF INTEREST
None declared.

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