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Effects of coronary artery calcified plaque and stent on severity and survival of COVID-19 patients: a decision tree model study

Aim We aimed to investigate the relationship between the presence of calcified plaques and stents in coronary arteries as evaluated by the chest computed tomography severity score (CT-SS) and mortality rates in patients with COVID-19.

Material and methods A single-center retrospective analysis was conducted of 492 patients (≥18 yrs) who were hospitalized between March and June 2020. All included patients had RT-PCR tests positive for COVID-19. A radiologist recorded pulmonary imaging findings and the presence of coronary calcified plaque and/or stent, sternotomy wires, and cardiac valve replacement on initial non-contrast chest CT. Also, cardiothoracic ratios (CTR) were calculated on chest CTs. Data were analyzed using univariate and multivariate analyses and a chi-squared automatic interaction detection (CHAID) tree analysis, which was developed as a predictive model for survival of COVID-19 patients according to chest CT findings.

Results The mean CT-SS value of the patients with coronary plaque was 11.88±7.88, and a significant relationship was found between CT-SS with coronary calcified plaque ($p<0.001$). No statistical difference was found between CT-SS and coronary stent ($p=0.296$). In multivariate analysis, older age was associated with 1.69-fold ($p< 0.001$), the presence of coronary calcified plaque 1.943-fold ($p=0.034$) and higher CT-SS 1.038-fold ($p=0.042$) higher risk of mortality. In the CHAID tree analysis, the highest mortality rate was seen in patients with coronary plaque and CTR>0.57.

Conclusion The presence of coronary artery calcified plaque and cardiomegaly were high risks for severe prognosis and mortality in COVID-19 patients and may help to predict the survival of patients.

Keywords COVID-19; Chest CT severity score; coronary artery calcified plaque; coronary artery stent

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Introduction

Coronavirus Disease 2019 (COVID-19) usually leads to mild and nonspecific symptoms [1]. However, in some COVID-19 patients, serious complications occur, such as acute respiratory distress syndrome (ARDS), multi-organ failure, and acute cardiac dysfunction. Patients with these complications require ventilation and treatment in the intensive care unit (ICU) [2–5].

Patients with a history of cardiovascular disease (CVD) are more vulnerable to COVID-19, and they may develop serious complications [3, 6–8]. In addition, COVID-19 may worsen existing CVD and cause new cardiac complications. The risk of developing serious disease and the need for ICU admission increase in patients with comorbidities, such as cardiovascular, cerebrovascular disease, diabetes, and hypertension [6].

The real-time polymerase chain reaction (RT-PCR) test is the standard for diagnosing COVID-19. Non-contrast chest computed tomography (CT) is performed to diagnose pneumonia and assess its severity in COVID-19 patients [9]. Coronary artery calcification (CAC) is a specific marker of atherosclerosis that can be easily detected on routine chest CTs that are usually performed for the evaluation of COVID-19 pneumonia [9]. However, no evaluation is routinely made for CAC detection during chest CT. In non-contrast CT, CAC is observed as an area of high attenuation in the coronary artery. Even when fully adjusted for standard CVD risk factors, the presence of CAC increases the risk of adverse CVD events by 10-fold [10].

Previous studies have investigated the association of CAC on chest CT with disease severity and with survival of COVID-19 patients [11, 12]. However, unlike previous studies, we evaluated in a large sample size, all cardiac pathological findings, such as cardiomegaly, coronary artery calcified plaque (CACP), and stent (CAS), as well as cardiac postoperative findings, and we investigated the effects of these CT scan cardiac findings on the prognosis and mortality rates of COVID-19 patients.

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Materials and methods

Due to the retrospective study characteristics in our study, the requirement for informed consent was waived. Patient information were obtained from the electronic records of our hospital and censored. The study was approved by the Ethics Committee of Amasya University Faculty of Medicine, and it was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices.

Study population and data collection

The study was a single-center, retrospective study conducted on an original cohort of 492 patients (aged ≥18 yrs) who were hospitalized between March and June 2020. All patients underwent at least one chest CT scan. The diagnosis of COVID-19 was made from positive RT-PCR test results. Patients with at least three negative RT-PCR tests or with image artefacts on the chest CT were excluded from the study. Pediatric patients were also excluded. Data were collected from the hospital's medical records. These data included patient demographic characteristics, laboratory findings at the time of admission, and length of stay in the hospital or ICU.

CT protocol

In our study, chest CT examinations were performed on a 128-slice multi-detector GE Healthcare Revolution EVO CT scanner (GE Medical Systems; Milwaukee, WI, USA), and no contrast agent was used.

Chest CT Image analysis

A radiologist, blinded to the clinical data and laboratory findings, and with more than 15 yrs of experience in general radiology, examined the CT images on a standard clinical picture archiving and diagnostic system (PACS) workstation.

Pulmonary imaging analysis

The imaging findings, such as ground glass opacities (GGOs), consolidation, crazy paving pattern, pleural and pericardial effusion were recorded. The severity of COVID-19 pulmonary involvement was visually interpreted by the semi-quantitative CT severity scoring system that was previously described by Pan et al [13]. Depending on the percentage of lobe involvement in COVID-19 pneumonia, each lobe was scored from 0 to 5: score 0, 0%; score 1, 1–5%; score 2, 5–25%; score 3, 25–50%; score 4, 50–75%; and score 5, ≥75% involvement. The total score was obtained by summing the lobar scores (range 0–25) [13]. Also, all CT images were interpreted according to the Coronavirus disease 2019 (COVID-19) Reporting and Data System (CO-RADS) classification based on suspicion of COVID-19 pneumonia [14].

Cardiac imaging analysis

The same radiologist evaluated the presence of CACP or CAS and cardiac postoperative findings, such as cardiac valve replacement and sternotomy wires in the mediastinal window. CACP was defined as an area of increased attenuation in the course of a coronary artery with a density >130 Hounsfield units (HU). All major branches of the coronary arteries were evaluated for CACP. Also, the maximum transverse cardiac diameter and the maximum transverse thoracic diameter were measured manually on axial CT images. The cardiothoracic ratio (CTR) was calculated as the greatest transverse cardiac diameter divided by the greatest transverse thoracic diameter [15]. CTR> 0.50 was considered an indicator of cardiomegaly [16].

Statistical analysis

Statistical analyzes were performed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp. Published 2017. Armonk, NY, USA). The normality of variable distribution was evaluated with the Kolmogorov-Smirnov test. Variables with normal distributions are reported as mean ± standard deviation (SD), and variables with non-normal distribution as median [interquartile range (IQR)]. Student's t-tests were used to compare the normally distributed, continuous variables, and Mann-Whitney U tests were used to compare non-normally distributed, continuous variables. Pearson's chi-squared or Fisher's tests were used to compare categorical variables. Fisher's tests were used for the Chi-square analysis of categorical variables with less than five values in cells.

The main factors affecting mortality were evaluated by univariate binary logistic regression analysis. Explanatory variables with a p value less than 0.25 in the univariate logistic regression analysis were included in a multivariate logistic regression analysis [17]. The Hosmer-Lemeshow goodness of fit test for multivariate logistic regression was used and if the test p-value>0.05, it was defined as a good fit for the model [18]. For all analyses, a p value less than 0.05 was defined as statistically significant.

A Chi-square automatic interaction detection (CHAID) decision tree model was developed as the predictive model for the survival of COVID-19 patients according to chest CT findings. Firstly, the following predictor variables were used: CACP, CAS, sternotomy with and without CVR, computed tomography severity score (CT-SS), GGOs, consolidations, crazy paving pattern, pericardial effusion, pleural effusion, and the CTR. The survival status of COVID-19 patients was used as the dependent variable. In CHAID analyzes, "nodes" are formed after bifurcations according to each factor. Nodes before the bifurcation are called "parent nodes" and nodes after the bifurcation are called "child nodes". We defined the minimum parent and child nodes as 20 and 5, respectively. Our decision tree had a depth of three levels from the root to node, with a total of 11 nodes, five intermediate nodes, and 6 terminal nodes. From the variables included in the model, five variables (coronary artery plaque, CTR, pericardial effusion, CT-SS, and crazy paving pattern) formed the decision tree. Coronary artery stent was not included in the model because it was not significant in terms of mortality. The analysis continued by choosing the most significant variable at each stage and branching out until there were no more significant risk factors [19]. A node was divided if the p value was compatible with the corrected significance value (p<0.05); otherwise, there was no division, and this node was called a terminal node.

Results

The study population included 492 patients with a mean age of 64.25±14.12 yrs. 284 (58.7%) were male; 289 (58.7%) had CACP; 74 (15%) had CAS; 19 (3.9%) had sternotomy wires with or without cardiac valve replacement.

There was a significant association between the presence of CACP and CAS with older age (p<0.001). 180/288 (62.5%) male patients had CACP, and a significant relationship was found between CACP and male gender (p=0.044). However, the presence of the CAS was not associated with gender. 32/492 (6.5%) of the patients were treated as outpatients; 136/492 (27.6%) were treated in the ICU. 151/492 (30.7%) of the patients died. There was a significant association between the presence of CACP and with a higher risk of ICU admission (p<0.001) and with mortality (p<0.001). The presence of CAS was associated only with a higher mortality rate (p=0.046).

According to the chest CT image, the presence of CACP was significantly associated with crazy paving pattern (p<0.001), consolidation (p=0.099), pleural effusion (p<0.001) and the presence of CAS (p<0.001). CAS was related to pericardial and pleural effusion (p=0.011, p=0.007, respectively) in the CT images. There were significant associations between the presence of CACP and comorbidities, including pulmonary disease (p<0.001), DM (p=0.001), and neurological disease (p=0.002). DM was also associated with the presence of CAS (p=0.026, Table 1).

The mean CTR of patients without CACP was 0.49±0.06, and the mean CTR of patients with CACP was 0.54±0.07. Thus, there was an association between CACP and high CTR (p<0.001). Also, the presence of CAS was

Table 1. Comparison of demographic data, CT findings, and comorbidities according to the presence of coronary plaque or stent

Variable	Condition	Coronary Plaque				Coronary Stent			
		Absent n (%)	Present n (%)	Total	p value	Absent n (%)	Present n (%)	Total	p value
Gender	Female	95 (46.6)	109 (53.4)	204	0.044	177 (86.8)	27 (13.2)	204	0.346
	Male	108 (37.5)	180 (62.5)	288		241 (83.7)	47 (16.3)	288	
Survival	Alive	177 (51.9)	164 (48.1)	341	<0.001	297 (87.1)	44 (12.9)	341	0.046
	Death	26 (17.2)	125 (82.8)	151		121 (80.1)	30 (19.9)	151	
ICU-Non-ICU	Non-ICU	154 (47.5)	170 (52.5)	324	<0.001	273 (84.3)	51 (15.7)	324	0.936
	ICU	24 (17.6)	112 (82.4)	136		115 (84.6)	21 (15.4)	136	
Inpatients/ Outpatients	Outpatient	25 (78.1)	7 (21.9)	32	<0.001	30 (93.8)	2 (6.3)	32	0.202
	Inpatient	178 (38.7)	282 (61.3)	460		388 (84.3)	72 (15.7)	460	
Cardiomegaly	Absent	116 (57.4)	86 (42.6)	202	<0.001	181 (89.6)	21 (10.4)	202	0.016
	Present	87 (30)	203 (70)	290		237 (81.7)	53 (18.3)	290	
GGOs	Absent	37 (51.4)	35 (48.6)	72	0.059	59 (81.9)	13 (18.1)	72	0.439
	Present	166 (39.5)	254 (60.5)	420		359 (85.5)	61 (14.5)	420	
Consolidation	Absent	149 (43.7)	192 (56.3)	341	0.099	289 (84.8)	52 (15.2)	341	0.846
	Present	54 (35.8)	97 (64.2)	151		129 (85.4)	22 (14.6)	151	
Crazy paving pattern	Absent	136 (49.3)	140 (50.7)	276	<0.001	234 (84.8)	421 (5.2)	276	0.901
	Present	67 (31)	149 (69)	216		184 (85.2)	32 (14.8)	216	
Pericardial effusion	Absent	180 (42.9)	240 (57.1)	420	0.082	364 (86.7)	56 (13.3)	420	0.011
	Present	23 (31.9)	49 (68.1)	72		54 (75)	18 (25)	72	
Pleural effusion	Absent	193 (44.7)	239 (55.3)	432	<0.001	374 (86.6)	58 (13.4)	432	0.007
	Present	10 (16.7)	50 (83.3)	60		44 (73.3)	16 (26.7)	60	

Pearson's chi-squared or Fisher test were used to compare categorical variables in coronary artery plaque or stent groups.
Fisher's test was used in the Chi-square analysis of categorical variables with less than 5 data in cells.

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associated with high CTR values (p=0.043). The mean CT-SS value of all patients was 10.46±7.78. The mean value of CT- SS of the patients with CACP was 11.88±7.88 and a statistical relationship was found between high CT-SS with the presence of CACP (p<0.001). However, no statistical difference was found between CT-SS with the presence of CAS (p=0.296). Significant relationships were found between the CACP and laboratory findings, including high inflammatory findings, such as elevated CRP (p=0.003), ESR (p=0.010), ferritin (p=0.014), and high coagulation factors such as fibrinogen (p=0.001), international normalized ratio (INR) (p=0.002). According to laboratory parameters, only high serum BUN was associated with the presence of CAS (p=0.003). No relationship was found between the presence of CAS and high inflammatory laboratory findings (Supplementary Table 2).

In addition, the presence of CACP was associated with a shorter ICU stay (p=0.017) and with a shorter time from hospitalization to death (p=0.001) and from ICU admission to death (p=0.035). However, there was no significant difference in these times between patients with and without CAS (Supplementary Table 3).

In multivariate analysis, older age was associated with 1.69-fold (p<0.001), the presence of coronary calcified plaque 1.943-fold (p=0.034) and higher CT-SS 1.038-fold (p=0.042) higher risk of mortality (Table 4).

Decision tree model results

As shown in Figure 1, in the CHAID analyses, the first decision split was based on CACP. Therefore, our CHAID analysis concluded that CACP (node 0) was the most important variable among chest CT findings for the survival rate of COVID-19 patients (p<0.001). At the second level, patients at node 1 with CACP were divided according to CTR. At this level, node 4 patients with CTR>0.57 had high mortality rates (63.9%)

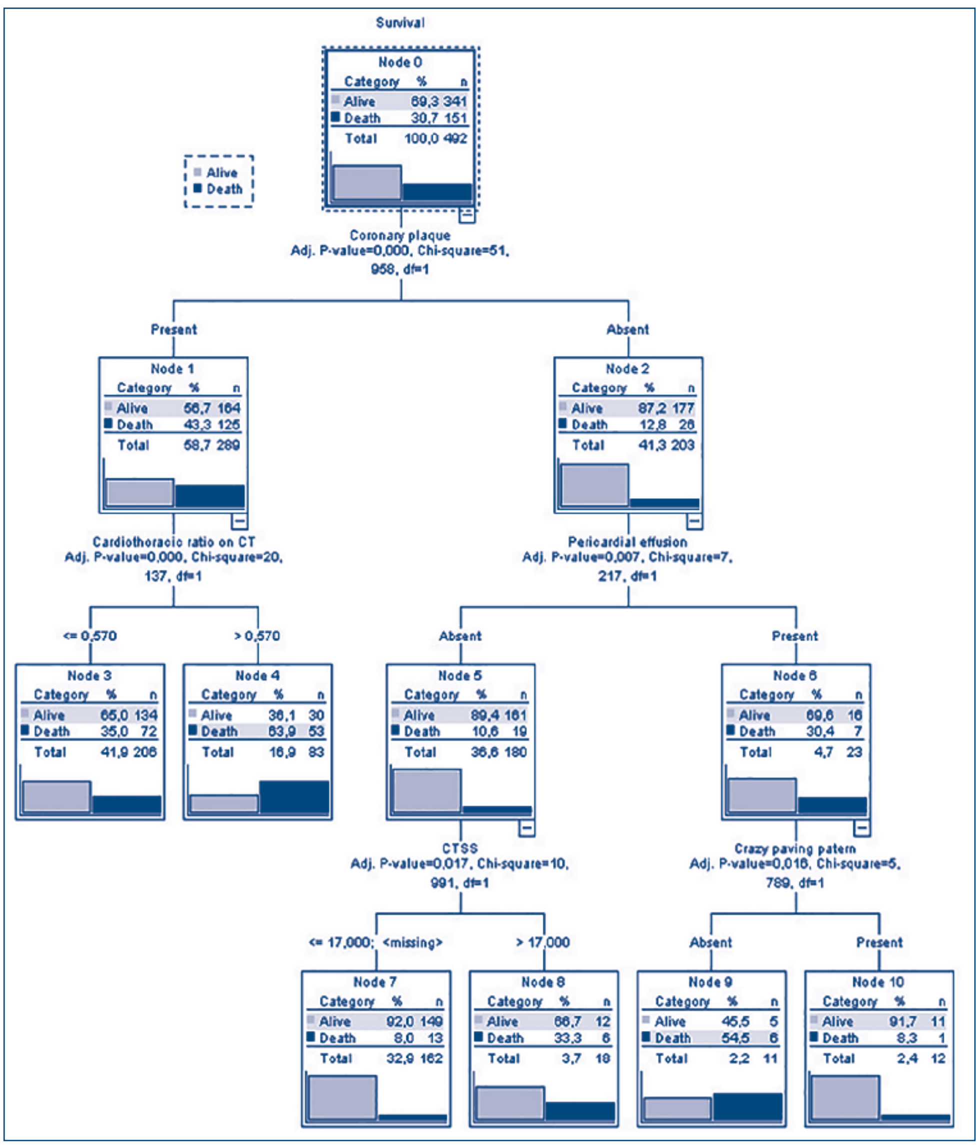
Table 4. Univariate and multivariate analysis of mortality

Variable	Univariate Analysis				Multivariate Analysis			
	p value	OR	95% C.I. for OR		p value	OR	95% C.I. for OR	
			Lower	Upper			Lower	Upper
CT-SS	<0.001	1.054	1.028	1.081	0.042	1.038	1.001	1.076
Cardiomegaly	<0.001	2.294	1.515	3.473	0.767	0.924	0.548	1.558
Coronary plaque	<0.001	5.189	3.234	8.326	0.034	1.943	1.051	3.594
Coronary stent	0.048	1.674	1.005	2.787	0.318	0.732	0.398	1.349
Gender	0.938	0.985	0.668	1.453	-	-	-	-
Diabetes mellitus	0.580	1.121	0.748	1.678	-	-	-	-
Liver diseases	0.903	0.902	0.173	4.702	-	-	-	-
Pulmonary diseases	0.177	1.410	0.857	2.321	0.805	1.077	0.597	1.942
Neurological diseases	0.004	3.309	1.482	7.388	0.146	1.986	0.788	5.005
Kidney diseases	0.193	2.301	0.656	8.071	0.998	1.002	0.157	6.392
Age	<0.001	1.082	1.062	1.103	<0.001	1.069	1.043	1.095
Neutrophil count (1.65-4.97; 10^9/l)	0.003	1.075	1.025	1.127	0.154	1.036	0.987	1.088
Lymphocyte count (1.17-3.17; 10^9/l)	0.030	0.731	0.550	0.971	0.752	0.951	0.695	1.301
CRP (0-5; mg/l)	<0.001	1.007	1.003	1.010	0.186	1.003	0.998	1.009
Ferritin (22-322; µg/l)	0.055	1.000	1.000	1.001	0.798	1.000	1.000	1.000
ESR. (0-30; mm/H)	0.498	1.001	0.998	1.005	-	-	-	-
Fibrinogen (200-400; mg/dl)	0.230	1.001	1.000	1.002	0.194	0.999	0.997	1.001
INR (0.88-1.3)	0.011	4.748	1.426	15.810	0.077	2.138	0.922	4.956
D-dimer (0-0.5; µg/ml)	0.001	1.261	1.104	1.440	0.233	1.097	0.942	1.279
Blood urea nitrogen (16.6-48.5; mg/dl)	<0.001	1.023	1.015	1.032	0.422	0.996	0.985	1.006
Serum creatinine (0.7-1.2; mg/dl)	0.002	1.690	1.210	2.359	0.047	1.585	1.006	2.498

Hosmer–Lemeshow Test = 0.401. (The Hosmer–Lemeshow goodness of fit test for multivariate logistic regression was used and if the test p-value >0.05, it was defined as a good fit for the model) CT-SS, computed tomography severity score; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; INR: international normalized ratio.

compared to node 3 patients with CTR<0.57 (35%) (p<0.001). The patients in node 2 with CACP were divided according to pericardial effusion. At the third-level split, patients without pericardial effusion (node 5) were split according to CT-SS. At this level, node 8 patients with CT-SS>17 had high mortality rates (33.3%) compared to node 7 patients with CT-SS≤17 (8%). On the right side of the decision tree, in the second level division, patients with pericardial effusion (node 6) were separated according to the crazy-paving pattern, one of the chest CT parenchymal findings. At the fourth level, patients without crazy-paving patterns (node 9) had higher mortality rates (54.5%) compared to patients with crazy-paving patterns (node 10, 8.3%). Among all nodes, the mortality rate was the highest among patients with coronary artery plaque and CTR>0.57 (node 4, 63.9%; Figure 2), which was more than twice the average for all patients (node 0, 30.7%).

Figure 1. A chi-square automatic interaction detection (CHAID) decision tree analysis to identify predictors of survival status based on the CT findings of all COVID-19 patients



Discussion

In this retrospective analysis, we investigated the association between the presence of coronary artery plaque (CACP) or stent (CAS) and cardiac surgery with clinical outcome, CT-SS, and mortality of patients with COVID-19. The presence of CACP and CAS was associated with older age. We found a significant relationship between high CT-SS and the presence of CACP. However, no statistical difference was found between the presence of CAS with high CT-SS. There was a significant association between the presence of CACP with a higher risk of ICU admission and mortality. Also, in the multivariate analysis, we found that the presence of CACP was associated with a 1.943-fold higher risk of mortality. Also, our CHAID decision tree analysis showed that patients with CTR>0.57 and with CACP had the highest mortality rate based on significant chest CT findings. However, on the tree analysis, CAS was not a statistically significant predictor variable for mortality.

Many studies have shown that the presence of CAC in patients stratifies the risk of long-term mortality due to cardiovascular complications and all-cause mortality better than traditional risk factors [20–24]. Vascular calcifications cause endothelial dysfunction and may cause a worse clinical outcome, since hypoxic damage can increase myocardial stress. The presence of vascular calcification confers susceptibility to increased viral replication, stronger inflammatory stimuli, and, thus, more common and worse cardiovascular complications of COVID-19. Cardiovascular calcifications are important imaging findings that can predict cardiovascular risk factors and clinical outcomes in COVID-19 patients [9]. COVID-19 symptoms are more severe in patients with CVD. The probable reason for this is the increase in ACE-2 secretion in COVID-19 patients [25]. Many studies reported that pre-existing CVD was associated with increased mortality and worse outcomes in COVID-19 patients [3, 7, 26–28]. Morbidity and mortality are higher in COVID-19

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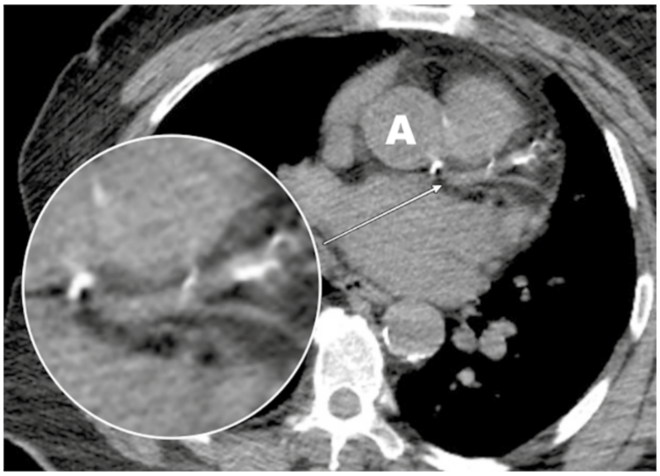
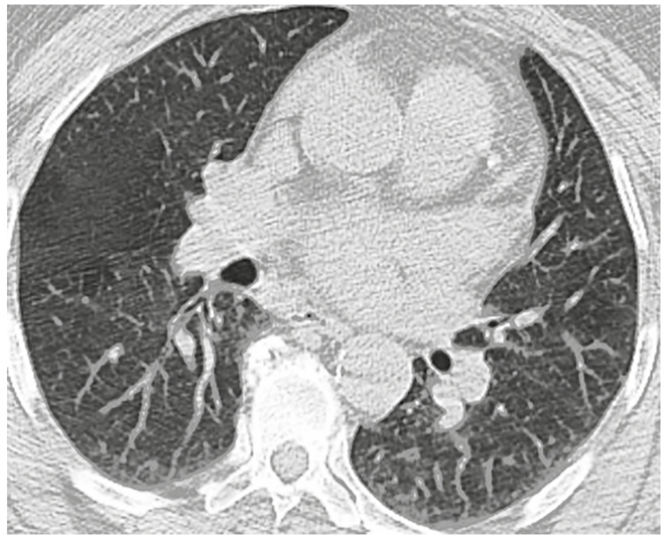
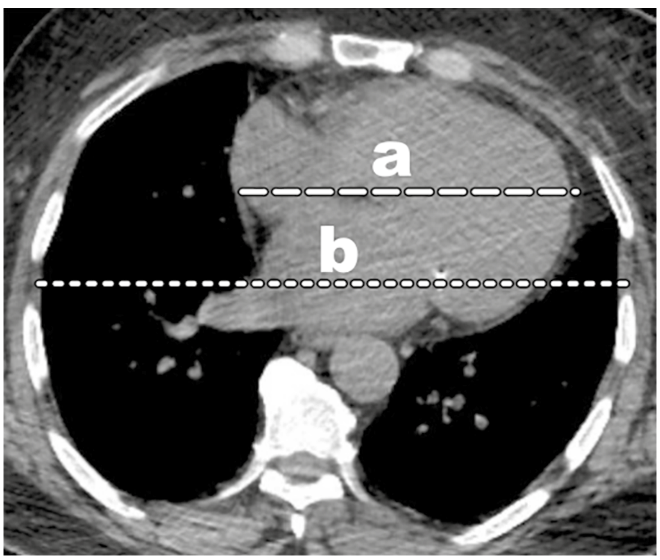
Figure 2. A 72-year-old woman with a history of chronic heart disease was admitted to our hospital with complaints of fever, cough, and sore throat. Her RT-PCR test was positive. She was treated in the hospital for 14 days and in the intensive care unit for 13 days. She died due to multi-organ failure



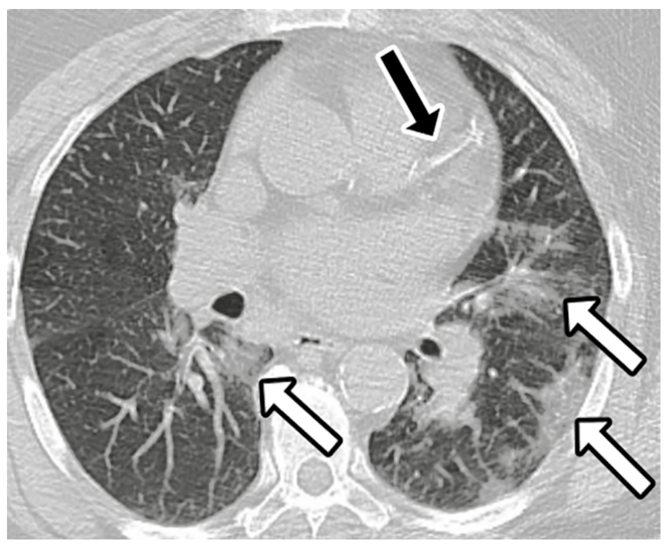
Axial mediastinal window of non-contrast chest CT showing calcified plaques in the left anterior descending artery (LAD) (white arrow). A: ascending aorta.



Axial lung window of initial chest CT showing no pulmonary involvement. CT-SS = 0.



The calculation of the cardiothoracic ratio is shown by dividing the largest transverse heart diameter by the largest chest diameter (a/b) in the axial mediastinal window of chest CT. The cardiothoracic ratio was 0.58, which indicates cardiomegaly.



Axial lung window of second chest CT showing bilateral focal ground-glass opacities (white arrows). CT-SS = 14. Calcifications were seen in the LAD (black arrow).

patients with CV risk factors, such as HT and DM [26, 29]. Older patients with HT, coronary heart disease, and DM history may have a worse clinical outcome in COVID-19 patients [30]. Mortality rates of our study population significantly increased with older age by 1.069-fold, the presence of CACP by 1.943-fold and high CT-SS by 1.038-fold. The multivariate analysis of our study showed no significance association between the presence of CAS and mortality rates. This might be due to the continuous use of anticoagulant drugs in patients with CAS after previous cardiovascular operations, and this medication might protect them. Gupta Y S. et al. also found no significant association between stent placement and intubation or mortality rates of COVID-19 patients [31]. They hypothesized that the patients with a stent may have benefitted from anticoagulation medications. In addition, a previous study suggested that hospitalized patients with COVID-19 on anticoagulation therapy have reduced mortality risk [25]. Also, stents provide revascularization by opening occluded coronary arteries, and thus long-term survival increases [32].

Previous studies have reported that cardiomegaly predicts increased mortality and morbidity in various acute and chronic diseases. A high CTR in patients with respiratory tract diseases is associated with a worse prognosis and disease severity disease [33, 34]. It has been reported that hospitalized COVID-19 patients with high CTR values have a higher mortality rate [15].

Coronary artery calcification is indicative of atherosclerotic plaque and is associated with the risk of CVD [35–37]. In patients at high CVD risk, CAC is associated with a higher incidence of both non-fatal and fatal outcomes [38]. Dillinger JG et al. were the first to determine the relationship of CAC in the non-cardiac-gated chest CT with COVID-19 patient outcomes [11]. They found that patients with COVID-19 and with a calcified coronary plaque were associated with more severe disease and a worse prognosis [11]. The presence of CAC and thoracic aortic calcification in thorax CT were reported as predictors of death in COVID-19 patients [39]. Nair et al. found that as the extent of CAC increased in COVID-19 patients, the need for oxygen support, ICU admission, assisted ventilation, or death increased [12]. Previous studies investigated the association of coronary artery calcification on chest CT with disease severity and survival of COVID-19 patients [11, 12]. However, in our study, unlike previous studies, we evaluated all cardiac pathological findings including cardiomegaly, coronary artery plaque and/or stent, and cardiac postoperative findings. We found that the presence of CACP was associated with high CT-SS, high risk for ICU admission, and death.

This study has some limitations. First, the study was performed retrospectively in a single center. A multicenter study is needed for further validation. Second, the patients had non-cardiac CT, CAC scoring was not performed. Third, only one radiologist performed the image evaluations. Fourth, CTR was measured on chest CTs of patients, and these measurements may be affected by changes in cardiac motion and breathing.

In conclusion, we found that the presence of coronary artery calcified plaque and cardiomegaly were associated with the severity of COVID-19 and may predict survival in patients with COVID-19. We suggest that the evaluation of cardiovascular imaging findings in routine chest CT can provide useful prognostic information, and this evaluation may be useful in risk stratification of patients and in guiding treatment of patients with COVID-19 pneumonia.

No conflict of interest is reported.

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