Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Archives of Cardiovascular Disease 115 (2022) 388—396

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CLINICAL RESEARCH

Cardiopulmonary predictors of mortality in patients with COVID-19: What are the findings?☆

Prédicteurs cardio-pulmonaire de la mortalité chez les patients ayant la COVID-19 : quel éclairage?

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Received 26 December 2021; received in revised form 6 April 2022; accepted 11 April 2022
Available online 8 June 2022

KEYWORDS
COVID-19;
Cardiac injury;

Summary
Background. — Since 2019, coronavirus disease 2019 (COVID-19) has been the leading cause of mortality worldwide.
Aims. — To determine independent predictors of mortality in COVID-19, and identify any associations between pulmonary disease severity and cardiac involvement.

Abbreviations: CAC, coronary artery calcification; CI, confidence interval; COVID-19, coronavirus disease 2019; CT, computed tomography; LAH, left anterior hemiblock; LPH, left posterior hemiblock; OR, odds ratio; PAC, premature atrial contraction; PVC, premature ventricular contraction; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

☆ Tweet: We are thrilled to announce that our article titled ''Cardiopulmonary predictors of mortality in patients with COVID-19: What are the findings?'' has been accepted in Archives of Cardiovascular Diseases.

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https://doi.org/10.1016/j.acvd.2022.04.008

CT score;
Troponin;
Electrocardiography

Methods. — Clinical, laboratory, electrocardiography and computed tomography (CT) imaging data were collected from 389 consecutive patients with COVID-19. Patients were divided into alive and deceased groups. Independent predictors of mortality were identified. Kaplan-Meier analysis was performed, based on patients having a troponin concentration > 99th percentile (cardiac injury) and a CT severity score ≥18.
Results. — The mortality rate was 29.3%. Cardiac injury (odds ratio [OR] 2.19, 95% confidence interval [CI] 1.14—4.18; P = 0.018), CT score ≥18 (OR 2.24, 95% CI 1.15—4.34; *P* = 0.017), localized ST depression (OR 3.77, 95% CI 1.33—10.67; *P* = 0.012), hemiblocks (OR 3.09, 95% CI 1.47—6.48; *P* = 0.003) and history of leukaemia/lymphoma (OR 3.76, 95% CI 1.37—10.29; *P* = 0.010) were identified as independent predictors of mortality. Additionally, patients with cardiac injury and CT score ≥ 18 were identified to have a significantly shorter survival time (mean 14.21 days, 95% CI 10.45—17.98 days) than all other subgroups. There were no associations between CT severity score and electrocardiogram or cardiac injury in our results.
Conclusions. — Our findings suggest that using CT imaging and electrocardiogram characteristics together can provide a better means of predicting mortality in patients with COVID-19. We identified cardiac injury, CT score ≥18, presence of left or right hemiblocks on initial electrocardiogram, localized ST depression and history of haematological malignancies as independent predictors of mortality in patients with COVID-19.

MOTS CLÉS
COVID-19 ;
Atteinte myocardique ;
Élévation de la troponine ;
Score calcique pulmonaire ;
Électrocardiogramme

Résumé
Justification. — Depuis 2019, l'infection à coronavirus 2019 (COVID-19) constitue une cause importante de mortalité dans le monde.
Objectif. — Déterminer les prédicteurs indépendants de la mortalité dans la COVID-19 et identifier les associations entre sévérité de l'atteinte pulmonaire et l'atteinte cardiaque.
Méthode. — Des données cliniques, biologiques, électrocardiographiques et de scanner thoracique ont été collectées chez 389 patients consécutifs ayant une infection COVID-19. Ces patients ont été divisés selon le statut, vivant ou décédé. Les prédicteurs indépendants de la mortalité ont été identifiés. L'analyse de Kaplan Meier a été réalisée en s'appuyant sur la cohorte de patients ayant une concentration de troponine > au 99e percentile (attestant de l'atteinte myocardique) ainsi que le score de sévérité au scanner thoracique ≥18.
Résultats. — La mortalité est de 29,3 %. L'atteinte myocardique (odd ratio 2,19, IC 95 % 1,14—4,18, *p* = 0,018). Le score de scanner thoracique ≥ 18 (odd ratio 2,4, IC 95 % 1,15—4,34, *p* = 0,017), le sous décalage segmentaire du segment ST (odd ratio 3,77, IC 95 % 1,33—10,76, *p* = 0,012), la présence d'hémiblocs (odd ratio 3,09, IC 95 % 1,47—6,48, *p* = 0,043) et l'antécédent de lymphome ou de leucémie (odd ratio 3,76, IC 95 % 1,37—10,29, *p* = 0,010) ont été identifiés comme des prédicteurs indépendants de la mortalité. De plus, les patients ayant une atteinte myocardique et un score ≥18 au scanner thoracique, ont été identifiés comme ayant une survie actuarielle réduite (moyenne 14,21 jours, IC 95 % 10,45—17,98) comparativement aux autres groupes. Il n'y avait pas d'association entre la sévérité du score au scanner thoracique et les anomalies électrocardiographique ou l'élévation de troponine.
Conclusion. — Nos observations suggèrent qu'une atteinte du parenchyme pulmonaire au scanner thoracique et les caractéristiques électrocardiographiques associées peuvent permettre une meilleure caractérisation des prédicteurs de la mortalité chez les patients ayant une COVID-19. Nous avons identifié l'atteinte myocardique, le score thoracique au scanner ≥18, la présence d'un hémibloc gauche ou droit sur l'électrocardiogramme à l'admission, le sous décalage localisé du segment ST er l'antécédent de néoplasie hématologique comme des prédicteurs indépendants de la mortalité chez les patients ayant une COVID-19.

Background

In December 2019, a novel coronavirus infection (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) started spreading from the Wuhan region of China. The disease caused by this infection was named coronavirus disease 2019 (COVID-19) and was a global pandemic by March 2020. In late 2020, vaccination began, and new hope was found.

It was proposed that patients infected with SARS-CoV-2 might develop severe or critical disease with substantial pulmonary involvement [1,2]. The cardiovascular system was also found to be affected in patients with COVID-19, with five primary manifestations: (1) myocardial injury; (2) heart failure; (3) arrhythmias and sudden cardiac arrest; (4) thromboembolism and coagulation abnormalities; and (5) acute coronary syndrome [3]. It was suggested that SARS-CoV-2 could target both the lung and the heart via the angiotensin-converting enzyme 2 (ACE-2) receptor [4,5]. This raised the following question: are there any associations between pulmonary and cardiac involvement in COVID-19? A case report by Inciardi et al. reported acute myopericarditis in a 53-year-old woman who tested positive for COVID-19 without evidence of pulmonary disease [6]. On the other hand, Shi et al. reported associations between elevated troponin concentrations and pulmonary involvement in radiographic studies [7]. A study by Angeli et al. suggested that electrocardiogram abnormalities may be independent of the severity of pulmonary disease [8]. A few studies were conducted to reveal if any of the electrocardiogram abnormalities were predictive of mortality, but the findings were inconsistent. An observational study by McCullough et al. identified premature atrial contractions (PACs), bundle branch blocks and T wave inversion as independent predictors of mortality [9]. The multivariable analysis in a study by Haji Aghajani et al. showed that abnormal R wave progression and supraventricular and ventricular arrhythmias in the initial electrocardiogram of patients with COVID-19 were predictive of mortality [10]. As a result, in the present study we aimed to determine if there is any association between pulmonary disease severity on computed tomography (CT) imaging and cardiac involvement (based on electrocardiogram indices and troponin concentrations). In addition, important electrocardiogram predictors of mortality were identified.

Methods

Patient selection and study design

The current study was a cross-sectional analysis carried out in Shariati hospital, a tertiary hospital in Tehran, Iran, from 06 October 2020 to 20 December 2020. The study was approved by the local ethics committee and written informed consent was not required (IR.TUMS.MEDICINE.REC.1399.824); however, informed consent was obtained from all individual participants included in the study. The study population consisted of 389 consecutive patients admitted to the ward or intensive care unit with high suspicion of COVID-19 acute respiratory disease. Patients were included based on either having a positive real-time reverse transcription polymerase chain reaction (RT-PCR) on nasopharyngeal swabs and clinical symptoms of COVID-19 or meeting all of the following criteria: clinical symptoms suggestive of COVID-19; CT imaging and laboratory findings indicative of COVID-19; recent exposure to an infected person with confirmed COVID-19; residence in or travel to a region with high prevalence of transmission; and absence of other identifiable cause [11].

All of the patients underwent a chest CT scan and standard 12-lead electrocardiography within 12 hours of admission. In order to identify electrocardiogram abnormalities caused only by SARS-CoV-2 infection, patients with current use of medications that could alter the electrocardiogram, an undiagnosable electrocardiogram because of a pacemaker or a history of any cardiac dysrhythmias, such as atrial fibrillation or unspecified heart palpitations, were excluded from the study.

Cardiac injury was defined as having a high-sensitivity troponin concentration higher than the 99th percentile of the normal range. Cardiac involvement was defined as having electrocardiogram abnormalities and/or cardiac injury.

Mortality was considered the primary outcome for this study; electrocardiogram abnormalities and cardiac injury were the secondary outcomes. All patients were followed up until discharge or death; this follow-up period was considered the primary outcome for the Kaplan-Meier analysis.

CT imaging

A single multidetector CT scan (Philips Brilliance 16; Philips Medical Systems, Best, the Netherlands) was used for all examinations, with the patient lying supine in end-inspiratory breath hold. The imaging was unenhanced, and the tube voltage was set according to the patients' body mass index (≤ 30 or > 30) at 100 kV or 120 kV, respectively. Other parameters used for scanning were the same for all patients, and were as follows: 45 mAs; pitch factor, 1—1.5; collimation, 16×1.5 mm; increment, 1.5; matrix, 512; and section thickness after reconstruction, 3 mm. Image reconstruction was done with sharp kernels (filter ''L'') with a lung window (1500 width;—350 centre) and medium-soft kernels (filter ''B'') with a soft-tissue window (400 width; 60 centre) [12]. From the 389 patients included in the study, 93 patients had previously had CT scans in other centres, and their imaging was not included in the study because of low image quality. Overall, the CT scans of 296 patients were included in this study.

The lungs were divided into six anatomical zones (right upper zone, right middle zone, right lower zone, left upper zone, left middle zone and left lower zone). Each anatomical zone was given a score based on the percentage of the lung involvement, as follows: 0, no involvement; 1, 1—25% involvement; 2, 26—50% involvement; 3, 51—75% involvement; and 4, $\geq$76% involvement [12]. The CT severity score was then established by the summation of the scores of all of the six zones, with a maximum score of 24. An expert pulmonologist in chest CT diagnosis, actively involved in the management of the patients with COVID-19 during the pandemic, and a radiologist, each with more than 5 years of experience, independently evaluated all of the scans while blinded to patient characteristics and clinical outcomes. If the final CT score differed by more than 1 point or there

were any other discrepancies in the evaluation, a consensus was reached by the investigators. A CT score ≥ 18 was used as the cut-off point for identifying severe pulmonary involvement based on the findings of a study by Francone et al. [13].

Electrocardiographic analysis

Standard 12-lead electrocardiography, with 25 mm/s and 1 mV/cm calibration and a 100 Hz filter setting, was obtained from all patients in a supine position. Electrocardiograms were interpreted independently by two cardiologists with experience of more than 10,000 electrocardiogram interpretations per year. The evaluation was performed while blinded to the patient characteristics and outcomes. Any discrepancies were solved by consensus. Data extracted from the electrocardiogram were as follows: heart rate; rhythm, categorized as normal sinus rhythm or atrial fibrillation; the presence of PACs or premature ventricular contractions (PVCs), ST-segment elevation and depression; ventricular hypertrophy; localized T wave inversion; Bazett-corrected QT interval (in ms); PR interval (in ms); atrioventricular block; axis deviation; any bundle branch block; intraventricular conduction delay (QRS duration of > 110 ms); fragmented QRS; pathologic Q wave; poor R wave progression; corrected JT interval (Bazett-corrected QT interval—QRS, in ms); and left or right hemiblocks.

Statistical analysis

Statistical analysis was performed using SPSS software, version 22 (IBM Corporation, Armonk, NY, USA). According to the central limit theorem, continuous variables were considered to be normally distributed. Continuous variables are represented as means ± standard deviation, whereas categorical variables are represented as frequencies. To compare the average means of continuous variables between alive and deceased groups, an independent *t* test was performed. Categorical variables were analysed using the χ^2 test. If one of the four cells in the 2 × 2 table had an expected count of < 5, Fisher's exact test was used. Univariate logistic regression was performed to identify the association between variables and mortality. Variables with $P < 0.1$ were eligible for the multivariable analysis. A backward stepwise logistic regression model was used for multivariable analysis, and the following variables were included in the model: cardiac injury; CT score ≥ 18; localized ST depression; left or right hemiblocks; leukaemia/lymphoma; C-reactive protein; diabetes; age > 65 years; and PAC or PVC. Odds ratios (ORs) and 95% confidence intervals (CIs) were also computed. The χ^2 analysis was used to identify whether electrocardiogram abnormalities and elevated troponin concentrations were more common in patients with severe pulmonary involvement (CT score ≥18). A *P*-value < 0.05 was considered statistically significant for all analyses.

Kaplan—Meier survival analysis was used to compare mean survival time between subgroups. *P*-values were calculated using the Gehan-Breslow-Wilcoxon (generalized Wilcoxon) method in this analysis. Both pairwise and pooled *P* values were determined.

Results

The mean age of the study population was 62.89 ± 16.03 years, and 41.6% of the patients were female. A total of 104 (26.7%) patients in the overall population were from the intensive care unit. The mortality rate was 29.3%. In the deceased group, patients were significantly older (67.04 ± 16.26 years) compared with the alive group (61.06 ± 15.62 years; $P = 0.001$). Furthermore, comorbidities, such as diabetes (51.8% vs 37.5%; $P = 0.009$), chronic kidney disease (11.4% vs 5.1%; $P = 0.026$) and history of leukaemia or lymphoma (12.3% vs 5.5%; $P = 0.020$), were more common in the deceased group. A positive COVID-19 PCR result was not significantly different between the two groups (78.9% vs 73.6%; $P = 0.28$). Troponin concentration > 99th percentile (cardiac injury) was also more common among deceased patients (37.3% vs 17.8%; $P < 0.001$). Table 1 compares the demographic, clinical and laboratory characteristics of the two groups.

CT score and CT score ≥ 18 were the only imaging variables that were significantly different between the deceased and alive groups: 13.52 ± 7.11 vs 11.46 ± 6.03 ($P = 0.018$) and 34.4% vs 19.0% ($P = 0.004$), respectively. Among the electrocardiogram variables, PAC or PVC (14.5% vs 4.9%; $P = 0.001$), localized ST depression (12.7% vs 4.5%; $P = 0.004$), localized ST elevation (4.5% vs 1.1%; $P = 0.05$) and presence of hemiblocks (23.6% vs 12.0%; $P = 0.005$) were more prevalent in the deceased group (Table 2).

Additionally, when patients were categorized into two categories, with and without CT score ≥ 18, there were no associations between CT score ≥ 18 and cardiac involvement indicators (troponin concentration > 99th percentile, PAC or PVC, presence of hemiblocks and ST-T wave changes; all $P > 0.05$).

Cardiac injury (OR 2.19, 95% CI 1.14—4.18; P = 0.018), CT score ≥ 18 (OR 2.24, 95% CI 1.15—4.34; P = 0.017), localized ST depression (OR 3.77, 95% CI 1.33—10.67; P = 0.012), hemiblocks (OR 3.09, 95% CI 1.47—6.48; P = 0.003) and leukaemia/lymphoma (OR 3.76, 95% CI 1.37—10.29; P = 0.010) were identified as independent predictors of mortality in patients with COVID-19 (Table 3).

Fig. 1 depicts Kaplan-Meier survival curves of patients with COVID-19, based on having cardiac injury and CT score ≥18; Table 4 compares the mean survival times of these patients. Patients with cardiac injury and CT score ≥18 had a significantly lower survival time (mean 14.21 days, 95% CI 10.45—17.98 days) than all the other subgroups (P values are presented in Table 5). There was no other pairwise significant difference in mean survival times between the subgroups of patients with COVID-19.

Discussion

In the present study we investigated the clinical, laboratory, CT scan and electrocardiogram characteristics of patients with COVID-19, and their associations with mortality. Our results showed that age > 65 years and a history of diabetes and chronic kidney disease were more correlated with mortality, which is in line with the findings of previous studies [12,14,15]. Deceased patients had a higher mean pulse rate on physical examination. This finding was

Table 1 Demographic and clinical characteristics of the patients.

	Alive ($n = 275$)	Deceased ($n = 114$)	*P*
Age (years)	61.06 ± 15.62	67.04 ± 16.26	0.001
Age > 65 years	111 (42.5)	64 (57.7)	0.007
Male sex	155 (56.8)	70 (61.9)	0.35
Length of hospitalization (days)	10.80 ± 7.17	14.68 ± 11.05	0.001
ICU admission	29 (10.5)	75 (65.8)	<0.001
Signs and symptoms			
Fever	135 (49.5)	52 (45.6)	0.49
Cough	143 (52.4)	47 (41.2)	0.045
Myalgia	112 (41.0)	30 (26.3)	0.006
Dyspnoea	173 (63.4)	66 (57.9)	0.31
SpO_2 > 93%	61 (23.6)	16 (14.5)	0.05
Temperature > 37.7 °C	25 (10.5)	14 (14.0)	0.36
Pulse rate (beats/min)	89.26 ± 17.33	93.44 ± 18.23	0.045
Respiratory rate (breaths/min)	21.03 ± 8.24	20.52 ± 6.51	0.58
Co-morbidity			
Diabetes	103 (37.5)	59 (51.8)	0.009
Ischaemic heart disease	48 (17.5)	27 (23.7)	0.16
Hypertension	87 (31.6)	45 (39.8)	0.12
Congestive heart disease	9 (3.3)	2 (1.8)	0.52
Chronic kidney disease	14 (5.1)	13 (11.4)	0.026
Leukaemia/lymphoma	15 (5.5)	14 (12.3)	0.020
Laboratory data			
COVID-19 PCR (positive)	198 (73.6)	86 (78.9)	0.28
White blood cell count × $10^3/mm^3$	10.33 ± 22.59	19.23 ± 50.42	0.073
Lymphocytopenia (count < 1000)	171 (65.3)	63 (65.6)	0.95
Thrombocytopenia (count < 150,000)	49 (17.8)	34 (29.8)	0.009
Haemoglobin (g/dL)	12.67 ± 2.53	12.32 ± 3.05	0.29
Creatinine (μmol/L)	1.48 ± 1.89	1.88 ± 1.78	0.06
Lactic dehydrogenase (U/L)	691 ± 306	855 ± 466	0.001
CRP (mg/L)	59.16 ± 23.78	69.33 ± 44.10	0.004
Creatine phosphokinase (U/L)	248 ± 556	266 ± 440	0.77
Ferritin (ng/mL)	925 ± 1224	1404 ± 1982	0.09
Troponin concentration > 99^{th} percentile (cardiac injury)	48 (17.8)	41 (37.3)	< 0.001

Continuous variables are expressed as mean ± standard deviation; categorical variables are expressed as number (%). COVID-19: coronavirus disease 2019; CRP: C-reactive protein; ICU: intensive care unit; PCR: polymerase chain reaction; SpO_2: oxygen saturation.

in accord with the results of the study by Haji Aghajani et al., in which sinus tachycardia was significantly associated with mortality [10]. Tachycardia can occur in patients with severe COVID-19, as a result of fever, systemic inflammation, shortness of breath, hypoxia and dehydration [10]. Furthermore, lactate dehydrogenase and C-reactive protein concentrations were significantly higher in the deceased group. It has been proposed that high lactate dehydrogenase concentrations in patients with COVID-19 reflect multiple organ injury, and can predict disease severity and mortality [16]. Similarly, a raised C-reactive protein concentration, a marker for systemic inflammation, has been shown to be correlated with more adverse outcomes in subjects with COVID-19 [17].

Our study also showed that indicators of arrhythmia (PACs or PVCs, hemiblocks and abnormal axis) and cardiac injury (ST depression and ST elevation) were significantly more common in the electrocardiograms of deceased patients with confirmed COVID-19. The results of previous studies are in accord with these findings [9,10,14]. Although PACs or PVCs showed a significant association with mortality in the univariate analysis, no such association was identified in a multivariable model adjusted for confounding variables. Acute myocardial infarction, coronary heart disease, chronic obstructive pulmonary disease and structural heart disease have all been previously associated with PACs on the electrocardiogram [18—21]. Similarly, PVCs can have multiple aetiologies [22], and the suggestion of PACs or PVCs as independent predictors of mortality in previous studies may be far-fetched, as patients with COVID-19 appear to have many co-morbidities [9,14].

The presence of any hemiblock was identified as an independent predictor of mortality, with an OR of 3.09. This is contrary to the results of the study by Haji Aghajani et al. [10], who identified no significant associations between left anterior hemiblock (LAH) or left posterior hemiblock (LPH)

Table 2 Computed tomography imaging and electrocardiographic characteristics.

	Alive	Deceased	*P*
	(*n* = 275)	(*n* = 114)	
Initial CT findings			
Ground glass opacity	196 (95.1)	86 (94.5)	0.78
Central distribution	27 (13.2)	10 (11.1)	0.62
Peripheral distribution	187 (91.2)	83 (92.2)	0.78
Consolidation	91 (44.2)	44 (48.9)	0.45
Emphysema	28 (13.7)	16 (17.8)	0.36
Honeycombing	5 (2.4)	3 (3.3)	0.70
Reticular pattern	50 (24.4)	25 (27.8)	0.54
Reverse halo sign	15 (7.3)	9 (10.0)	0.44
Pleural effusion	36 (17.6)	19 (21.1)	0.47
Nodule/cavity	15 (7.3)	7 (7.8)	0.89
Pericardial effusion	17 (8.3)	7 (7.8)	0.88
Cardiomegaly	70 (34.1)	30 (33.3)	0.89
Bronchiectasis	16 (7.8)	8 (8.9)	0.76
Interlobular septal thickening	28 (13.7)	17 (18.9)	0.26
Mediastinal lymphadenopathy	21 (10.3)	10 (11.4)	0.785
Calcified coronary artery	107 (52.2)	56 (62.2)	0.11
CT score	11.46 ± 6.03	13.52 ± 7.11	0.018
CT score ≥ 18	39 (19.0)	31 (34.4)	0.004
Initial ECG characteristics			
Normal sinus rhythm (yes)	254 (95.1)	101 (91.8)	0.21
Pulse rate (beats/min)	86.73 ± 18.01	92.26 ± 21.92	0.012
PR interval (ms)	170 ± 47	166 ± 52	0.44
QTc (ms)	397± 46	404 ± 49	0.19
JTc (ms)	313 ± 46	319 ± 48	0.27
PAC or PVC	13 (4.9)	16 (14.5)	0.001
BBB (any)	32 (12.0)	18 (16.4)	0.26
Hemiblock (right or left)	32 (12.0)	26 (23.6)	0.005
IVCD	2 (0.7)	2 (1.8)	0.58
Fragmented QRS	46 (17.3)	18 (16.4)	0.83
Localized ST depression (injury)	12 (4.5)	14 (12.7)	0.004
Localized ST elevation (injury)	3 (1.1)	5 (4.5)	0.05
Localized T wave inversion (ischemia)	33 (12.4)	13 (11.8)	0.87
Pathologic Q wave	18 (6.8)	8 (7.3)	0.86
Atrial fibrillation	12 (4.5)	8 (7.3)	0.27
Abnormal axis (any)	40 (15.0)	33 (30.0)	0.001
Poor R wave progression	9 (3.4)	4 (3.6)	1.00

Continuous variables are expressed as mean ± standard deviation; categorical variables are expressed as number (%). BBB: bundle branch block; CT: computed tomography; ECG: electrocardiogram; IVCD: intraventricular conduction delay; JTc: corrected JT interval (QTc—QRS); PAC: premature atrial contraction; PVC: premature ventricular contraction; QTc: corrected QT interval using the Bazett formula.

and mortality in 893 patients with COVID-19. It has been proposed that LAH may be an independent predictor of mortality in patients with suspected coronary artery disease. Some studies have even reported a higher mortality rate in patients with isolated LAH and myocardial infarction than in patients without LAH [23,24]. LPH plus right bundle branch block has also been associated with higher mortality after a coronary event [23—25]. It has even been suggested that hemiblocks can at times obscure the diagnosis of myocardial infarction [26]. Previous studies have demonstrated that patients with COVID-19 are susceptible to coronary events [27]. In our study, indicators of coronary events and cardiac injury (ST depression, ST elevation and troponin concentration > 99th percentile) were also common among subjects with COVID-19. As a result, overlooking hemiblocks in the electrocardiograms of these patients can be detrimental to their prognosis. We also hypothesized that the association between abnormal axis and mortality in our study may be the result of the high frequency of hemiblocks on the patients' electrocardiograms. However, axis deviation on the electrocardiogram can have multiple aetiologies, and we cannot rule out a possible role for other anatomical and conduction abnormalities of the heart in the mortality of subjects with COVID-19.

Table 3 Independent predictors of mortality in patients with coronavirus disease 2019.

Variables	OR	95% CI	*P*
Troponin concentration > 99th percentile (cardiac injury)	2.19	1.14–4.18	0.018
CT score≥18	2.24	1.15–4.34	0.017
Localized ST depression (injury)	3.77	1.33–10.67	0.012
Hemiblock (right or left)	3.09	1.47–6.48	0.003
Leukaemia/lymphoma	3.76	1.37–10.29	0.010
CRP (mg/L)	1.01	0.99–1.02	0.07

The following variables were automatically removed in the backward model: diabetes; premature atrial contraction or premature ventricular contraction; and age > 65 years. The Hosmer-Lemeshow test had a *P* value of 0.093, which indicates a good model fit. CI: confidence interval; CRP: C-reactive protein; CT: computed tomography; OR: odds ratio.

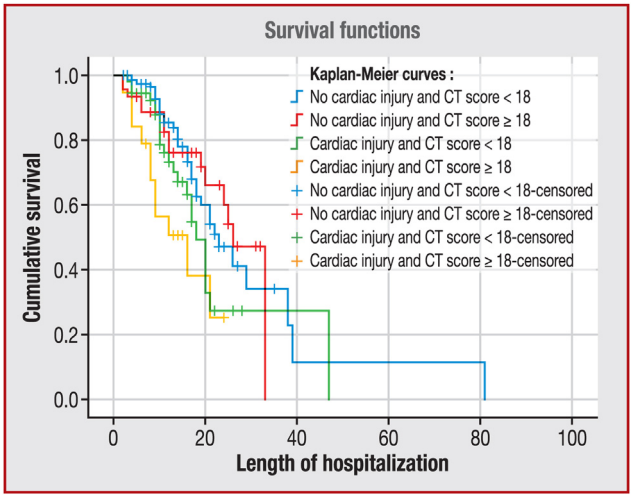

Figure 1. Kaplan-Meier analysis to compare group differences in survival in patients with COVID-19. CT: computed tomography; Cum: cumulative.

The present study is the first investigation into the associations between electrocardiography indicators and CT scores of patients with COVID-19. We observed no significant associations between electrocardiography findings (PAC or PVC, presence of hemiblocks and ST-T wave changes) and CT score ≥18. Additionally, there were no significant associations between CT score and troponin concentration > 99th percentile. Chest CT abnormalities of patients with COVID-19 usually appear after 5 days of symptom onset, whereas elevation of cardiac injury biomarkers has been reported to occur 10 days after the first symptom appears [28]. It has been proposed that direct viral infiltration of myocardial tissue and indirect effects of hypoxaemia and systemic inflammation both play an important role in inducing cardiac injury in COVID-19; however, it is still unclear which of the factors is more important [28]. A similar phenomenon is also observed in patients with systemic sclerosis (a disease likened to COVID-19 because of its similar pathobiology), in whom cardiac injury can occur irrespective of pulmonary disease [29,30]. Previously, there have been conflicting reports on whether cardiac involvement in patients with COVID-19 can occur without pulmonary disease or not [6–8]. A study by Shi et al. reported associations between cardiac injury and unilateral or bilateral involvement of the lungs [7]. The study subjects with cardiac injury appeared to have other co-morbidities and a severe form of COVID-19 infection compared with patients without cardiac injury; we assume that this difference between the study groups may have affected the results [7]. An investigation by Zhang et al. identified significant associations between troponin concentrations and CT score [15]; although troponin concentrations were increased in the higher CT score subgroups in this article, many of the patients still had troponin concentrations lower than the upper limit of normal (no cardiac injury). This study also used a different CT scoring method compared with ours, and the number of subjects in each of the CT score subgroups was relatively low [15]. From the above findings, it appears that cardiac and pulmonary involvement in patients with COVID-19 can occur in isolation, but it is still unknown why some patients with severe disease with a high degree of pulmonary involvement do not experience cardiac injury.

CT score ≥ 18 and cardiac injury had ORs of 2.24 and 2.19, respectively, in predicting mortality. Previous studies have shown similar results [7,8,13]. When patients were categorized into four subgroups in the Kaplan-Meier analysis, subjects with no cardiac injury and CT score < 18 did not show a significantly longer survival time than those in the no cardiac injury and CT score ≥18 group, whereas CT score ≥ 18 was a strong predictor of mortality in the cardiac injury group. Additionally, patients with both cardiac injury and severe pulmonary involvement (CT score ≥18) demonstrated the shortest overall survival (mean 14 days). In general, these findings suggest that CT score cut-off values and cardiac injury biomarkers should be used in conjunction to predict prognosis.

Similar to other studies, CT scan patterns (e.g. ground glass opacity, reticular pattern, honeycombing and consolidation) did not show a significant association with mortality [12]. Some studies have also demonstrated that COVID-19-associated CT scan patterns do not have an association with fibrosis development in further follow-up CT scans [31]. Consequently, CT scan patterns seem to be only important in the diagnosis of COVID-19 and have no importance in the prognosis. We also investigated the presence of coronary artery calcification (CAC) in CT images of patients with COVID-19. There were no significant associations between mortality and CAC in our results. Previous studies have demonstrated that high CAC scores are correlated with a higher frequency of major adverse cardiovascular events in patients with

Table 4 Mean survival times in patients with coronavirus disease 2019.

	Number of patients	Estimate (days)	95% CI
No cardiac injury and CT score < 18	166	29.84	19.96—39.73
No cardiac injury and CT score ≥ 18	47	24.18	20.48—27.88
Cardiac injury and CT score < 18	56	23.50	17.47—29.53
Cardiac injury and CT score ≥ 18	20	14.21	10.45—17.98

CI: confidence interval; CT: computed tomography.

Table 5 Pairwise comparisons between the groups for survival time.

	No cardiac injury and CT score < 18	No cardiac injury and CT score ≥ 18	Cardiac injury and CT score < 18
No cardiac injury and CT score < 18		0.36	0.06
No cardiac injury and CT score ≥ 18	0.36		0.34
Cardiac injury and CT score < 18	0.06	0.34	
Cardiac injury and CT score ≥ 18	< 0.001	0.020	0.038

The value in each cell represents the *P* value for that comparison. The *P* value using the pooled comparison method was < 0.001 for the overall model. The *P* values were calculated using the weighted Breslow (generalized Wilcoxon) method. CT: computed tomography.

suspected coronary heart disease [32]. A previous study by Gupta et al. showed that CAC score was significantly correlated with mortality in patients with COVID-19 [33]. This finding contrasts with the results of our study, and we assume that the discrepancy arises as a result of the scoring system used by Gupta et al. [33]. In addition, the inclusion of patients with coronary artery bypass grafts and coronary stents in the interpretation of CAC in our study may have skewed our results.

Study limitations

This study has several limitations. First, we used a modified version of the CT scoring method that was suggested by Zhou et al., which is different to the method used by Francone et al.; however, we believe that the difference is negligible, as our findings also suggested significant associations between CT score ≥18 and mortality in the univariate analysis [12,13,34]. Second, in the Kaplan-Meier analysis, patients in less severe subgroups were likely to be discharged earlier than those in more severe subgroups, resulting in a high early censoring rate in less severe subgroups. Therefore, the weighted Breslow (generalized Wilcoxon) method was used for analysis, as it gives more weight to early deaths in the survival curve, and can compensate for a high early discharge rate of patients who are less severely ill. Finally, RT-PCR was not performed for all of the patients, and COVID-19 infection was only confirmed in some of the subjects using a CT scan plus the criteria mentioned in the Methods section.

Conclusions

In conclusion, we identified cardiac injury, CT score ≥18, localized ST depression, hemiblocks and history of leukaemia/lymphoma as independent predictors of mortality in patients with COVID-19. Additionally, there were no associations between CT score ≥18 and cardiac involvement, suggesting that cardiac injury may occur even in the absence of severe COVID-19 pneumonia. Finally, our study revealed that patients with both cardiac injury and severe pulmonary involvement had the shortest survival time. We deduce that considering all of the imaging, electrocardiography, laboratory and clinical variables may be a more appropriate approach when it comes to identifying high-risk patients with COVID-19 and predicting mortality.

Sources of funding

None.

Disclosure of interest

The authors declare that they have no competing interest.

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