



Predictive value of CT in the short-term mortality of Coronavirus Disease 2019 (COVID-19) pneumonia in nonelderly patients: A case-control study

Seyed Mohammad Hossein Tabatabaei^a, Habibollah Rahimi^b, Fahimeh Moghaddas^c,
Hamid Rajebi^{d,*}

^a Radiology Department, Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran

^b Biostatistics and Epidemiology Department, School of Public Health, Kashan University of Medical Sciences, Kashan, Iran

^c Faculty of Medicine, Kashan University of Medical Sciences, Kashan, Iran

^d Neuroradiology Department, Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States

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ABSTRACT

Rationale and objectives: Identifying CT predictors of mortality in nonelderly healthy patients with COVID-19 pneumonia will aid to distinguish the most vulnerable patients in this age group and thus alter the management. We aimed to evaluate the prognostic value of multiple CT features of COVID-19 pneumonia on initial presentation in nonelderly patients without underlying medical conditions.

Methods: In this retrospective case-control study, thirty laboratory-confirmed COVID-19 patients with no known major underlying disease who underwent a chest CT scan and expired of pneumonia within the following 30 days after admission, were included as case group. Sixty control subjects individually matched on their age, gender, without underlying medical conditions, who received same-criteria standard care and were discharged from the hospital in 30-day follow-up were included in the control group. A conditional logistic regression model was applied.

Results: Applying a univariate conditional logistic regression model, it was revealed that bilateral lung disease, anterior involvement, central extension, GGO, consolidation, air bronchograms, pleural effusion, BMI ≥ 25 kg/m² and CT severity score were the significant preliminary predictors (all p-values < 0.05). Next, by applying a multivariate conditional logistic regression model, it was determined that the CT severity score is the only statistically significant CT predictor of mortality (Odds Ratio = 1.99, Confidence Interval: 1.01–4.06, p-value < 0.05). The ROC curve analysis revealed a score of 7.5 as the cut-off point of CT severity score with the highest sensitivity (0.83) and specificity (0.87).

Conclusion: Our study demonstrates that CT severity score is a reliable predictor factor of mortality in nonelderly previously healthy individuals with COVID-19 pneumonia. Assessment of disease extension in addition to the morphological pattern is necessary for CT reports of COVID-19 patients. This may alert the clinicians to alter the management for this specific group of patients, even when they are clinically silent or have a mild presentation.

1. Introduction

A worldwide outbreak of viral pneumonia named Coronavirus Disease 2019 (COVID-19) is considered a global health threat due to its rapid spread, unavailability of approved medication or vaccines, and surging mortality. According to centers for disease control and prevention daily report, there are 6,825,697 confirmed cases in the United States with 199,462 total deaths by June 22, 2020, hence a 3 %

mortality rate [1].

A few recent studies have identified non-radiologic demographic and clinical predictors of mortality in COVID-19 pneumonia, including but not limited to patients' age, ethnicity, and various underlying medical conditions [2–5]. Although the disease was primarily thought to be an entirely nonfatal illness in nonelderly healthy patients without underlying medical conditions, the reports from around the world have been opposing [6].

* Corresponding author at: Department of Neuroradiology, Massachusetts General Hospital, Harvard Medical School, 55 Fruit Street, Boston, MA, 02114, United States.

E-mail addresses: hamid.rajebi@gmail.com, hrajebi@mgh.harvard.edu (H. Rajebi).

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Chest Computed Tomography (CT) is not routinely recommended in COVID-19 pneumonia based on current ACR guidelines [7] but it has the capability to diagnosis the disease in asymptomatic, suspected and equivocal cases, follow-up the disease progression and detect the complications when respiratory status deteriorates [8,9].

Identifying admitting CT predictors of mortality in nonelderly healthy patients without underlying medical conditions will aid to distinguish the most vulnerable patients in this age group and thus alter the management. A few more recently published observational studies have proposed potential imaging-based prognostic indices to predict mortality [10–12], but statistically higher-level studies are warranted. To our knowledge, a dedicated case-control study has not yet been performed for the assessment of radiological prognostic factors in COVID-19 pneumonia. Furthermore, and upon literature review, no study has specifically focused on imaging analysis of COVID-19 pneumonia in healthy nonelderly patients.

In this case-control study, we aimed to evaluate the prognostic value of multiple CT features of COVID-19 pneumonia on initial presentation in nonelderly patients without preexisting underlying medical conditions. We hypothesized that initial CT findings may reliably be able to predict short-term mortality in younger healthy individuals with COVID-19 pneumonia.

2. Materials and methods

2.1. Case and control groups

Upon IRB approval (ID: IR.KAUMS.REC.1399.008), this retrospective case-control study was conducted between Feb 20, 2020, and Apr 19, 2020, at Shahid Beheshti hospital of Kashan University of Medical Sciences, in Kashan, Iran, one of the disease epicenters in the country. Medical records of all hospitalized patients aged 50 years or younger with laboratory-confirmed COVID-19 pneumonia who underwent a non-contrast chest CT scan and expired of COVID-19 pneumonia within the following 30 days after admission were extracted. Patients with known major underlying disease (including cardiovascular, hypertension, pulmonary, renal, or immunocompromised, diabetes mellitus and cancer) were excluded. Ultimately, thirty patients were enrolled in the study. For the purpose of our case-control analysis, we defined these patients as cases.

To design our case-control analysis and increase the power of the study, we used a 1: 2 case-control ratio with sixty control subjects individually matched on their age and sex. The underlying medical conditions of controls and their initial presentation were similar to the cases (no major underlying disease), but following confirmation of COVID-19 pneumonia and performing non-contrast chest CT, the pneumonia was clinically improved within the 30-day follow-up and all the patients in the control group were discharged from the hospital.

All patients in case and control groups received standard institutional care for COVID-19 pneumonia during their hospitalization, based on BMJ best practice and Massachusetts General Hospital guidelines, which included prophylactic subcutaneous heparin (5000 units, every 12 h) [13,14].

2.2. Clinical and laboratory findings

Duration of hospitalization, length of symptoms onset to initial chest CT, ICU admission/orotracheal intubation, type of dominant symptoms on presentation (fever, cough, dyspnea, fatigue/myalgia, shivering) and initial O₂ Saturation (SpO₂) on admission were recorded in case and control groups. We also evaluated the presence of leukocytosis (WBC count > 11,000/1 μ L) and lymphopenia (Lymphocyte count <1000/1 μ L) during the hospitalization course. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) on admission were also recorded. Tobacco use was also investigated and recorded in both groups. We also recorded the administered drugs during the hospitalization in both

groups. Body mass index (BMI) was also calculated for each individual in case and control groups, and patients were categorized into normal (BMI = 18.5–24.9 kg/m²), overweight (25–29.9 kg/m²) and obese (\geq 30 kg/m²) subgroups.

2.3. Image acquisition

All CT scans were performed using a multidetector scanner (Alexion TSX-034A, Toshiba, Japan). An institutional protocol was applied with the detailed acquisition parameters as follows; tube voltage: 120kVp; tube current: 50–90 mA s with automatic exposure control, slice thickness: 3 mm, pitch factor: 1. CT images were acquired at full inspiration with the patient installed in the supine position, and without administration of intravenous contrast medium. The mean CT DIvol was 5.1 mGy (range: 3.8–7.8 mGy).

2.4. Image interpretation

Two radiologists (7 and 5 years of experience) reviewed the chest CT scans independently and with a consensus approach on a picture archiving and communication system (MARCO PACS, Tehran, Iran). The admitting CT was interpreted. All included chest CTs were coded randomly and anonymized by personnel who were not involved in reading the studies, to make the readers blind in terms of the final outcome. For each patient, first the CXR and then the chest CT were interpreted. All CT images were viewed with both lung (WW, 1600 HU; WL, –550 HU) and mediastinal (WW, 400 HU; WL, 40 HU) window settings.

The major CT findings were described based on Fleischner Society glossary of terms for thoracic imaging [15]. The readers classified pulmonary lesions as ground glass opacity with or without visible intralobular lines (crazy paving), consolidation, reverse halo, or other findings of organizing pneumonia including linear, curvilinear or perilobular opacities. The affected pulmonary lobes were recorded (right upper lobe, right middle lobe, right lower lobe, left upper lobe, and left lower lobe). A semi-quantitative scoring system was used to quantitatively estimate the extension of pulmonary involvement of all the mentioned abnormalities based on the area involved [16]. Each of the five pulmonary lobes was visually scored from 0 to 4 as; 0: no involvement, 1: 1 %–25 % involvement, 2: 26 %–50 % involvement, 3: 51 %–75 % involvement, 4: 76 %–100 % involvement. The scores were added together to provide a total CT severity score ranging from 0 (no involvement) to 20 (maximum involvement). The laterality of the lesions was also recorded, and the distribution of the lesions was classified as peripheral and central. Peripheral lung was defined as the outer one-third of the lung, and the central lung was defined as the inner two-thirds of the lung. Anterior or posterior locations were defined utilizing a horizontal line dividing the lungs into the anterior and posterior halves. Furthermore, the readers assessed the presence of air bronchogram, pleural and pericardial effusions. Also, the indication for chest CT (rule out pneumonia in cases with long test-to-result time interval for PCR, evaluation of disease extent/severity, persistent low O₂ saturation or other) was recorded in each individual.

2.5. Statistical analysis

Regarding individual-matching in our study design, to explore each CT-scan finding and BMI status as the predictor of patient outcome (mortality vs. discharge, as a binary variable), the conditional logistic regression model was applied. First, by using the univariate model, the significant predictors were identified. In the next step, the multivariate conditional logistic regression model was applied, using the forward method. To evaluate the goodness-of-fit of the model, pseudo R² statistic was calculated and the prediction power of the model was checked by measuring the correlation between the predicted value (\hat{y}) and the dependent variable (mortality). The p-value < 0.05 was considered

statistically significant. After determining the significant predictor(s), the sensitivity and specificity (accuracy) to predict mortality and the predictive power were assessed via ROC curve.

3. Results

The cases were thirty expired COVID-19 patients and the controls were sixty discharged-matched pairs of COVID-19 patients, in a 30-day follow-up. Eighteen males and twelve female patients with a mean age of 44.2 ± 5.9 were in the case group. Thirty-six males and twenty-four females with a mean age of 44.3 ± 5.9 were in the control group. Mean BMI in case and control groups were $26.9 \pm 3.5 \text{ kg/m}^2$ and $24.5 \pm 2.8 \text{ kg/m}^2$, respectively (p -value < 0.05). Twenty of the 30 patients in the case group (20/30, 66.7 %) and 26 of the 60 patients of the control group (26/60, 43.3 %) were overweight or obese (p -value < 0.05).

Detailed clinical/laboratory/medication and radiologic features in both case and control groups are summarized in Tables 1 and 2 respectively. The median duration of hospitalization was 9 and 5 days and the interquartile range was 6.75 and 3 days for case and control groups, respectively.

Applying a conditional logistic regression model and by utilizing a univariate analysis, it was revealed that bilateral lung disease, anterior involvement, central extension, GGO, consolidation, air bronchograms, pleural effusion, $\text{BMI} \geq 25 \text{ kg/m}^2$ and CT severity score were the significant preliminary predictors (all p -values < 0.05). Next, by applying a multivariate conditional logistic regression model and using forward method, it was determined that the CT severity score is the only statistically significant CT predictor of mortality (Odds Ratio = 1.99, Confidence Interval: 1.01–4.06, p -value < 0.05). Hence, by one score increase in CT severity score, the odds of death increase by 1.99 times. The univariate and multivariate analysis results are summarized in Table 3.

Table 1
Clinical, laboratory and medication data in case and control groups.

Results Clinical/Laboratory /Medication Data	Study groups	Study groups		p-value
		Case (Expired) N = 30 (%) Or Mean (SD)	Matched-Control (Discharged) N = 60 (%) Or Mean (SD)	
Clinical Data	Status			
Duration of symptoms to CT	Mean (SD)	8.1 (2.7)	4.6 (1.2)	<0.001
Fever	Present	26 (92.8)	48 (87.2)	0.71
Cough	Present	22 (78.5)	35 (63.6)	0.16
Dyspnea	Present	17 (60.7)	26 (47.2)	0.24
Fatigue/Myalgia	Present	12 (42.8)	26 (47.2)	0.70
Shivering	Present	16 (57.1)	28 (50.9)	0.59
Tobacco use	Present	7 (23.3)	11 (18.3)	0.57
SpO2 at initial presentation	Mean (SD)	87.9 (2.8)	91.0 (2.5)	<0.001
Duration of Hospitalization	Mean (SD)	10.1 (6.3)	5.3 (2.4)	<0.001
ICU admission/Intubated	Present	14 (46.6)	3 (5.0)	<0.001
Laboratory Data	Status			
Leukocytosis	Present	19 (63.3)	5 (8.3)	<0.001
Lymphopenia	Present	25 (83.3)	28 (46.6)	<0.01
ESR	Mean (SD)	40.6 (28.4)	25.3 (19.3)	<0.01
CRP	Mean (SD)	50.8 (19.4)	30.0 (16.8)	<0.001
Medication	Status			
Hydroxychloroquine	Received	29 (96.6)	54 (91.5)	0.65
Lopinavir/Ritonavir (Kaletra)	Received	28 (93.3)	41 (69.4)	<0.05
Ribavirin	Received	15 (50.0)	10 (16.9)	<0.01
Tamiflu	Received	5 (16.6)	3 (5.0)	0.11

Pseudo R^2 , as the goodness-of-fit measure of the model, was calculated 0.77 in the acceptable range. The prediction power of the model was calculated 0.88 with inter-correlation of the dependent variable (groups) and the model prediction (yhat).

To assess the power of the CT severity score, as a continuous variable, to predict mortality, the ROC curve was depicted (Graph 1). The graph showed acceptable predictive power of variable with $\text{AUC} = 0.89$ (CI: 0.81–0.97). The ROC curve analysis revealed a score of 7.5 as the cut-off point of CT severity score with the highest sensitivity (0.83) and specificity (0.87). Therefore, score ≥ 7.5 cut-off point could distinguish 83 % of patients who will expire, and score ≤ 7.5 could distinguish 87 % who would get discharged in a 30-day follow-up.

4. Discussion

This study is the first published case-control investigation of COVID-19 pneumonia in the literature which comprehensively focuses on initial CT features to predict mortality in the nonelderly patients with no underlying medical conditions. Our statistical analysis reveals a good power to the study with high goodness to fit.

Our study shows that the CT severity score, a representative of the extent of the lung parenchymal involvement, can reliably predict mortality in healthy younger individuals with COVID-19 pneumonia (Figs. 1 and 2). This finding emphasizes the fact that a CT report of COVID-19 pneumonia should include the number of involved lobes and degree of the extension in addition to the morphological and locational (peripheral/central and anterior/posterior) patterns. The extent of the disease can be qualitatively reported as mild, moderate, or severe disease, or by means of a semi-quantitative method as we have described.

A few recent retrospective observational studies have investigated CT features in clinically ill patients and severe form of the COVID-19 pneumonia. Yu et al. reported that extension of the disease, pleural effusion, interlobular septal thickening and air bronchogram are more common in severe form of the disease [12]. Our prior published study also demonstrated that consolidation, air bronchogram, central lung involvement, pleural effusion and crazy paving are more common in ICU admitted and expired patients [10]. In this statistically stronger case-control study based on a multivariate regression analysis, none of these morphological and locational features were significant predictors of mortality in healthy nonelderly COVID-19 pneumonia patients.

Although chest CT is not routinely recommended in the detection of COVID-19 pneumonia, multiple recent studies have evaluated its seminal role in the follow-up of the patients [8,9]. Younger patients as depicted in our study, are otherwise healthy most of the times and may present with mild dyspnea or low-grade fever but they may deteriorate later in the course of the disease. Hence, findings of initial chest CT will aid the clinicians in triaging this specific group of COVID-19 pneumonia patients and they may benefit from more intensive care when they have a higher degree of lung parenchymal involvement, even when they are clinically asymptomatic or have mild form of the disease. This study also opens a debate on potential more utilization of chest CT in younger healthy individuals, with less strict clinical indications in comparison to older patients. Concerns about radiation exposure especially in this age group can be notably reduced by applying an acceptable low-dose chest CT protocol [17].

As mentioned, a CT severity score of ≥ 7.5 has the highest sensitivity and specificity in the ROC curve to predict mortality. The range of this score varies from zero to twenty based on our method. A score higher than 7.5 is at the range of moderate to severe lung parenchymal involvement. This highlights the hypothesis that younger patients with mild or silent clinical symptoms may have moderate or severe extensive lung involvement in their initial CT (or quantitatively score higher than 7.5), a pertinent criteria that should be relayed to the clinicians as this put this group of patients in higher triage and care priorities.

Our study also shows a statistically higher BMI in the case group in comparison to the control group with more overweight and obese

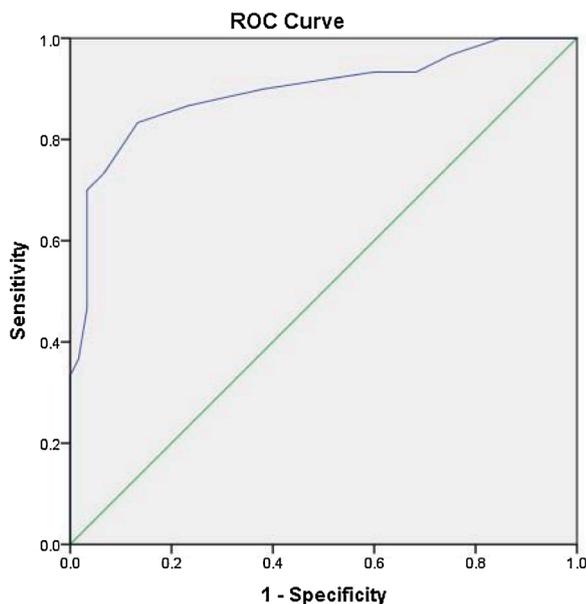
Table 2
Chest CT features in case and control groups.

Results Predictors	Study groups	Case (Expired) N = 30 (%)	Matched-Control (Discharged) N = 60 (%)	p-value
Chest CT features	Status			
CT indication	<ul style="list-style-type: none"> ■ Rule out pneumonia ■ Disease extent/severity ■ Persistent Low O2 Sat. ■ Other 	11 (36.7)	18 (30)	0.72
		14(46.7)	31 (51.7)	
		4 (13.3)	6 (10)	
		1 (3.3)	5 (8.3)	
Laterality	Bilateral	29 (96.7)	47 (78.3)	< 0.05
Anterior	Positive	28 (93.3)	37 (61.7)	<0.01
Posterior	Positive	29 (96.7)	58 (96.7)	1
Peripheral*	Positive	30 (100.0)	59 (98.3)	N/A
Central	Positive	27 (90.0)	26 (43.3)	<0.001
Ground glass opacities	Positive	24 (80.0)	59 (98.3)	<0.01
Consolidation	Positive	29 (96.7)	35 (58.3)	<0.001
Crazy paving	Positive	3 (10.0)	5 (8.3)	0.79
Reverse Halo	Positive	9 (30.0)	10 (16.7)	0.14
Air bronchograms	Positive	22 (73.3)	9 (15.0)	<0.001
Reticular	Positive	8 (26.7)	19 (31.7)	0.62
Pleural effusion	Positive	12 (40.0)	2 (3.3)	<0.001
Abnormal CXR on presentation*	Positive	29 (96.7)	32 (53.3)	<0.001
Pericardial effusion*	Positive	5 (16.7)	0 (0.0)	N/A
CT severity score: [Mean (SD)]	0 - 20	11.4 (4.4)	4.8 (2.7)	<0.001

* Due to the lack of variability or zero cases in one of the groups, it was not statistically possible to use these features in our regression model.

Table 3
Univariate and multivariate analysis of various CT factors and BMI status in predicting mortality of COVID-19 pneumonia.

CT-scan features	Univariate Model				Multivariate Model			
	Odds Ratio	p-value	Confidence Interval (95 %)		Odds Ratio	p-value	Confidence Interval (95 %)	
Body Mass Index status								
Bilateral lung disease	7.89	0.05	0.98	63.56	0.08	0.25	<0.01	6.08
Anterior lung involvement	7.08	0.01	1.59	31.42	0.81	0.89	0.04	15.51
Central lung extension	8.26	<0.01	2.41	28.30	0.15	0.20	<0.01	2.75
Ground glass opacities	0.08	0.02	0.01	0.69	<0.01	0.55	<0.001	47639.35
Consolidation	18.44	<0.01	2.39	141.84	17.90	0.15	0.32	972.00
Air bronchogram	17.35	<0.001	4.03	74.67	4.23	0.50	0.06	290.36
Pleural effusion	12	<0.01	2.68	53.61	3.96	0.48	0.08	189.89
Overweight + Obese	3.69	0.02	1.16	11.75	8.52	0.13	0.52	139.51
CT severity score	1.54	<0.001	1.22	1.94	1.99	0.04	1.01	4.06



Graph 1. ROC curve of CT severity core in predicting mortality.

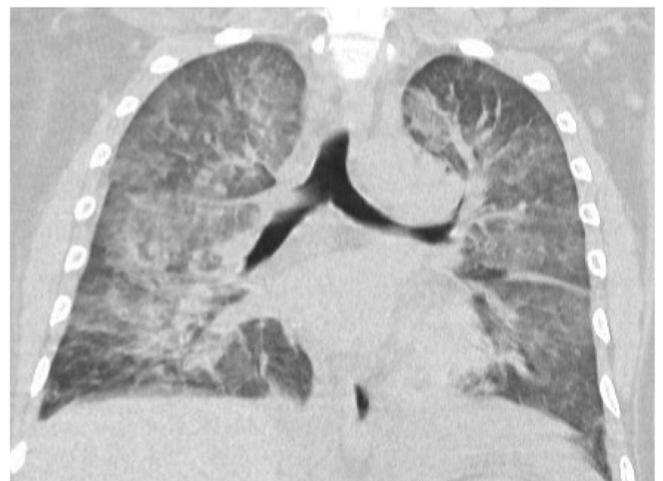


Fig. 1. Coronal reformat unenhanced chest CT scan of a 45-year-old man who died of COVID-19 pneumonia. Chest CT score was measured 18, and all five pulmonary lobes were affected.

patients. Although BMI ≥ 25 kg/m² was a significant predictor of mortality in univariate analysis, it did not reach to statistical significance in our multivariate analysis. A dedicated etiologic study with larger number of cases and in different age groups is warranted to investigate

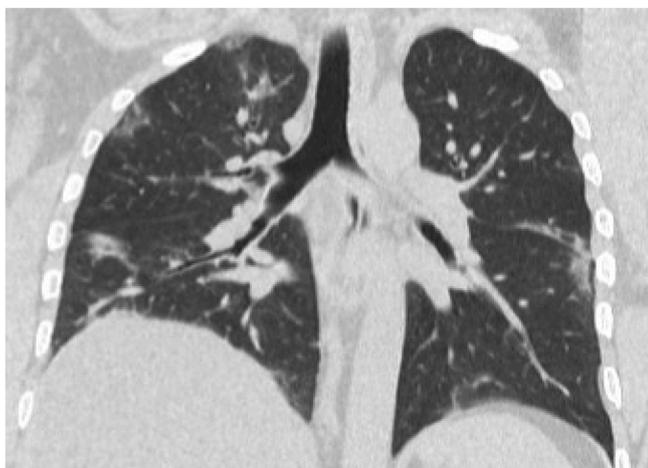


Fig. 2. Coronal reformat unenhanced chest CT scan of a 41-year-old man with COVID-19 pneumonia who was discharged from the hospital following clinical improvement. There were four lobes involved, and CT severity score was 5.

the predictability of this factor. Obesity has been reported as an independent risk and prognostic factor for the disease severity and the requirement of advanced medical care in COVID-19 [18]. Klang et al. concluded that morbid obesity is an independent risk factor for mortality of COVID-19 in hospitalized patients under the age of 50 years [19], the same age range as our study. Obesity can restrict ventilation by impeding diaphragm excursion and reducing protective cardiorespiratory reserve. It also impairs the immune responses to viral infection and is pro-inflammatory [20,21]. Hence, it can mediate the progression to critical illness and organ failure in a proportion of patients with COVID-19 [20].

One of the limitations of our study is the small number of patients in the case group. Although CT severity score was the only statistically significant CT predictor of mortality in our multivariate analysis, larger studies may demonstrate other CT predictors. Also, we used a subjective semiquantitative system to calculate the score of each lobe, which can be substituted with a more quantitative computerized method in future studies. It is notable that the predictive power and diagnostic value of the determined cut-off, in addition to the accuracy of the test, depend on the prevalence of the mortality in the studied population and therefore, future studies in different settings are warranted. Another limitation to our study is that we have evaluated 30-day mortality predictors while some COVID-19 pneumonia cases may still be in the hospital more than 30 days after their admission especially at older ages, although all patients in our study were expired or discharged within 30 days of hospitalization. This factor warrants studies with longer follow-up periods. It is also worth mentioning that currently no drug regimen has been developed and proved to be effective against for COVID-19 infection and potentially well-founded medications may change the course of the disease.

In conclusion, our study demonstrates that the CT severity score is a reliable predictor factor of mortality in nonelderly previously healthy individuals with COVID-19 pneumonia. Assessment of disease extension in addition to the morphological pattern is necessary for CT reports of COVID-19 patients. This may alert the clinicians to alter the management for this specific group of patients even when they are clinically silent.

CRediT authorship contribution statement

Seyed Mohammad Hossein Tabatabaei: Conceptualization, Data curation, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Habibollah Rahimi:** Formal

analysis, Methodology, Software, Validation. **Fahimeh Moghaddas:** Conceptualization, Investigation, Resources. **Hamid Rajebi:** Conceptualization, Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare no conflict of interest. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

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