Is pleural effusion in COVID-19 interstitial pneumonia related to in-hospital mortality?

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ABSTRACT

The recent severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2) pandemic has highlighted the importance of pulmonary computed tomography (CT) for diagnosis and prognostic stratification of this new viral pneumonia. 1370 lung CT scans (performed at the time of admission) of consecutive patients hospitalized for SARS-CoV-2 in Northern Italy during the first epidemic wave were analyzed by a radiological CoreLab. The presence of pleural effusion on pulmonary CT scan was present in 188 patients (13.3% of the population) and identified a population with more comorbidities. Patients with pleural effusion had more cardio-respiratory complications with higher mortality. Pleural effusion was an independent predictor of death on multivariate analysis with an HR of 1.4 (95% confidence interval 1-1.9). Pulmonary CT pleural effusion was an independent predictor of mortality.

Introduction

Coronavirus disease 2019 (COVID-19), caused by infection from severe acute respiratory syndrome-related coronavirus 2, has spread worldwide. It causes a respiratory illness ranging from subclinical disease to severe interstitial pneumonia requiring orotracheal intubation and mechanical ventilation.

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The chest computer tomography (CT) at the hospital admission allows COVID-19 interstitial pneumonia diagnosis and its severity assessment.

The CT features have an evolution pattern, including ground-glass opacity, consolidation, interlobular septal thickening, adjacent pleural thickening, and air-bronchograms.[1] The pneumonia is most commonly bilateral, involving the lower lobes.

Pleural effusion, pericardial effusion, lymphadenopathy, and pneumothorax are some of the uncommon but possible findings observed with disease progression. Pleural effusion (PE) has been reported in 5-7% of the cases, with a higher prevalence in patients with more severe lung involvement.[2,3]

The present study aims to evaluate the role of pleural effusion, as detected by the admission chest CT, in predicting mortality of patients hospitalized for COVID-19.

Materials and Methods

A total of 1370 consecutive patients with a laboratory-confirmed COVID-19 infection who underwent chest CT at hospital admission were enrolled.

Clinical, laboratory and radiological data were collected from the participating centers, and CTs were analyzed by an expert cardiothoracic radiologist of a Core-lab blinded to patients' outcomes.

Demographics and comorbidities, including hypertension, diabetes, coronary artery disease, chronic lung disease, chronic kidney disease, and malignancy, were reported. Baseline hemoglobin, white blood cell count, creatinine, lactate dehydrogenase, and C-reac-

tive protein (CRP) were analyzed. Lung well-aerated volume, pneumonia extension (scored as lung involvement of 25%, 25-50%, 50-75%, >75%), pleural and pericardial effusion were evaluated at the CT.

In-hospital outcomes were categorized as hospitalization with non-invasive ventilation, orotracheal intubation, mechanical ventilation, or in-hospital death. Time interval from admission to death event was also reported. Acute coronary syndrome, pulmonary embolism, and cerebral stroke were defined as major cerebrovascular complications during hospitalization. The population was divided into two subgroups: patients experiencing interstitial pneumonia with PE and those without PE. T-student was applied for the quantitative variables and the chi-square for the qualitative variables. Statistically significant variables at the univariate were included in the multivariate analysis (Cox-regression) using time from hospital admission to the death event.

Results and Discussion

All the patients (mean age 67±13 years; 68.8% male) had a radiological diagnosis of pneumonia. A total of 188 (13.7%) subjects had a pleural effusion at baseline CT with bilateral distributions in 59.8% of patients. Patients with pleural effusion were older (72±12 years *vs* 66±13 years, P=0.001), with a slightly more significant burden of comorbidities (hypertension, diabetes, chronic lung disease, chronic kidney disease, coronary artery disease, and malignancy) (Table 1).

Compared to patients without PE, PE patients had lower baseline hemoglobin levels (12.2±1.9 *vs* 13.6±1.8 g/dL, P=0.001) and higher CRP values (17.8±14 *vs* 13.8±12 mg/dL, P=0.001). Patients with PE had a lower aerated lung volume (1709±1076 *vs* 2521±1388 mL, P=0.001) and a greater lung involvement (≥50%, 42.0% *vs* 17.7%, P=0.001). 14.9% of

Table 1. Demographical, clinical, radiological variables and outcomes of patients with and without pleural effusion diagnosed at pulmonary computed tomograpy at the time of hospitalization.

Variables	All patients	Patients with PE	Patients without PE	P-value
Population demographics				
No. patients, N (%)	1370	188 (13.7)	1182 (86.3)	-
Age, years ±SD	67±13	72±12	66.5±13	0.001
Female sex (%)	31.2	33	30.9	0.56
Clinical history				
Hypertension (%)	56.9	58.3	56.6	0.66
Diabetes (%)	19.3	21.4	18.9	0.43
Coronary artery disease (%)	8.5	9.6	8.2	0.57
Chronic lung disease (%)	10.6	15.1	9.9	0.029
History of oncological malignancy (%)	5.6	15.1	4	0.001
Laboratory variables				
Hemoglobin, g/dL±SD	13.4±1.8	12.2±1.9	13.6±1.8	0.001
Creatinine, mg/dL±SD	1.1±0.4	1.16±0.51	1.08±0.4	0.028
LDH, U/L±SD	389±157	390±156	382±165	0.56
CRP, mg/dL±SD	14.4±12	17.8±14	13.8±12	0.001
Chest computed tomographic radiological variables				
Presence of coronary calcification (%)	58.5	61.5	58	0.35
Aerated lung volume, mL±SD	2405±1378	1709±1076	2521±1388	0.001
Interstitial lung involvement <25%	30.4	20	32.1	0.001
Interstitial lung involvement 25-50%	42.7	43.7	36.4	0.001
Interstitial lung involvement 50-75%	18	32.8	15.5	0.001
Interstitial lung involvement >75%	3.1	9.2	2.2	0.001
Right pleuric effusion (%)	10.9	76.4	-	-
Left pleuric effusion (%)	11.8	83.1	-	-
Bilateral pleuric effusion (%)	8.5	59.8	-	-
Pericardial effusion (%)	5.6	14.9	4.1	0.001
Pleuro-pericardial effusion (%)	2.1	14.9	0	0.001
Hospital outcomes variables				
Non-invasive ventilation without intubation (%)	16.8	19	16.4	0.37
Mechanical invasive ventilation (%)	13.8	13.8	13.8	0.98
Time to death from hospital admission (days±SD)	11.5±11	10.5±8.6	12.5±11	0.42
Acute coronary syndrome (%)	0.8	2.1	0.5	0.019
Stroke (%)	1	1.5	0.9	0,.43
Pulmonary embolism (%)	3.6	7.7	2.9	0.001
Hospital mortality (%)	20.70	26.2	19.8	0.044

PE, pleural effusion; SD, standard deviation; LDH, lactate dehydrogenase; CRP, C-reactive protein.

the PE patients had a combined pleural-pericardial effusion. Of note, they also experienced a higher rate of acute coronary syndrome (2.1% *vs* 0.5%, P=0.0019) and pulmonary embolism (7.7% *vs* 2.9%, P=0.001) during the hospitalization. No differences were detected in terms of orotracheal intubation between the sub-groups, but in-hospital mortality occurred more frequently in PE patients (26.2% *vs* 19.8%, P=0.044). In the Kaplan-Meier curve, the risk of 30-day death diverged significantly between the two groups (Log-rank 0.045) (Figure 1). In the multivariate Cox regression model, age, creatinine, interstitial involvement, and pleural effusion were independent predictors of 30-day death (Table 2). After the extent of lung involvement (>50%), the presence of pleural effusion was the most significant categorical variable with an HR of 1.4 [95% confidence interval (CI) 1.0-1.96]. Sex, basal reactive C protein, and clinical history (history of lung disease, diabetes mellitus, and history of cancer disease) were not statistically significant in the multivariate model. Basal creatinine was the most important quantitative predictor (HR 2.8 CI 95% 2.2-3.6), more predictive than age.

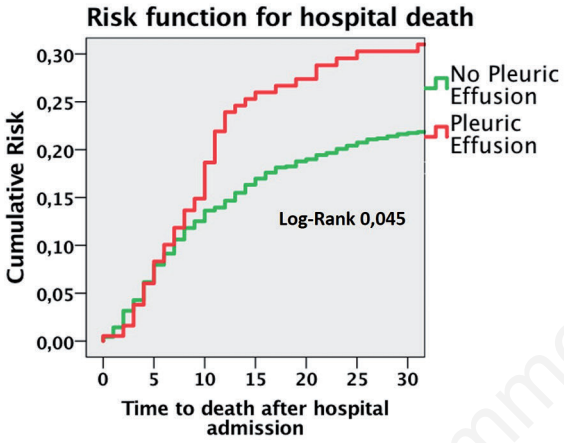

Figure 1. Kaplan-Meier for hospital mortality based on the presence or absence of pleural effusion to the thoracic computed tomographic scan performed upon admission to the hospital. The presence of pleural effusion was significantly associated with an increased risk of death in the first 30 days of hospitalization (Log-rank 0.045).

Conclusions

Among patients with COVID-19-related interstitial pneumonia, PE is independently associated with higher in-hospital death. Accordingly, PE may help clinicians better identify COVID-19 patients at higher risk of poor outcomes, thus allowing healthcare resources optimization. The diagnosis of pleural effusion can be easily made through physical examination and using ultrasound and/or CT.

The diagnosis of a pleural effusion (clinical, ultrasound, or radiological) in the early stages of COVID-19 pneumonia must be a warning sign for clinicians and suggests more prompt monitoring and treatment of these patients at greater risk of adverse outcomes.

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Table 2. Cox multivariate regression for age, creatinine, C-reactive protein, pulmonary interstitial radiological involvement <50%, history of chronic lung disease and cancer, pulmonary embolism, pleural and pericardial effusion.

Baseline risk factors	Sign.	HR	95% CI lower	95% CI upper
Age (years)	0.000	1.077	1.063	1.091
Sex	0.093	1.289	0.959	1.732
Creatinine (mg/dL)	0.000	2.825	2.210	3.611
C-reactive protein (mg/dL)	0.725	1.002	0.992	1.011
Lung interstitial involvement >50%	0.000	2.588	1.861	3.599
Presence of pleuric effusion	0.047	1.406	1.005	1.967
History of lung disease	0.605	1.092	0.783	1.521
Diabetes mellitus	0.519	1.096	0.830	1.448
History of malignancy	0.861	0.957	0.587	1.560