# Clinical-radiological correlations in COVID-19-related venous thromboembolism: preliminary results from a multidisciplinary study


## Abstract

**Introduction:** Among the multiple complex pathophysiological mechanisms underlying COVID-19 pneumonia, immunothrombosis has been shown to play a key role. One of the most dangerous consequences of the prothrombotic imbalance is the increased incidence of micro- and macro-thrombotic phenomena, especially deep vein thrombosis (DVT) and pulmonary embolism (PE).

**Methods:** We investigated the correlation between radiological and clinical-biochemical characteristics of a cohort of hospitalized COVID-19 patients.

**Results:** PE was confirmed in 14/61 (23%) patients, five (35.7%) had DVT. The radiographic findings, quantified by Qanadli score, correlated with the clinical score and biochemical markers. The ratio between the right and left ventricle diameter measured at CT scan correlated with the length of hospital stay.

**Conclusion:** In our cohort radiological parameters showed a significant correlation with clinical prognostic indices and scores, thus suggesting that a multidisciplinary approach is advisable in the evaluation of PE in COVID-19 patients.


## Introduction

Recent studies demonstrate that severe COVID-19 patients are at high risk for venous thromboembolism (VTE) and mortality.[1] The outbreak of the pandemic led physicians to work in multidisciplinary specialized teams worldwide so that the need for an integrated approach matching clinical, laboratory and radiology data became undeniable.

In the setting of an acute potentially rapidly evolving infectious disease, with concerns related not only to individual patient's outcome but also to risks for healthcare operators, the correct risk stratification and prognostic evaluation is of paramount importance.

Our study aimed at analyzing the relationship between radiological findings and clinical characteristics in hospitalized COVID-19 patients who developed pulmonary embolism (PE).

## Materials and Methods

Observational retrospective cohort study carried out at Luigi Sacco Hospital in Milan, the referral center for highly transmissible diseases in Northern Italy. All patients admitted to COVID-19 specialized wards were screened for VTE. The study adhered to the principles of the Declaration of Helsinki for medical research involving human subjects, was approved by local IRB, and written informed consent was acquired from all subjects or their surrogates.

Within the patients' list, we identified subjects hospitalized because of respiratory symptoms, with SARS-CoV-2 infection confirmed by real-time PCR on naso-pharingeal swabs.

To assess signs of deep vein thrombosis (DVT), the patients underwent lower limbs venous compression ultrasound (CUS) at admission.

All the CT pulmonary angiograms were acquired on a 64 row multidetector CT (GE HealthCare, Chicago, IL) after injection of 80 mL of high concentration iodine contrast agent at a flow-rate of 4 ml/s with the use of a bolus-tracking technique. Images were reconstructed with a slice-thickness of 1 mm, in mediastinal and parenchimal window. Two chest radiologists (with 20 and 15 years of experience), blinded to patient status as well as clinical and biological features, independently analyzed all CT examinations searching for PE. Moreover, they calculated Qanadli score.[2, 3] In case of discordance, a simultaneous reading to reach consensus was achieved.

Demographic-clinical characteristics and laboratory data at admission were extracted from the digital medical charts of our hospital.

All CT chest angiograms performed between March 28 and June 6, 2020 were extracted from the hospital picture archiving and communication system database.

Geneva score was calculated for all patients with DVT and PE, and Pulmonary Embolism Severity Index (PESI) score [4] for all cases of PE.

All patients received low molecular weight heparin at prophylactic dosage.

Data are presented as mean (range), or number and percentage, as appropriate. Correlations were assessed with non-parametric Spearman's r, and $p<0.05$ was considered statistically significant. Categorical variables were assessed with Fisher's exact test. Statistical analysis was carried out using GrapPad Prism 8 (GraphPad Software, San Diego, CA) and SPSS 26 (IBM Corp., Armonk, NY).

**Results**

In the study period, 145 patients underwent chest CT angiographies because of respiratory symptoms, and 61 of them (42%) were positive for SARS-CoV-2.

CT angiography revealed PE in 14 COVID-19 patients (23%). No differences were highlighted in interstitial pulmonary involvement between COVID-19 patients with and without PE.

Data extraction from our hospital database revealed that last year we found 18 PE cases over 112 CT angiograms (16%) performed during the same time span.

Table 1 shows the characteristics of patients with confirmed PE. None had a history of previous DVT or PE, one patient had a recent history of bone fracture, and two patients had undergone recent surgical intervention. Eight patients (57.1%) had been hospitalized within the previous three months.

CUS revealed DVT in five PE cases (35.7%).

In one patient PE was massive and induced severe hemodynamic compromise, requiring timely admission to ICU.

Qanadli score had a significant correlation with PESI, D-dimer, serum high-sensitivity troponin, serum albumin, arterial pressure of oxygen to inspired fraction of oxygen ratio ($pO_2/FiO_2$), and length of hospital stay (Figure 1). PESI had a significant correlation with albumin (r=-.655, 95%CI -.884 to -.174, p=.013) and length of hospital stay (r=.728, 95%CI .307 to .911, p=.004).

Furthermore, the ratio between the right and left ventricle diameter ($V_R/V_L$) measured at CT scan [5] correlated with the length of hospital stay (r=.719, 95%CI .189 to .924, p=.015).

All studied patients survived.

**Discussion**

Our study found that the Qanadli score correlated with the severity of clinical findings and metabolic alterations in COVID-19 patients. In fact, this radiological score showed good correlations with the degree of respiratory dysfunction, length of hospital stay, and the troponin value as a marker of myocardial injury due to PE. Moreover, the CT estimation of the right ventricle overload, expressed as $V_R/V_L$ ratio, correlated with the clinical impact of PE as shown by the length of hospital stay.

In our cohort, patients who developed VTE (either DVT or PE) had a pretest probability in the intermediate-high range, as also confirmed by the Geneva score. The spectrum of mortality risk assessed by PESI score was wide, ranging from class I to class V risk strata, but no patients died in our cohort.

The strong correlation between radiological scores, such as Qanadli and $V_R/V_L$ ratio, and clinical impact of PE underlines the value of the radiological contribute in a multidisciplinary approach to provide COVID-19 patients with the most appropriate and timely management.

We speculate that the correlation found between Qanadli score and albumin values is not negligible. We have recently provided insights into the role of increased endothelial permeability in the pathogenesis of COVID-19, of which hypoalbuminemia is one of the useful markers.[6] Therefore, the results presented highlight the complex mechanisms underlying the so called immunothrombosis which develops in COVID-19, including endothelial damage, abnormal blood flow dynamics, hypercoagulability state, platelet-neutrophil interactions and release of Neutrophil Extracellular Traps or even autoimmune mechanisms.[7]

A limitation of our study is that many critically ill patients did not undergo CT angiography because of marked disproportion between available resources and demand as well as risks related to transport for both patients themselves and healthcare professionals taking care of them during the surge of the epidemic.

Our results strongly suggest that a multidisciplinary approach integrating radiological and clinical-laboratory findings is of pivotal importance in the evaluation and management of PE in COVID-19 patients.

## References


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**Table 1**

**Characteristics of the studied subjects.**

| Variable | Whole population (n=14) | Positive CUS (n=5) | Others (n=9) | p |
|---|---|---|---|---|
| | | | | |
| **Age (years)** | 64.9 (32-92) | 68 (57-82) | 63.2 (32-92) | .797 |
| **WBC ($10^3$ cells·ml$^{-1}$)** | 10.89 (6.96-23.69) | 11.56 (6.96-23.69) | 10.52 (6.99-14.62) | .518 |
| **Neutrophils ($10^3$ cells·ml)** | 8.76 (4.92-20.74) | 10.4 (5.2-20.74) | 7.86 (4.92-12.02) | .518 |
| **Lymphocytes ($10^3$ cells·ml)** | 1.34 (0.360-3.45) | 0.76 (0.36-1.12) | 1.67 (0.58-3.45) | .06 |
| **Hemoglobin (g·dl$^{-1}$)** | 19.3 (7.8-114) | 11.3 (7.8-13.7) | 23.7 (10.3-114) | .298 |
| **Platelets ($10^3$ plts·ml$^{-1}$)** | 303.9 (171-572) | 252.8 (171.-365.) | 332.1 (216-572) | .147 |
| **D-dimer (ng·ml$^{-1}$)** | 7092 (448-26362) | 13646 (4732-26362) | 3450 (448-6447) | .019 |
| **PT (INR)** | 1.22 (1.03-1.48) | 1.32 (1.19-1.45) | 1.17 (1.03-1.48) | .06 |
| **PTT (Ratio)** | 1.18 (0.93-1.38) | 1.2 (1.02-1.35) | 1.16 (0.93-1.38) | .797 |
| **Fibrinogen (mg·dl$^{-1}$)** | 5.53 (3.04-7) | 4.92 (3.04-5.97) | 5.8 (4.06-7) | .26 |
| **Creatinine (mg·dl$^{-1}$)** | 1.1 (0.66-1.7) | 1.18 (1.01-1.7) | 1.06 (0.66-1.42) | 1 |
| **Urea (mg·dl$^{-1}$)** | 43.5 (26-96) | 54 (27-96) | 38.4 (26-88) | .368 |
| **Troponin (ng·l$^{-1}$)** | 54.1 (4-355) | 101.8 (9-355) | 24.2 (4-90) | .222 |
| **CRP (mg·l$^{-1}$)** | 47 (1.-246.) | 42 (1-101) | 50 (1-247) | |
| **arterial pH** | 7.47 (7.42-7.52) | 7.46 (7.44-7.49) | 7.47 (7.42-7.52) | .699 |
| **arterial $pCO_2$ (mmHg)** | 35.3 (25-47) | 31.4 (25-36) | 37.4 (29-47) | .147 |
| **arterial $pO_2$ (mmHg)** | 72 (38-121) | 62 (38-81) | 79 (54-121) | .19 |
| **arterial lactate (mmol·l$^{-1}$)** | 1.3 (0.6-3.3) | 1.5 (0.7-3.3) | 1.2 (0.6-1.7) | 1 |
| **arterial Sat (%)** | 95.6 (88-100) | 94.7 (89-99) | 96 (88-100) | .71 |
| **$FiO_2$** | 0.387 (0.21-0.8) | 0.45 (0.21-0.8) | 0.34 (0.21-0.8) | .606 |
| **PEEP ($cmH_2O$)** | 0 (0-0) | 0 (0-0) | 0 (0-0) | 1 |
| **$PaO_2/FiO_2$** | 271.8 (47-576) | 209.2 (47-361) | 306.6 (97-576) | .364 |
| **SAP (mmHg)** | 129 (80-160) | 135 (115-160) | 126 (80-150) | .606 |
| **DAP (mmHg)** | 71 (50-90) | 69 (60-80) | 73 (50-90) | .606 |
| **HR (bpm)** | 94.2 (73-130) | 95.4 (80-125) | 93.6 (73-130) | 1 |
| **RR (bpm)** | 23 (20-36) | 20 (20-20) | 24 (20-36) | .667 |
| **Temperature (°C)** | 36.5 (36-37.2) | 36.5 (36-37.2) | 36.4 (36-37.2) | .699 |
| **PESI** | 88.1 (34-130) | 99.2 (73-130) | 82 (34-115) | .24 |
| **GENEVA** | 5.5 (3-9) | 6.8 (5-9) | 4.8 (3-9) | .06 |
| **Qanadli** | 17.9 (0-75) | 30 (7.5-75) | 12.5 (0-27.5) | .33 |
| **VD/VS** | 0.93 (0.7-1.6) | 0.95 (0.7-1.6) | 0.91 (0.8-1.07) | .315 |
| **Length of hospital stay (days)** | 22.2 (6-64) | 30.8 (7-64) | 17.4 (6-37) | .518 |
| **Albumin (g·dl$^{-1}$)** | 2.8 (2.1-3.4) | 2.5 (2.1-2.7) | 3 (2.2-3.4) | 0.19 |
| **Time from symptoms onset to CT scan study (days)** | 22.1 (1-43) | 22.4 (5-43) | 21.9 (1-43) | .898 |
| **Time from admission to CT scan (days)** | 2.1 (0-16) | 2.8 (0-14) | 1.8 (0-16) | .898 |

Values are shown as mean (range).

**Figure 1**

**Correlation between radiological score of thromboembolic burden (Qanadli score) and clinical-biochemical markers.**

Correlation of Qanadli score with PESI (r=.774, 95%CI .372 to 0.931, p=.003), D-dimer (r=.679, 95%CI .188 to .899, p=.013), high-sensitivity troponin (r=.683, 95%CI .161 to .906, p=.017), serum albumin (r=-.592, 95%CI -.867 to -.043, p=.036), arterial pressure of oxygen to inspired fraction of oxygen ratio (pO2/FiO2) (r=-.687, 96%CI -.902 to -.202, p=.011), and length of hospital stay (r=.585, 95%CI .032 to .864, p=.038).

*hs-Troponin*, high sensitivity troponin; *LOS-H*, length of hospital stay.