

# Mortality, deep vein thrombosis, and D-dimer levels in patients with COVID-19

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## SOUHRN

**Cíl:** Cílem této studie bylo měřit hodnoty D-dimeru a zjistit jejich vztah k hluboké žilní trombóze (HŽT) a mortalitě pacientů s onemocněním COVID-19.

**Metoda:** Z populace přibližně 1 200 pacientů, u nichž se provádělo vyšetření HŽT obou dolních končetin dopplerovským ultrazvukem, byl vytvořen vzorek sestávající ze 100 pacientů s HŽT a 100 jedinců bez HŽT. Kromě pohlaví a věku účastníků se stanovovaly hodnoty D-dimeru v následujících intervalech > 20 µg/ml, 10 až 20 µg/ml, 5 až 10 µg/ml, 3 až 5 µg/ml a < 3 µg/ml. Sledoval se vztah mezi kategorií hodnot D-dimeru a mortalitou.

**Výsledky:** Průměrné hodnoty D-dimeru ve skupinách s/bez HŽT byly 11,90, resp. 4,97 µg/ml; tento rozdíl byl statisticky významný ( $p = 0,0001$ , párový t test). Mortalita byla vyšší než 35 % u pacientů bez HŽT a s hodnotami D-dimeru > 3 µg/ml. Ve skupině s HŽT byla mortalita vyšší než 55 % nezávisle na hodnotě D-dimeru.

**Závěr:** Stanovení hodnot D-dimeru je naprosto zásadní při screeningu hluboké žilní trombózy u pacientů s onemocněním COVID-19, protože vyšší hodnoty D-dimeru jsou spojeny s vyšší mortalitou a přítomností hluboké žilní trombózy.

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## ABSTRACT

**Aim:** The aim of the present study was to analyze D-dimer levels and associate these levels with deep vein thrombosis and mortality in patients with COVID-19.

**Method:** From a population of approximately 1200 patients evaluated for the investigation of deep vein thrombosis (DVT) of the lower limbs using bilateral venous Doppler ultrasound, 100 positive for DVT and 100 negative for DVT were selected to compose the present sample. Data were collected on sex, age and D-dimer levels. D-dimer levels were categorized as follows: > 20 µg/mL, 10 to 20 µg/mL, 5 to 10 µg/mL, 3 to 5 µg/mL and < 3 µg/mL. The association between D-dimer category and mortality was evaluated.

**Results:** The mean D-dimer level was 11.90 and 4.97 µg/mL in the groups with and without DVT; this difference was significant ( $p = 0.0001$ , paired t-test). The mortality rate was higher than 35% in patients without DVT and with D-dimer > 3 µg/mL. In the group with DVT, the mortality rate was higher than 55% independently of the D-dimer level.

**Conclusion:** The assessment of the D-dimer level is fundamental in screening for deep vein thrombosis in patients with COVID-19, as higher levels are associated with greater mortality and the presence of deep vein thrombosis.

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## Introduction

Studies involving patients with COVID-19 suggest that ultra-high plasma D-dimer levels indicate the severe form of the disease and should be considered a screening tool or indicator of the prognosis in cases of infection by COVID-19.<sup>1</sup> The D-dimer level may be associated with the severity of inflammation in SARS-CoV-2-related pneumonia prior to coagulopathy and thrombosis, which may explain the association between high D-dimer levels and greater mortality rate.<sup>2</sup>

Evaluating clinical biomarkers that predict mortality in COVID-19 with greater precision, researchers have found that changes in D-dimer levels and in the tendency after anticoagulation therapy are highly predictive of in-hospital mortality and may assist in guiding the allocation of resources and future studies on emerging treatments for severe COVID-19.<sup>3</sup>

A meta-analysis reported that the D-dimer level was identified as an independent predictor of mortality in COVID-19. A set of values, such as 0.5 µg/mL, 1 µg/mL, and 2 µg/mL, can be determined as the cutoff point for D-dimer for clinical use.<sup>4</sup> The presence of tachypnea (> 22 bpm) and no radiological signs suggestive of infection by SARS-CoV-2 on the chest radiography and D-dimer > 3000 ng/mL have been identified as predictive factors of deep vein thrombosis in patients with COVID-19.<sup>5</sup>

A review study showed that inflammatory factors, such as interleukin-6, ferritin, leukocytes, neutrophils, lymphocytes, platelets, C-reactive protein, procalcitonin, lactate dehydrogenase, aspartate aminotransferase, creatinine and D-dimer, are important biomarkers of cytokine storm syndrome. High levels of interleukin-6 and hyperferritinemia should be considered warning signs of systemic inflammation and a poor prognosis in cases of COVID-19.<sup>6</sup>

The aim of the present study was to analyze D-dimer levels and associate these levels with deep vein thrombosis and mortality in patients with COVID-19.

## Patients and methods

Two hundred consecutive patients were evaluated from a population of approximately 1200 patients submitted to deep vein Doppler ultrasound of the lower limbs for the investigation of deep vein thrombosis. The patients were hospitalized with COVID-19 in the wards and intensive care units of the hospital affiliated with the São Jose do Rio Preto School of Medicine-Brazil.

### Inclusion criterion

Hospitalized patients undergoing treatment for COVID-19.

### Exclusion criterion

Outpatients with COVID-19.

### Patient selection

From a population of approximately 1200 patients evaluated for the investigation of deep vein thrombosis (DVT) of the lower limbs using bilateral venous Doppler

ultrasound, 100 positive for DVT and 100 negative for DVT were selected to compose the present sample.

### Statistical analysis

Descriptive statistics of the data, Fisher's exact test, and the paired t-test considering a 5% alpha error.

### Ethical considerations

This study received approval from the institutional review board of the São Jose do Rio Preto School of Medicine-Brazil#4.826.094.

### Development

Two hundred consecutive patients were selected from a population of approximately 1200 patients evaluated for the investigation of DVT of the lower limbs using bilateral venous Doppler ultrasound and were divided into two groups: 100 positive for DVT and 100 negative for DVT. Data were collected on sex, age and D-dimer levels. D-dimer levels were categorized as follows: > 20 µg/mL, 10 to 20 µg/mL, 5 to 10 µg/mL, 3 to 5 µg/mL and < 3 µg/mL. The association between D-dimer category and mortality was evaluated. The data were entered into an Excel table and analyzed using the Stats Direct statistical program.

## Results

The groups with and without DVT were composed of 66 and 58 men, respectively, with no significant difference between groups regarding sex ( $p = 0.2$ , Fisher's exact test). Mean age was 58.58 years in the group with DVT and 58.61 in the group without DVT. The mean D-dimer level was 11.90 and 4.97 µg/mL in the groups with and without DVT; this difference was significant ( $p = 0.0001$ , paired t-test).

Figure 1 illustrates the median and interquartile range of D-dimer levels in the two groups. Table 1 shows that the mortality rate was higher than 35% in patients without DVT and with D-dimer > 3 µg/mL. In the group with DVT, the mortality rate was higher than 55% independently of the D-dimer level (Table 2). Table 3 displays the D-dimer levels in the overall sample of 200 patients, revealing a general mortality rate higher than 50% when the D-dimer level was > 3 µg/mL and around 29.68% when below this cutoff point. The average mortality rate among the patients hospitalized in the wards and intensive care units was 22.7%.

## Discussion

The present study investigated the association between D-dimer levels and mortality in 200 hospitalized patients with COVID-19 (100 with and 100 without deep vein thrombosis). In the group with DVT, mortality was higher than 50% independently of the D-dimer level.

In patients without DVT and with D-dimer < 3 µg/mL mortality was around 18.8%, suggesting a lower mortality rate in patients without thrombosis. This finding is in agreement with data from a study in the publication phase, in which the mortality rate was 67% in patients

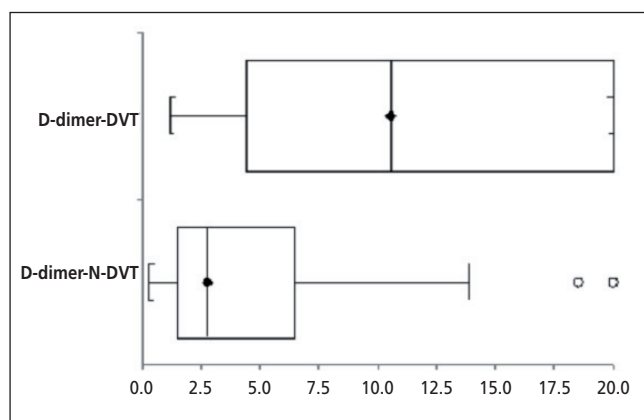


Fig. 1 – Median and interquartile range of D-dimer levels in COVID-19 patients with and without deep vein thrombosis.

with DVT and 31% in those without DVT. Lung impairment 50 to 70% increased the mortality rate to 71.15% in patients with DVT and 36.19% in those without DVT. This suggests that DVT is a factor as important as lung impairment with regards to mortality in patients with COVID-19.

Another aspect analyzed was the possibility of a safe D-dimer level in the evaluation of DVT. However, we found that patients with low D-dimer levels ( $< 1 \mu\text{g/mL}$ ) could have thrombosis and those with very high levels ( $20 \mu\text{g/mL}$ ) could be negative for DVT. Moreover, the mortality rate was lower than 30% when D-dimer levels were  $< 3 \mu\text{g/mL}$ , although this rate is higher than the average for the hospital (22.7%). Some studies suggest a cutoff point of  $> 3 \mu\text{g/mL}$  for the request for venous Doppler ultrasound and the evaluation of thrombosis and pulmonary embolism, but lower levels are safer.<sup>7</sup>

Patients with D-dimer levels higher than  $10 \mu\text{g/mL}$  and without DVT may have other thrombotic sites, such

as the lungs and abdominal, that were not diagnosed in this evaluation. Another possibility is the occurrence of an associated serious disease, as reported in the literature. Therefore, high D-dimer levels are associated with greater mortality.

As many patients hospitalized with COVID-19 are asymptomatic with regards to DVT,<sup>8</sup> Doppler ultrasound screening may be warranted for all patients in intensive care. We began a pilot study analyzing patients with more than ten days of intubation and found that more than 70% were positive for DVT. Another aggravating factor is that the change in the viral variant to SARS-CoV-2 P.1 tripled the number of patients with DVT in the intensive care units. Thus, COVID-19 has a dynamic nature in its form of presentation and treatment approaches should be evaluated based on the situation of each region, considering the different aspects of the disease.

## Conclusion

The assessment of the D-dimer level is fundamental in screening for deep vein thrombosis in patients with COVID-19, as higher levels are associated with greater mortality and the presence of deep vein thrombosis.

## Conflict of interest and funding

The authors declared no have financial support and conflict interest.

## Author's contribution

Design and conduct of the study: Godoy JMP, Da Silva MOM, Amorim H, Vidal da Silva AF, Russeff GLS.

Collection data: Godoy JMP, Da Silva MOM, Amorim H, Vidal da Silva AF, Russeff GLS.

Management: Da Silva MOM, Amorim H, Vidal da Silva AF, Russeff GLS.

Table 1 – D-dimer categories and prevalence of mortality in each category among 100 COVID-19 patients without deep vein thrombosis

D-dimer 20	D-dimer 20 deaths	D-dimer $>10 < 20$	D-dimer $>10 < 20$ deaths	D-dimer $>5 < 10$	D-dimer $>5 < 10$ deaths	D-dimer $>3 < 5$	D-dimer $>3 < 5$ deaths	D-dimer $< 3$	D-dimer $< 3$ deaths
7	3 (42.85%)	8	6 (75%)	13	5 (38.46%)	19	79 (36.8%)	53	10 (18.86%)

Table 2 – D-dimer categories and prevalence of mortality in each category among 100 COVID-19 patients with deep vein thrombosis

D-dimer 20	D-dimer 20 deaths	D-dimer $>10 < 20$	D-dimer $>10 < 20$ deaths	D-dimer $>5 < 10$	D-dimer $>5 < 10$ deaths	D-dimer $>3 < 5$	D-dimer $>3 < 5$ deaths	D-dimer $< 3$	D-dimer $< 3$ deaths
9	28 (75.67%)	8	10 (55.55%)	8	11 (57.89%)	5	10 (66.66%)	2	9 (81.81%)

Table 3 – D-dimer categories and prevalence of mortality in each category in overall sample of 200 COVID-19 patients (100 with and 100 without deep vein thrombosis)

D-dimer 20	D-dimer 20 deaths	D-dimer $>10 < 20$	D-dimer $>10 < 20$ deaths	D-dimer $>5 < 10$	D-dimer $>5 < 10$ deaths	D-dimer $3 < 5$	D-dimer $3 < 5$ deaths	D-dimer $< 3$	D-dimer $< 3$ deaths
13	31 (70.4%)	10	16 (61.53%)	16	16 (50%)	17	17 (50%)	45	19 (29.68)

Analysis and interpretation of the data: Godoy JMP.

Preparation: Godoy JMP, Da Silva MOM, Amorim H, Vidal da Silva AF, Russeff GLS.

Review: Godoy JMP, Da Silva MOM, Amorim H, Vidal da Silva AF, Russeff GLS.

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Decision to submit the manuscript for publication: Da Silva MOM, Amorim H, Vidal da Silva AF, Russeff GLS.

All authors agree with the manuscript.

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