

## STUDY OF HYPERCOAGULABILITY IN PATIENTS WITH COVID-19 AND ITS REPERCUSSIONS

---

*Bianca Mansur Nonato*

*Luana Assis Marquez*

*Vitor Reis Caliman*

*Diana de Oliveira Frauches*

All content in this magazine is licensed under a Creative Commons Attribution License. Attribution-Non-Commercial-Non-Derivatives 4.0 International (CC BY-NC-ND 4.0).



**Abstract: Objective:** To verify the potential of D-dimer as a predictor of venous thromboembolism (VTE) in patients hospitalized for COVID-19 and risk factors for elevated D-dimer, for VTE and for evolution to death. **Method:** The study consisted of a retrospective cohort, which collected data from the electronic medical records of 238 patients over 18 years of age, hospitalized with a diagnosis of COVID-19 registered at the Santa Casa de Misericórdia Hospital in Vitória, in 2020. Absolute and relative frequency distributions were used for statistical analysis, as well as calculating the relative risk (RR) and its confidence interval at the 95% reliability level. The project was approved by Emescam's Research Ethics Committee (CAAE: 47510121.8.0000.5065). **Results:** Of the 238 patients, 92 were excluded because they did not have confirmation of SARS-CoV-2 infection by RT-PCR recorded in their medical records. It was not possible to calculate the RR of elevated D-dimer related to the occurrence of VTE, making it impossible to analyze the marker. In the other analyses, no associations were found for the outcomes elevated D-dimer, VTE and death, with the exception of prolonged length of hospital stay in relation to VTE (RR: 9.10 / CI: 1.12-73.67) and death (RR: 4.62 / CI: 1.80-11.86). **Conclusion:** The study did not prove many of the associations documented in the literature, including the relationship between elevated D-dimer and VTE in patients hospitalized for COVID-19. Thus, further studies are needed with larger numbers of patients and occurrences of VTE, allowing the formation of more informed conclusions that improve the management of these patients.

**Keywords:** Venous Thromboembolism; Hospitalization; Coronavirus Infections; Venous Thrombosis; COVID-19.

**Financial Support:** EMESCAM Scholarship.

## INTRODUCTION

COVID-19 is a disease caused by the SARS-CoV-2 virus. Originally detected in the city of Wuhan in China, it quickly spread across international borders, becoming a major concern for health systems around the world, generating care overload and socioeconomic impact (LIANG, 2021).

In Brazil, more than 30 million confirmed cases and 665,000 deaths from the disease were recorded in 2022, denoting the impact of the disease, as well as the need to seek new information about the virus and its effects on the human body. (BRASIL, 2022)

One of these effects is the state of hypercoagulability, which involves cases of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) (LIANG, 2021). The incidence of DVT was between 18.3% and 22.1% in severe COVID-19 hospitalized patients, 28.3% in COVID-19 hospitalized patients and 38.0% among those with severe COVID-19 hospitalized or not, making it relevant to understand this type of complication for the care and management of these patients.

It is important to note that these phenomena occur due to the virus entering the cells of the intimal layer of blood vessels, binding to the angiotensin-converting enzyme 2, which is responsible for causing endothelial lesions that result in alterations to the thrombo-hemorrhagic balance, favoring fibrin production and thrombus formation (LIU, 2021).

In this process, various residues such as the D-dimer are generated, and it is possible to measure them in blood samples to expected standards, in an attempt to predict if and when the patient with COVID-19 will be at greater risk of thrombotic events. (LIANG, 2021) However, the evidence on the ability of the D-dimer to predict the occurrence of VTE is still inconclusive, although the relationship

between its increase and the severity of the clinical condition has already been established (YANG, 2021).

The aim of this study is to investigate possible risk factors for D-dimer elevation and the relationship between an altered level of this marker and the occurrence of VTE. The contribution of D-dimer elevation and the occurrence of VTE, as well as the length of hospitalization, to the occurrence of death from COVID-19 will also be studied.

## METHOD

The study consisted of a retrospective cohort, in which data was collected from the electronic medical records of patients hospitalized for COVID-19 at the Santa Casa de Misericórdia de Vitória Hospital (HSCMV) in 2020. Patients over the age of 18 with a diagnosis of COVID-19 recorded on the hospital management platform were included. Patients with signs or symptoms of VTE on initial care, those already hospitalized with VTE, those under the age of 18 and those without confirmation of SARS-CoV-2 infection by RT-PCR test were excluded.

In relation to the dependent variable elevated D-dimer, the independent variables were gender, age group, risk comorbidities for COVID-19 complications defined by the Ministry of Health (BRASIL, 2021), length of hospitalization and VTE prophylaxis. In a second analysis, we investigated whether the same variables and high D-dimer influence the occurrence of VTE. Finally, the contribution of elevated D-dimer, the occurrence of VTE and hospitalization time to the evolution to death was verified. Patients who were transferred were excluded from this last analysis.

The age groups up to 59 years and 60 years and over were considered, with 60 years and over considered to be at risk of complications from COVID-19 (BRASIL, 2021). The length of hospitalization was classified as 1 to 7 days

and 8 or more days, as the risk of complications is expected to increase with prolonged hospitalization (FERREIRA, 2018). The comorbidities considered were those foreseen by the Ministry of Health as risk factors for severe evolution of COVID-19 (BRASIL, 2021). VTE prophylaxis was understood as the administration of anticoagulant medication after the start of hospitalization and in the absence of signs, symptoms and complementary tests indicative of VTE.

A level greater than or equal to 500 ng/ml was taken to classify elevated D-dimer in a blood sample, using only the value of the first sample taken after hospitalization in cases where there was no VTE or the value prior to and closest to the date of documentation of the complementary examination for VTE, when this was carried out (ROSSI, 2020).

VTE was considered to be any thrombus formation and/or embolization in the venous circulation documented by complementary tests, with or without signs and symptoms of VTE in the anamnesis and physical examination. Complementary tests indicative of VTE included Doppler of the lower limbs and thoracic angiotomography with typical alterations (ALBRICKER, 2022).

Absolute and relative frequency distributions were used for statistical analysis, as well as calculating the relative risk (RR) and its confidence interval, at a 95% reliability level.

The research project was approved by Emescam's Research Ethics Committee (CAAE: 47510121.8.0000.5065).

## RESULTS AND DISCUSSION

Of the total of 238 patients over the age of 18 hospitalized with a diagnosis of COVID-19 at the HSCMV in 2020, 92 were excluded because they did not have RT-PCR confirmation of SARS-CoV-2 infection recorded in their medical records.

The characteristics of the 146 patients included are shown in Table 1. Of these, 54.79% were female and 45.21% male. The most prevalent age groups were between 40 and 59 years old (30.82%) and between 70 and 79 years old (25.34%), with the lowest incidence being between 20 and 39 years old (9.59%).

Variables	N°	%
Sex		
Male	66	45,21
Female	80	54,79
Age group		
20 a 39	14	9,59
40 a 59	45	30,82
60 a 69	31	21,23
70 a 79	37	25,34
80 and more	19	13,01
Comorbidities at risk of complications		
No	45	30,82
Yes	101	69,18
Length of stay		
1 to 7 days	88	60,27
8 to 14 days	34	23,29
15 to 21 days	5	3,42
22 to 28 days	11	7,53
29 days and more	8	5,48
High D-dimer		
No	10	9,90
Yes	91	90,10
VTE prophylaxis		
No	8	5,48
Yes	138	94,52
TEV		
No	139	95,20
Yes	7	4,80
Evolution		
High	111	76,03
Death	21	14,38
Transfer	14	9,59
Total	146	100,00

Table 1 - Patient characteristics

Source: Prepared by the authors (2022)

Note: D-dimer was not measured in 45 patients (30.82%).

D-dimer was measured in 101 patients (69.18%), 90.10% of whom showed an increase in this marker. Some kind of VTE prophylaxis was carried out in 94.52% of patients and there were 7 (4.80%) cases of VTE (4 in the lower limbs and 3 in the lungs). Discharge was the most common outcome (76.03%), followed by death (14.38%) and transfer (9.59%). Most patients were hospitalized for between 1 and 7 days (60.27%), but 23.29% were hospitalized for between 8 and 14 days and a minority were hospitalized for between 15 and 21 days (3.42%).

The distribution of comorbidities is shown in Table 2. It was observed that 101 (69.18%) patients had at least one comorbidity, 44 with one comorbidity and 57 with two or more comorbidities. The most frequent comorbidities were systemic arterial hypertension and diabetes simultaneously (39 cases), systemic arterial hypertension (36), severe or decompensated pneumopathies (14), myocardiopathies (10), diabetes (9) and chronic kidney disease (9). Other comorbidities were also found in smaller numbers, such as malignant neoplasms (8), cerebrovascular disease (7), obesity (5), chronic liver disease (2), immunosuppression (2) and chromosomal diseases with immune fragility (1).

Comorbidities	N°	%
Hypertension and diabetes mellitus	39	27,46
Hypertension	36	25,35
Severe or decompensated pneumopathies	14	9,86
Myocardiopathies	10	7,04
Diabetes mellitus	9	6,34
Chronic kidney disease	9	6,34
Malignant neoplasm	8	5,63
Cerebrovascular disease	7	4,93
Obesity	5	3,52
Chronic liver disease	2	1,41
Immunosuppression	2	1,41
Chromosomal diseases with a state of immune fragility	1	0,70
Total	142	100,00

Table 2 - Distribution of comorbidities at risk of COVID-19 complications

Source: Prepared by the authors (2022)

Only females and those aged 60 and over had an increased risk of high D-dimer, but no statistically significant difference was found in any of the independent variables studied (Table 3).

According to the literature, gender and 60 years or more are risk factors for high D-dimer, although increased D-dimer values can be attributed to other events, such as pregnancy in the case of females, and chronic inflammatory diseases or cardiovascular diseases in the case of the elderly, given the low specificity of the marker, especially in older age groups (ALBRICKER, 2022). The literature also shows that comorbidities, especially cardiovascular diseases, and prolonged hospitalization favor an increase in D-dimer (ALBRICKER, 2022). Such disagreements may be due to the small number of patients included in this study, when compared to other studies.

Similarly, the small number of cases of VTE may explain why there was no statistically significant difference in the occurrence of this outcome according to the variables studied (Table 4), as a statistical association has been observed in other studies, especially for 60 years or more and length of stay (ROSSI, 2020).

It should be noted that the small number of cases of VTE made it impossible to investigate their relationship with elevated D-dimer, which prevented the formulation of statistical calculations about the potential of D-dimer as a marker of the occurrence of VTE in these patients.

The small proportion of VTE cases found in this study (4.8%) is not similar to other studies, which have shown a high incidence of VTE, with a wide variation in findings, ranging from 6.5% to 76.2% (MACARI, 2022; LIANG, 2021). Even with this variability, other studies have shown a significant increase in cases with the implementation of screening routines for VTE (MACARI, 2022). Thus, one of the possibilities to explain the low proportion of

patients who developed VTE is the lack of implementation of routine screening for VTE at the HSCMV.

In addition, some factors such as the high percentage of patients who received VTE prophylaxis and the possibility of errors in the indication or recording of complementary exams may also have influenced the low number of patients who suffered thrombotic events (SPYROPOULOS, 2020). It should be noted that, in this study, 94.52% of patients underwent VTE prophylaxis and the VTE case definition criterion adopted did not consider clinical criteria, requiring confirmation by Doppler of the lower limbs or angiotomography. Another hypothesis is that D-dimer, when normal, may be a protective marker for VTE, which would explain the lack of cases of VTE in patients who did not show an increase in the marker, a fact already observed in studies of elderly populations with COVID-19 (ALBRICKER, 2022).

As for evolution (Table 5), high D-dimer and VTE were not associated with death, while prolonged hospitalization increased the risk of this event (RR: 4.62; CI: 1.80-11.86).

Variables	Evolution				RR	IC
	Death		High			
	Nº	%	Nº	%		
High D-dimer						
No*	1	11,11	8	88,89		
Yes	13	15,66	70	84,34	1,41	0,21-9,56
TEV						
No*	19	15,20	106	84,80		
Yes	2	28,57	5	71,43	1,88	0,54-5,51
Length of stay						
1 a 7*	5	6,41	73	93,59		
8 and more	16	29,63	38	70,37	4,62	1,80-11,86

Table 5 - Study of factors for the occurrence of death

Source: Prepared by the authors (2022)

Note: 14 patients who left by transfer were excluded.

\* Reference category

Variables	High D-dimer				RR	IC
	Yes		No			
	N°	%	N°	%		
Sex						
Male*	38	84,44	7	15,56		
Female	53	94,64	3	5,36	1,12	0,97-1,29
60 years or older						
No*	39	84,78	7	15,22		
Yes	52	94,55	3	5,45	1,16	0,97-1,28
Comorbidities						
1 or more	63	90,00	7	10,00	1,00	0,87-1,15
None*	28	90,32	3	9,68		
Comorbidities (2)						
2 or more	29	85,29	5	14,71	0,92	0,79-1,08
None or 1*	62	92,54	5	7,46		
Hypertension and diabetes						
Yes	15	78,95	4	21,05	0,87	0,67-1,13
No comorbidity*	28	90,32	3	9,68		
Hypertension and/or diabetes						
Yes	50	89,29	6	10,71	0,99	0,85-1,14
No comorbidity*	28	90,32	3	9,68		
Length of stay						
1 to 7 days*	55	90,16	6	9,84		
8 days and more	36	90,00	4	10,00	1,00	0,87-1,14

Table 3 - Study of factors for D-dimer elevation

Source: Prepared by the authors (2022)

\* Reference category

Variables	TEV				RR	IC
	Yes		No			
	N°	%	N°	%		
Sex						
Male*	4	6,06	62	93,94		
Female	3	3,75	77	96,25	0,62	0,14-2,67
60 years or older						
No*	2	3,39	57	96,61		
Yes	5	5,75	82	94,25	1,70	0,34-8,45
Comorbidities (1)						
1 or more	5	4,95	96	95,05	1,11	0,22-5,53
None*	2	4,44	43	95,56		
Comorbidities (2)						
2 or more	2	3,51	55	96,49	0,62	0,13-3,11
None or 1*	5	5,62	84	94,38		
Hypertension and diabetes						
Yes	1	2,56	38	97,44	0,58	0,05-6,12
No comorbidity*	2	4,44	43	95,56		

Hypertension and/or diabetes						
Yes	5	5,95	79	94,05	1,34	0,27-6,63
No comorbidity*	2	4,44	43	95,56		
High D-dimer						
No*	0	0,00	10	100,00		
Yes	4	4,40	87	95,60	-	
VTE prophylaxis						
No	0	0,00	8	100,00	-	
Yes*	7	5,07	131	94,93		
Length of stay						
1 to 7 days*	1	1,14	87	98,86		
8 days or more	6	10,34	52	89,66	9,10	1,12-73,67

Table 4 - Study of factors for the occurrence of VTE

Source: Prepared by the authors (2022)

\* Reference category

These results also disagree with the literature, which points to elevated D-dimer and the occurrence of VTE as reliable markers for an increased chance of death in COVID-19 patients (SHAH, 2020). The explanation for this may again lie in the low number of patients included compared to other studies that have analyzed this outcome, as well as the relatively low percentage of patients who had their D-dimer quantified (69.18%).

With regard to length of stay, the results do not strengthen the existing evidence, which shows that patients with more than 7 days of intent due to COVID-19 have a lower risk of death (DEITOS, 2022). This difference may be due to the profile of comorbidities and infrastructure that differ between the hospitals studied.

Limitations of the study include the relatively small number of patients included, the possible selection of less severe cases in hospital screening for admission to the HSCMV, the inclusion of patients without D-dimer measurement and the lack of a more sensitive criterion for defining VTE. In addition, the medical records used as a source of data are subject to recording bias and may not reflect the real situation of the patients in all cases.

The study's strengths include the fact that it is a pioneer in investigating the relationship between elevated D-dimer and VTE, as well as risk variables for COVID-19 inpatients in Espírito Santo. It could also become the basis for new studies in other hospitals, as well as a subsidy for evaluating new public policies in the care of COVID-19 inpatients in our country.

## CONCLUSION

The study failed to prove many associations documented in the literature, including the relationship between elevated D-dimer and VTE in patients hospitalized for COVID-19. Thus, more studies are needed, with a larger number of patients and occurrences of VTE, so that it is possible to measure the relative risk, allowing for more informed conclusions that improve the management of these patients.

It is recommended that these new studies adopt more sensitive criteria for cases of VTE, exclude patients without a measured D-dimer and separate groups of patients based on whether or not they have taken prophylactic regimens.

## THANKS

We would like to thank Diana de Oliveira Frauches for her helpful advice and guidance.

We would like to thank Brenno Augusto Seabra De Mello Netto for his co-supervision.

We would also like to thank the Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória for the structure provided and for the financial support through the PIBIC-EMESCAM program.

## REFERENCES

- ALBRICKER, A. C. L. *et al.* Joint guideline on venous thromboembolism - 2022. *Arq Bras Cardiol.* 2022 Apr;118(4):797-857. English, Portuguese. doi: 10.36660/abc.20220213. Erratum in: *Arq Bras Cardiol.* 2022 Jun 10;118(6):1153. PMID: 35508060; PMCID: PMC9007000.
- BRASIL. Ministério da Saúde. Painel Coronavirus. 2019. Disponível em: <https://covid.saude.gov.br/>. Acesso em: 26 agosto 2022
- BRASIL. Ministério da Saúde. Secretaria de vigilância em saúde. Guia de vigilância epidemiológica : emergência de saúde pública de importância nacional pela doença pelo coronavírus 2019 – covid-19, 2021. Disponível em: [www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/publicacoes-svs/coronavirus/guia-de-vigilancia-epidemiologica-covid-19\\_2021.pdf/view](http://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/publicacoes-svs/coronavirus/guia-de-vigilancia-epidemiologica-covid-19_2021.pdf/view). Acesso: 20. aug. 2022.
- DEITOS, J. *et al.* Perfil epidemiológico e desfecho clínico de pacientes internados com COVID-19 em um Hospital Universitário de Campo Grande –MS. *Research, Society and Development*, v. 11, n.4, e6111427046, 2022. ISSN 2525-3409. doi: <http://dx.doi.org/10.33448/rsd-v11i4.27046>.
- LIANG, K. *et al.* Clinical features of COVID-19 patients with venous thromboembolism. *Clin Appl Thromb Hemost.* 2021 Jan-Dec;27:10760296211013104. doi: 10.1177/10760296211013104. PMID: 34169772; PMCID: PMC8236764. Disponível em: [journals.sagepub.com/doi/10.1177/10760296211013104](https://journals.sagepub.com/doi/10.1177/10760296211013104). Acesso em: 5. aug. 2022.
- LIU, B. M. *et al.* Significância clínica da medição dos níveis de citocina sérico como biomarcadores inflamatórios em casos adultos e pediátricos COVID-19: Uma revisão. *Citocinas.* Jun; 142:155478, 2021. doi: 10.1016/j.cyto.2021.155478. Epub 2021 Fev 23. PMID: 33667962; PMCID: PMC7901304.
- MACARI, B. F. *et al.* Incidence of venous thromboembolic events in patients diagnosed with COVID-19: A literature review. *Research, Society and Development*, [S. l.], v. 11, n. 5, p. e24511528273, 2022. doi: 10.33448/rsd-v11i5.28273. Disponível em: [rsdjournal.org/index.php/rsd/article/view/28273](https://rsdjournal.org/index.php/rsd/article/view/28273). Acesso em: 18. aug. 2022.
- ROSSI, F. H. Tromboembolismo venoso em pacientes COVID-19. *J Vasc Bras.* 2020;19:e20200107.<https://doi.org/10.1590/1677-5449.200107>. Disponível em: <https://www.scielo.br/j/jvb/a/PJVXkwCHBcVtGZv7bZ939Dm/?lang=pt> Acesso: 24. aug. 2022.
- SHAH, S. *et al.* Elevated D-Dimer levels are associated with increased risk of mortality in Coronavirus Disease 2019: a systematic review and meta-analysis. *Cardiol Rev.* 2020;28(6):295-302. doi:10.1097/CRD.0000000000000330. Disponível em: [www.ncbi.nlm.nih.gov/pmc/articles/PMC7437424/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC7437424/). Acesso em: 2. aug. 2022.
- SPYROPOULOS, A. C; LEVY, A. H, AGENO, W. *et al.* Scientific and Standardization Committee Communication: clinical guidance on the diagnosis, prevention and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost.* 2020;18(8):1859-65. PMID:32459046. Disponível em: [www.ncbi.nlm.nih.gov/pmc/articles/PMC7283841/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC7283841/). Acesso em: 18. aug. 2022.
- LIU, M. D. Y. *et al.* A systematic review and meta-analysis of incidence, prognosis, and laboratory indicators of venous thromboembolism in hospitalized patients with coronavirus disease 2019. *Journal of Vascular Surgery: Venous and Lymphatic Disorders.* Volume 9, Issue 5,2021,Pages 1099-1111.e6, ISSN 2213-333X, doi: 10.1016 Disponível em: [www.sciencedirect.com/science/article/pii/S2213333X2100072X](http://www.sciencedirect.com/science/article/pii/S2213333X2100072X). Acesso em: 2. aug. 2022.
- YANG, C. *Et al.* Predictive roles of D-dimer for mortality of patients with community-acquired pneumonia: a systematic review and meta-analysis. *J Bras Pneumol.* 2021;47(6):e20210072. Disponível em: [www.jornaldepneumologia.com.br/details/3597/en-US/predictive-roles-of-d-dimer-for-mortality-of-patients-with-community-acquired-pneumonia-a-systematic-review-and-meta-analysis](http://www.jornaldepneumologia.com.br/details/3597/en-US/predictive-roles-of-d-dimer-for-mortality-of-patients-with-community-acquired-pneumonia-a-systematic-review-and-meta-analysis). Acesso em: 18. aug. 2022.