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RELEVANCE OF D-DIMER IN THE CLINICAL COURSE OF PATIENTS WITH COVID-19

RELEVÂNCIA DO DÍMERO D NA EVOLUÇÃO CLÍNICA DE PACIENTES COM COVID-19

Gabriella Letícia Bonone[1]*, Deborah de Castro Moreira[2], Gabriele Nascimento de Oliveira[3], Natan Nascimento de Oliveira[4], Dennis Armando Bertolini[5]

[1]*PhD student in the Graduate Program in Health Sciences, State University of Maringá, Maringá (PR), Brazil; [2]PhD in Health Sciences from the Graduate Program in Health Sciences (PCS) at the State University of Maringá – UEM, Maringá (PR), Brazil; [3]PhD student in the Graduate Program in Health Sciences, State University of Maringá, Maringá (PR), Brazil; [4]PhD student in the Graduate Program in Nursing (PSE) at the State University of Maringá – UEM, Maringá (PR), Brazil; [5]PhD in Infectious Diseases from the Federal University of São Paulo, UNIFESP, Brazil. Associate professor in the Department of Clinical Analysis and Biomedicine (DAB/UEM) and permanent lecturer in the Postgraduate Program in Health Sciences (PCS) at the State University of Maringá – UEM, Maringá (PR), Brazil.

*Corresponding Author: Gabriella Letícia Bonone – Email: pg55319@uem.br

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ABSTRACT: Patients with COVID-19 frequently present elevated D-dimer levels, indicating an increased risk of complications. This study evaluated the relevance of D-dimer in clinical management by analyzing data from 366 patients. Clinical, laboratory, epidemiological, and sociodemographic data were collected from 366 patients hospitalized in the ward and intensive care unit of the Regional University Hospital of Maringá, State University of Maringá (HUM), using the GSUS-HUM database. Pearson's chi-square test, Fisher's exact test, and Student's t-test were applied for data analysis. Subsequently, a generalized linear regression model with Gamma distribution and log-link function was constructed. Odds ratios were estimated by exponentiating the obtained coefficients, along with their respective 95% confidence intervals. The results demonstrated that elevated D-dimer levels were correlated with higher mortality, ICU admission, thrombosis, acute renal failure, endocarditis, sepsis, and the need for anticoagulant therapy. The generalized linear regression analysis indicated a significant association between D-dimer levels and these outcomes. Serum D-dimer at admission is therefore a crucial marker for assessing COVID-19 severity and patient prognosis.

KEYWORDS: COVID-19; D-dimer; Prognosis; SARS-CoV-2; Fibrin Fibrinogen Degradation Products.

RESUMO: Pacientes com COVID-19 frequentemente apresentam níveis elevados de dímero D, indicando um risco aumentado de complicações. Este estudo avalia a relevância do dímero D no manejo clínico, analisando dados de 366 pacientes. Coletamos dados clínicos, laboratoriais, epidemiológicos e sociodemográficos de 366 pacientes internados na enfermaria e na UTI do Hospital Universitário Regional de Maringá da Universidade Estadual de Maringá (HUM) utilizando o banco de dados GSUS-HUM. O teste qui-quadrado de Pearson, o teste exato de Fisher e o teste t de Student foram utilizados para a análise dos dados. Posteriormente, foi construído um modelo de regressão linear generalizada com distribuição Gamma e função log-link. A razão de chances foi estimada a partir da exponenciação dos coeficientes obtidos, juntamente com um intervalo de confiança de 95%. Os resultados mostram que o D-dímero elevado está correlacionado com maior mortalidade, admissão na UTI, trombose, IRA, endocardite, sepse e necessidade de anticoagulantes. A regressão linear generalizada indica uma associação significativa. O D-dímero sérico na admissão é um marcador crucial para avaliar a gravidade da COVID-19 e o prognóstico do paciente.

PALAVRAS-CHAVE: COVID-19; dímero D; Prognóstico; SARS-CoV-2; Produtos de Degradação da Fibrina e do Fibrinogênio.

INTRODUCTION

The emergence of SARS-CoV-2 represented a serious global public health crisis, rapidly spreading and infecting over 497 million people, with more than 6 million deaths reported worldwide by April 2022[1]. Brazil ranks among the most affected countries, with approximately 30 million confirmed cases and 661 thousand deaths recorded by that time[2].

Among the various clinical manifestations of COVID-19, coagulopathy has stood out as a major complication, particularly in severe cases. Elevated serum levels of D-dimer, fibrinogen, and factor VIII have been frequently observed in hospitalized patients, especially those in critical condition. These abnormalities contribute to a prothrombotic state, increasing the risk of local thrombus formation and systemic coagulation disorders, which can lead to life-threatening thromboembolic events such as pulmonary embolism[3].

International studies have demonstrated the potential role of D-dimer not only as a marker of disease severity and mortality but also as a predictor of venous thromboembolism (VTE) in COVID-19 patients. These findings support the use of D-dimer for early risk stratification and clinical decision-making regarding anticoagulant therapy[4]. Research conducted in countries such as China, Italy, and the United States has highlighted this association, emphasizing the prognostic value of D-dimer in clinical practice. However, differences in populations and health systems may limit the direct application of these findings to other regional contexts.

In Brazil, although some studies have addressed the relationship between COVID-19 and coagulation parameters[5–7], most of the national research has focused on the efficacy of anticoagulant therapy[8,9], while few have specifically examined the correlation between D-dimer levels and the clinical progression of Brazilian patients - especially within the public hospital system.

Given the severity of COVID-19 and its impact on healthcare systems, this study aims to analyze the relevance of D-dimer as a prognostic marker in the clinical progression of patients hospitalized with COVID-19 at the Hospital Universitário Regional de Maringá (HUM). By contributing to a better understanding of this biomarker in the Brazilian public health context, we seek to support more effective clinical interventions and strengthen the integration of scientific evidence with public health strategies.

METHODOLOGY

STUDY DESIGN

This is a cross-sectional, analytical, secondary database study. To construct this study, we followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[10].

LOCATION AND STUDY POPULATION

Sociodemographic and epidemiological data, along with D-dimer test results, were collected from 366 patients admitted to the Infirmary and Intensive Care Unit of HUM with confirmed COVID-19. Patients were considered eligible if they had both clinical and laboratory confirmation of COVID-19 and underwent D-dimer testing at the time of hospital admission. Exclusion criteria included absence of laboratory confirmation, a mismatch between test and admission dates, or discrepancies between identification data and D-dimer results.

The average number of hospitalizations in the HUM was used as a criterion for sample estimation, where it was calculated based on a proportion. As parts of the calculation formula, it was established the population size as 1,000 (average number of hospitalizations), 50% of anticipated frequency (to result in the largest sample size as the true percentage was unknown), confidence limit of 5% of 100 (meaning the anticipated frequency plus the confidence limit), and a design effect of 1 (as simple random sampling was performed). That resulted in a sample of 278 for 95% Confidence Level and 80% Power of Test.

VARIABLES OF INTEREST

Clinical data such as symptoms, comorbidities, D-dimer results, and epidemiological data were accessed from the patients' charts in the SUS Health Care Management System (GSUS) of the HUM of the State University of Maringá (UEM). The outcome variable chosen was the dosage of factor D-dimer on hospital admission and the others as death and ICU admission. Development of thrombosis, ARF, endocarditis, SEPSE, and the need for anticoagulant therapy were the independent variables used to evaluate the patients' clinical picture evolution.

STATISTICAL ANALYSIS

Pearson's Chi-square and Fisher's Exact tests were used to compare categorical variables, and the T-test to compare continuous data. For the descriptive analysis, having high D-dimer as the outcome variable, the following independent variables of interest were separated: gender; whether ICU admission was necessary; use of invasive mechanical ventilation; use of anticoagulants; use of corticoids; dialysis; whether the patient had a cardiorespiratory arrest, pancreatitis, acute renal failure (ARF), sepsis (SEPSE), thrombosis, endocarditis, and whether the patient died. Subsequently, a generalized linear regression (GLM) model with Gamma distribution and log-link function was built. The use of log-link function was necessary due to the highly skewed nature of the data. Therefore, the exponentiation of the coefficients obtained resulted in Odds Ratio (OR), together with a 95% confidence interval (95% CI) whose 95% significance level was considered for the analyses, supported by the software R, version 4.1.1.

RESEARCH ETHICS COMMITTEE

The project is part of a larger project entitled "Clinical and Immunological Surveillance of Patients Hospitalized with COVID-19 in the Northwestern Macroregion of the State of Paraná", which has been approved by the Standing Committee on Ethics in Research involving Humans from the State University of Maringá, according to Opinion No. 4,268,659.

RESULTS

Data from 366 patients were used, where the mean for D-dimer values was 2126 ng/mL and the median 850 ng/mL, and for log(D-dimer), the mean and median were 6.98 and 6.74, respectively (Table 1).

Table 1. Mean, median, standard deviation, first and third quartile, maximum and minimum of D-dimer and log(D-dimer) variables 366 patients affected by COVID-19.

Variable	Average	Median	Standard Deviation	First Quartile	Third Quartile	Maximum	Minimum
D-dimer	2126 ng/mL	850.00 ng/mL	3566.00	494.00	1871.00	20000.00	266.00
log(D-dimer)	6.98	6.74	1.03	6.20	7.53	9.90	5.58

For the organization of the variable D-dimer, two categories were established, D-dimer up to 850 ng/mL and D-dimer above 850 ng/mL, based on the median value for the description of categorical variables. Male gender was more frequent among the study participants but showed no statistically significant difference between D-dimer dosage and gender (Table 2).

Table 2. Descriptive analysis of categorical variables of interest of 366 patients affected by COVID-19.

Variables	D-dimer above 850 ng/mL		D-dimer up to 850 ng/mL	
	n	%	n	n
Sex				
Male	106	56.38	111	59.68
Female	83	44.15	75	40.32
ICU Admission				
No	89	47.34	149	80.11
Yes	97	51.60	36	19.35
Use of Invasive Mechanical Ventilation				
No	113	60.11	172	92.47
Yes	75	39.89	13	6.99
Use of Anticoagulants				
No	8	4.26	36	19.35
Yes	179	95.21	150	80.65
Corticosteroid Use				
No	12	6.38	33	17.74
Yes	174	92.55	153	82.26
Dialysis				
No	160	85.11	178	95.70
Yes	24	12.77	8	4.30
Cardiac Arrest				
No	161	85.64	179	96.24
Yes	27	14.36	7	3.76
Pancreatitis				
No	188	100.00	186	100.00
Yes	0	0.00	0	0.00
Acute Renal Failure				
No	168	89.36	184	98.92
Yes	20	10.64	2	1.08
SEPSE				
No	179	95.21	186	100.00
Yes	9	4.79	0	0.00
Thrombosis				
No	182	96.81	185	99.46
Yes	5	2.66	1	0.54
Endocarditis				
No	187	99.47	186	100.00
Yes	1	0.53	0	0.00
Death				
No	121	64.36	171	91.94
Yes	65	34.57	15	8.06

ICU admission was associated with a higher frequency of severe cases in those with higher D-dimer values (Table 2).

The Gamma regression model was adjusted to identify associated factors, as shown in Figure 1. Death, ICU admission, thrombosis, acute renal failure, endocarditis, SEPSE, and anticoagulant use were statistically associated with high D-dimer[4].

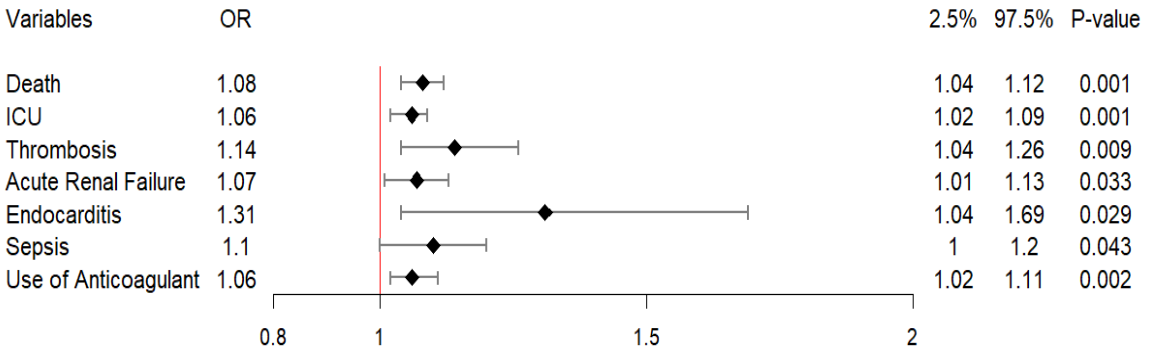

Figure 1. ForestPlot of the adjusted model of patients affected by COVID-19 admitted to Hospital Universitário Regional de Maringá. Legend: ICU- Intensive Care Unit; ARF- Acute Renal Failure; SEPSE- Septicemia.

DISCUSSION

Our findings confirm that elevated D-dimer levels are significantly associated with an increased risk of developing severe complications in patients hospitalized with COVID-19. Among these complications, we observed particularly strong associations with sepsis (SEPSE), acute renal failure (ARF) and endocarditis. Notably, our results indicate that for each unit increase in D-dimer, there is a 10% higher chance of the patient developing SEPSE - a finding that reinforces the potential role of D-dimer as an early prognostic marker in clinical settings.

These results are consistent with previous studies, such as Tang et al. (2020), which demonstrated that anticoagulant treatment was associated with reduced mortality in patients who developed coagulopathy in severe stages of COVID-19[12]. This aligns with our data, suggesting that early recognition of elevated D-dimer may inform timely therapeutic interventions and improve patient outcomes.

Although elevated D-dimer is a well-established marker of thrombotic activity, our study contributes novel evidence by linking its levels to the incidence of secondary infections such as endocarditis and the development of renal complications. These findings differ slightly from some earlier reports, which emphasized pulmonary embolism as the main outcome. The unexpected strength of association between D-dimer and infectious-inflammatory complications (such as SEPSE and endocarditis) may reflect the systemic endothelial injury and immune dysregulation promoted by SARS-CoV-2, warranting further investigation.

The pathophysiological mechanisms underlying these findings are complex. Endothelial injury caused by SARS-CoV-2 leads to the release of D-dimer into circulation[11]. D-dimer, as a fibrin degradation product, reflects ongoing coagulation and fibrinolysis and is known to be elevated in thromboinflammatory states[3]. Additionally, viral inactivation of angiotensin-converting enzyme 2 (ACE-2) contributes to renin-angiotensin system (RAS) dysfunction, promoting vascular permeability, inflammation, and fluid-electrolyte imbalance[13]. These changes likely play a role in the development of ARF and SEPSE, both of which were significantly associated with D-dimer levels in our cohort.

Studies have also suggested that SARS-CoV-2 may directly infect renal tissue, so it can cause cytopathic effects and contribute to acute kidney injury[14–16]. In the case of endocarditis, increased vascular permeability and systemic inflammation may facilitate infection of the endocardium[17]. While these hypotheses are supported in the literature, further research is needed to explore the mechanistic links observed in our data.

The present study has some limitations. D-dimer testing was not routinely performed on all patients, which limited the sample size. Additionally, some tests were conducted after hospital admission, and certain patients were transferred from other facilities without complete medical histories, or transferred from HUM to other locations. Follow-up on clinical outcomes was not possible. Furthermore, the absence of a more comprehensive multivariable adjustment restricts the ability to draw causal inferences from the findings, which should be considered when interpreting the results.

RELEVANCE TO HEALTH PROMOTION AND DISEASE PREVENTION

The findings of this study have important implications for public health. The use of D-dimer as an early biomarker of systemic inflammation and endothelial injury may assist healthcare professionals in identifying patients at higher risk of complications from COVID-19 upon hospital admission. This early detection allows for more timely and targeted interventions, potentially reducing the incidence of severe outcomes such as thrombosis, acute renal failure, endocarditis, sepsis, and death. From a health promotion perspective, integrating D-dimer testing into initial patient assessment protocols contributes to a more proactive approach to care, supporting clinical decision-making and optimizing hospital resources. Moreover, this strategy aligns with the principles of disease prevention by facilitating risk stratification and improving patient prognosis, especially in low-resource settings and during public health emergencies.

CONCLUSION

This study demonstrates that the elevation of serum D-dimer levels is associated with inflammatory and endothelial injury processes triggered by SARS-CoV-2 infection. Clinically, D-dimer may serve as a valuable biomarker to assess disease severity and predict adverse outcomes such as mortality, ICU admission, thrombotic events, renal failure, endocarditis, and sepsis. These findings support the implementation of D-dimer testing as part of initial evaluations in patients hospitalized with COVID-19. Future longitudinal studies and clinical trials are needed to validate the use of D-dimer as a tool for early intervention and to strengthen evidence-based protocols for the prevention of complications related to COVID-19.

PRACTICAL IMPLICATIONS

Based on our results, we recommend that D-dimer testing be routinely included in the initial triage of hospitalized COVID-19 patients. As a laboratory marker, it can assist in early clinical decision-making, including the timely initiation of anticoagulant therapy and the allocation of critical care resources such as ICU beds. Its use may help reduce adverse outcomes by enabling more targeted and proactive interventions.

FUTURE DIRECTIONS

To confirm the prognostic role of D-dimer, further longitudinal studies and randomized clinical trials are needed to evaluate its effectiveness as an early intervention criterion. Future research should also explore optimal cutoff values for different patient profiles, considering comorbidities, age and

disease severity, as well as investigate its potential application in other inflammatory or infectious conditions.

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