

Association between “D-dimeritis” in the emergency department and COVID-19 hospital burden

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Abstract

This study analyzed D-dimer tests requested by the two emergency departments of the University Hospital Trust of Verona during the Coronavirus disease 2019 (COVID-19) pandemic. Our findings show that the aggregate monthly number of D-dimer test requests from both emergency departments increased significantly (+39%) in 2021 compared to 2019, followed by a steady decline until 2024, when the aggregate monthly test requests were nearly threefold lower than before the pandemic. A strong association was observed between monthly D-dimer test requests and ICU admissions for COVID-19 in Verona ($r=0.90$; $p=0.037$), whereas no significant correlation was found with COVID-19 positive cases ($r=0.11$; $p=0.855$) or COVID-19 hospitalizations ($r=0.70$; $p=0.118$) in Verona. These results suggest that the heightened severity of COVID-19 cases during the early pandemic phase was a key driver of increased D-dimer test requests, while the subsequent decline may reflect reduced disease burden, improved test appropriateness through enhanced healthcare staff education, and a better understanding of COVID-19 pathophysiology.

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Introduction

D-dimer is now widely recognized as an important biomarker for the assessment of a vast array of thrombotic pathologies, in particular Venous Thromboembolism (VTE) and Disseminated Coagulation (DIC).¹ Its clinical relevance has gained considerable importance during the recent Coronavirus 2019 (COVID-19) pandemic, as increased D-dimer levels have been reliably associated with the risk of developing thromboembolic complications and unfavorable clinical progression in patients with SARS-CoV-2 (severe acute respiratory syndrome Coronavirus 2) infection,² as well as for differentiating Multisystem Inflammatory Syndrome in Children (MIS-C) from Kawasaki disease.³

In patients with COVID-19, SARS-CoV-2 triggers a series of prothrombotic conditions, in particular a hyperinflammatory state and endothelial dysfunction, which ultimately increase the risk of developing local (*i.e.*, pulmonary) and even diffuse thrombotic complications. This condition, commonly referred to as “COVID-19-associated coagulopathy”,⁴ is reflected in increased D-dimer generation, the levels of which are closely associated with the risk of critical illness, hospitalization, Intensive Care Unit (ICU) admission, and death.² Therefore, frequent monitoring of D-dimer levels has become a paradigm in the clinical management of COVID-19, leading to a significant increase in D-dimer testing requests worldwide (often referred to as “D-dimeritis”),⁵ as also evidenced in previous studies.^{6,7}

Now that the clinical pressure of COVID-19 on healthcare systems has eased considerably due to herd immunity (triggered by natural infection, vaccination, or both), better healthcare preparedness for pandemic emergencies and improved therapeutic management,⁸ it is predictable that the number of test requests for D-dimer from Emergency Departments (EDs) (*i.e.*, the healthcare site where the vast majority of patients with more aggressive forms of SARS-CoV-2 infection are initially admitted) may have experienced a reasonable decrease. We therefore planned this study to monitor the volume of D-dimer test requests from the ED throughout the pandemic and eventually correlate these changes with the variation of healthcare burden caused by COVID-19.

Materials and Methods

The study was conducted at the University Hospital Trust of Verona (Azienda Ospedaliera Universitaria Integrata di Verona), which includes two separate hospitals (Hospital Policlinic “Borgo Roma” and General Hospital “Borgo Trento”), both of which have an ED. According to the last available information, the number of visits in 2023 was 36,650 in the ED of the Hospital Policlinic and 54,338 in the ED of the General Hospital, respectively. The total number of D-dimer tests requested by the two EDs in the period between January 1, 2019, and October 31, 2024, was retrieved using a specific electronic search in the local Laboratory

Information System (LIS). The volumes of requests from the two sites were summed and finally expressed as the mean number of D-dimer tests requested from both sites per month throughout the study period. A second search was performed on the official website of the Italian National Institute of Health (Istituto Superiore di Sanità, ISS) to recover the number of COVID-19-positive cases, COVID-19 patients hospitalized, and COVID-19 patients admitted to the ICU in Verona. Data were available from February 21, 2020 (first COVID-19 case hospitalized in Verona) and March 16, 2024 (last available update on COVID-19). We analyzed the monthly number of SARS-CoV-2 positive cases, hospitalizations, and ICU admissions in Verona during the study period to calculate the Spearman's correlation with the aggregate monthly D-dimer test requests from the two EDs of the University Hospital Trust of Verona. The statistical analysis was performed using Analyse-it (Analyse-it Software Ltd, Leeds, UK). All data extracted with our searches were fully anonymized so that ethics committee approval and informed patient consent were not required.

Results

The results of our analysis are summarized in Figure 1, which reflects the trend of aggregate D-dimer monthly requests from the two EDs throughout the COVID-19 pandemic and shows that this volume increased considerably in 2021 after the test was included in a standard panel of laboratory biomarkers for diagnosing and monitoring COVID-19 cases at the University Hospital Trust of Verona in late 2020. This peak of test requests was then followed by a gradual decline, with the number of aggregate D-dimer test requests in 2024 being almost three times lower than in the last year before the pandemic (*i.e.*, 2019). The trend was almost identical for the two EDs of the University Hospital Trust of Verona (data not shown). No significant correlation was observed between the mean monthly number of D-dimer test requests from the EDs and the mean number of SARS-CoV-2 positive cases per month ($r=0.11$; 95% CI, -0.85 to 0.91; $p=0.855$) or the mean number of COVID-19 hospital admissions per month ($r=0.70$; 95% CI, -0.48 to 0.98; $p=0.118$) during the period when the official data could be retrieved from the ISS, while the correlation between the mean monthly number of D-dimer test requests and mean monthly number of ICU admissions for COVID-19 during the same period reached statistical significance ($r=0.90$; 95% CI, 0.09 to 0.99; $p=0.037$). The cumulative cost per test of D-dimer was €11,089 in 2019, €10,825 in 2019, €15,414 in 2021, €8244 in 2022, €5989 in 2023, and €3770 in 2024. From an economic perspective, the reduction in the number of D-dimer tests performed in 2024 compared to 2021 has hence generated a net saving of €11,644 for the University Hospital Trust of Verona.

Discussion and Conclusions

D-dimer has become a cornerstone in the diagnosis and clinical management of various human diseases, including COVID-19.⁹ Unsurprisingly, earlier studies have reported a marked increase in D-dimer test requests from EDs and other acute care settings during the initial phase of the pandemic, coinciding with the heightened clinical severity of SARS-CoV-2 infections.^{6,7} While this surge in testing was clinically justified, given the pivotal diagnostic and prognostic role of D-dimer, it also placed significant strain on clinical laboratories in terms of workload and costs.¹⁰ As the

burden of COVID-19 on the healthcare system has substantially diminished, it is critical to assess whether this reduction has been accompanied by a corresponding decline in D-dimer test from the ED. The results of our analysis support this assumption. After a pronounced peak in 2021, when the monthly number of D-dimer test requests increased by 39% compared to 2019 (175 vs. 126 tests), the volume of requests gradually declined, reaching a monthly average in 2024 that was nearly threefold lower than that recorded in 2019 (43 vs. 126 tests). Notably, a stronger correlation was observed between ICU admissions for COVID-19 and the frequency of D-dimer test requests compared to total COVID-19 hospitalizations, suggesting that increased clinical severity of SARS-CoV-2 infection, as reflected by ICU admission, was a key driver of the observed trend.

In addition to the clinical burden of COVID-19, two other factors likely contributed to the significant decline of D-dimer test requests from the ED in the past 2-3 years. First, joint meetings between the EDs and the clinical laboratory were organized in January 2022 and January 2023, which have strengthened the partnership between the ED and the clinical laboratory but have also likely contributed to improving the appropriateness of D-dimer test requests. Second, advancements in understanding the pathophysiology of COVID-19 have facilitated the development of more precise diagnostic and therapeutic approaches. This has allowed D-dimer testing to be better integrated into validated diagnostic algorithms, such as that outlined in a joint document by the Academy of Emergency Medicine and Care (AcEMC) and the Italian Society of Clinical Biochemistry and Clinical Molecular Biology (SIBioC).¹¹ A limitation of this study is the lack of consideration for potential confounding factors that may have influenced the number of D-dimer test requests throughout the observational period. Specifically, the inclusion of D-dimer in standard diagnostic panels during the COVID-19 pandemic could have contributed to increased test utilization, regardless of disease severity or clinical necessity. Evolving clinical guidelines, changes in physician decision-making, and variations in hospital protocols may have further

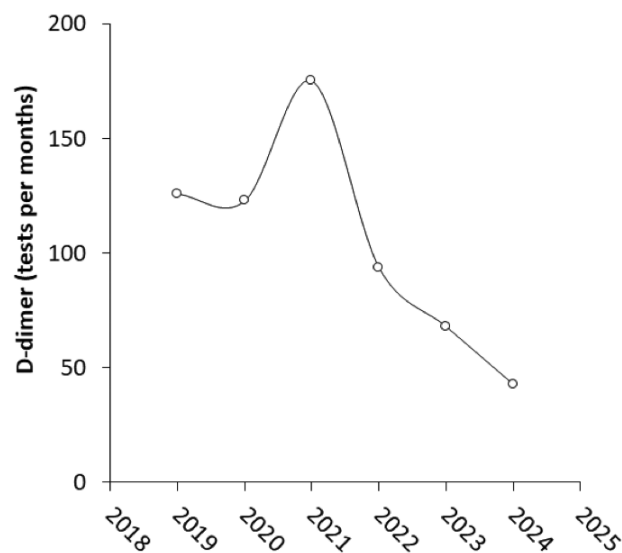


Figure 1. Aggregate monthly D-dimer test requests from the two emergency departments of the University Hospital Trust of Verona between 2019 and 2024.

impacted testing patterns.

Taken together, our results seem to attest that the increase in D-dimer testing during the peak of the SARS-CoV-2 pandemic can be better explained by the cognitive phase of the pathology rather than the clinical value of the test itself. Heightened public and medical awareness of the association between COVID-19 and thrombotic complications led to the widespread use of D-dimer testing, even in patients without clear clinical diagnostic indications. We cannot rule out that this surge may have been driven by precautionary measures about potential complications rather than real diagnostic need. Nonetheless, the number of D-dimer test requests declined sharply in the post-pandemic phase, even exceeding expectations. This decrease was not due to a diminished clinical value of the test but rather a change in cognitive perception. As the urgency and fear surrounding COVID-19-related thrombosis decreased, it is likely that D-dimer testing became more selective, limited to cases with clear symptoms or risk factors for thrombosis. This shift highlights how cognitive and societal factors can significantly influence medical testing behaviors, emphasizing the importance of considering these aspects when evaluating the utilization of diagnostic tools like D-dimer.

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