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EDITORIAL

Can D-dimer be Used as a Marker for Thromboembolic Events in Pediatric Patients With COVID-19?

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Editorial referring to the article: Elevated D-Dimer as a Marker For Thromboembolic Events in Pediatric Patients With Covid-19: A Systematic Review

D-dimer is a protein resulting from fibrin degradation. It is released into the circulation when clot degradation occurs and is therefore used as a marker for thromboembolic events and fibrinolysis.[1] The main role of D-dimer lies in its negative predictive value for the exclusion of thromboembolic events, when its level is below 500 ng/mL.[2] Because D-dimer functions as an inflammatory marker, various non-thromboembolic situations can contribute to an increase in its level, such as advanced age, pregnancy, postpartum period, neoplasms, renal insufficiency, and sepsis.[3] Age is a crucial factor when considering D-dimer a thromboembolic marker. Healthy populations over 70 years of age have shown a 50% increase in D-dimer levels without correlation with thrombotic or inflammatory events.[4]

During the COVID-19 pandemic, several studies have demonstrated a positive correlation of elevated D-dimer levels, prolonged coagulation time, and low platelet count with mortality from COVID-19.[1,2,5,6] Although D-dimers lack high specificity[2] as a diagnostic tool, they have been widely used as predictors of severity and complications in this setting, given that D-dimer tests are rapid, simple, and low-cost.[2-4] However, hyperinflammation caused by SARS-CoV-2 infection can lead to an increase in D-dimer unrelated to thrombosis, which implies its correlation with other tests and caution in interpreting the results.[5]

Children under 21 years of age develop less severe acute respiratory syndrome due to SARS-CoV-2 than adults, but with similar susceptibility to infection. The behavior of COVID-19 in children varies from asymptomatic forms and mild catarrhal symptoms to pediatric multisystem inflammatory syndrome (MIS-C).[7-9]

MIS-C is particularly severe and characterized by prolonged high fever, rash, gastrointestinal symptoms, conjunctivitis, lymphadenopathy, irritability, and headache.[8] A systemic inflammatory state is associated with elevated inflammation indices, neutrophilic leukocytosis, lymphopenia, and organ dysfunction, along with laboratory or epidemiological evidence of SARS-CoV-2 infection and exclusion of other microbiological causes.[9] Some severe cases present with shock due to cardiac dysfunction, with or without myocarditis, aneurysm, and coronary artery thrombosis.[8]

Is it possible to use D-dimer as a risk marker for thromboembolic events in the pediatric population with COVID-19? The systematic literature review proposed by Costa et al. analyzed 79 articles that included studies on the relationship between COVID-19 and thromboembolic events in pediatric patients (under 21 years of age), using D-dimer as a prognostic marker.[7] Of these studies, 7 were considered for final evaluation. D-dimer was not a good parameter to assess the risk of thromboembolic events in the pediatric age group. The main limitations are that D-dimer increases in any type of inflammation and, therefore, is not a specific marker, and it increases even without the occurrence of thromboembolic events.[7]

Some points are important to emphasize: severe presentation of COVID-19 in children is a rare event, and the risk of thromboembolic events is even rarer,[10] ranging from 0.07 to 0.14 per 10,000 children per year.[11] In the pediatric age group, contributing comorbidities for a thromboembolic event, such as atherosclerosis, diabetes, hypertension, and tobacco-related vasculopathy, are not present.[12] Therefore, even in the presentation of a

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hyperinflammatory and prothrombotic state, such as in MIS-C, the pediatric patient would be at lower risk than the adult patient.[7,10,12]

The evaluation of D-dimer as an inflammatory marker was demonstrated in another meta-analysis that analyzed 21 articles and found that D-dimer above the upper limit showed itself as a potential prognostic tool but with low positive correlation to assess length of hospital stay and clinical worsening. After the resolution of the inflammatory process of MIS-C, D-dimer returned to normal levels, with patients recovering without thrombotic sequelae.[9]

Therefore, based on the available information, D-dimer in children can be used as a marker of inflammation, with low specificity and without a direct connection to an increased thrombotic risk. Its use as a marker for initiating or discontinuing antithrombotic prophylaxis in COVID-19 in children should be discouraged.

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